NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation: Zio XT for detecting cardiac arrhythmias

Supporting documentation – Committee papers

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) when making their draft recommendations:

1. **EAC assessment report** – an independent report produced by an external assessment centre who have reviewed and critiqued the available evidence.
2. **Assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
3. **Addendum to the assessment report** – contains additional work and economic analyses done by the external assessment centre.
4. **Scope of evaluation** – the framework for assessing the technology, taking into account how it works, its comparator(s), the relevant patient population(s), and its effect on clinical and system outcomes. The scope is based on the sponsor's case for adoption.
5. **Adoption scoping report** – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.
6. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
7. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
8. **Patient survey results** – presents results from an online patient survey conducted by NICE on the use of Zio XT.
9. **Patient organisation submissions** – questionnaire responses and submissions received by patient organisations.

10. **EAC correspondence log** – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.
11. **Company fact check comments** – the manufacturer's response following a factual accuracy check of the assessment report.
12. **Technical Engagement Report** - summarises the outcome, rationale and considerations that were made during the technical engagement meeting.

Please use the above links and bookmarks included in this PDF file to navigate to each of the above documents.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

DHT005 Zio XT Service for detecting cardiac arrhythmias

External Assessment Centre report

Produced by:	**King's Technology Evaluation Centre**
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Date completed:	**17/01/2020**

Contains confidential information	Yes
Number of attached appendices	Three (A-C)

Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence presented in the submission to support their case for adoption in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance.

Declared interests of the authors

The Kaura et al. (2019) study was carried out, in part, at King's College Hospital NHS Foundation Trust. The King's Technology Evaluation Centre is part of the King's Health Partnership network.

Acknowledgements

Jacqueline Colwill is a Cardiac Physiologist and Cardiology Service lead at South Tyneside NHS Foundation Trust, no conflict declared.

Dr Gregory Lip is the Price-Evans Chair of Cardiovascular Medicine and Director of the Liverpool Centre for Cardiovascular Science at the University of Liverpool and Liverpool Heart & Chest Hospital, no conflict declared.

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Dr Mark Tanner is a Consultant Cardiologist Western Sussex Hospitals NHS Foundation Trust, no conflict declared.

Dr James Teo is a Consultant Stroke Neurologist at King's College Hospital NHS Foundation Trust, no conflict declared.

Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

ABBREVIATIONS

Term	Definition
AF	Atrial Fibrillation
CER	Continuous event recorder
CI	Confidence interval
CQC	Care Quality Commission
DDDRP PPM	Dual Chamber Rate Adaptive Permanent Pacemakers
DHSC	Department of Health & Social Care
DHT	Digital health technology
EAC	External Assessment Centre
ECG	Electrocardiogram
ESF	Evidence standards framework
IQR	Interquartile range
KiTEC	King's Technology Evaluation Centre
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
NHS	National Health Service
NHSFT	National Health Service Foundation Trust
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NICE QS	NICE quality standard
OR	Odds Ratio
PAF	Paroxysmal Atrial Fibrillation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised Controlled Trial
SD	Standard deviation
SVT	Supraventricular Tachycardia
TIA	Transient Ischaemic Attack
Vs	Versus

Executive Summary

The company included 22 studies as clinical evidence. These were reported as fulltext. The EAC excluded 6 studies from the company's selection due to population and/or outcomes not being relevant to the decision problem. One further study reported as fulltext was added by the EAC (Rho et al. 2018). The EAC added 13 abstracts, totaling 30 studies overall. Most of the included studies were observational in design and lacked direct comparators or were reported as abstracts. Of the studies reported as fulltext there was 1 UK-based RCT (Kaura et al. 2019), 3 prospective comparative studies (Barrett et al. 2014, Eysenck et al. 2019, Rosenberg et al. 2013) which were considered pivotal studies. Thirteen non-comparative studies were included. The sponsor included 20 references as economic evidence. Only published studies (Kaura et al. 2019, Ghosh et al. 2018 and Chandratheva et al. 2017) and 1 grey literature reference (NICE 2017) assessed Zio XT Service and were considered for assessment by the EAC. The EAC conducted its own search for economic evidence and retrieved 5 further publications containing economic data (Steinhubl et al. 2019, Eysenck et al. 2017a, Eysenck et al. 2017b, Eysenck et al. 2018, Eysenck et al. 2019. Three of these, (Eysenck et al. 2017a, Eysenck et al. 2017b, Eysenck et al. 2018), were conference abstracts reporting the study described by Eysenck 2019.

The company did not carry out a meta-analysis, stating that the evidence for the efficacy and safety of the Zio XT Service is extremely heterogeneous, in terms of populations, methodology, devices used, and outcomes reported. The EAC agreed.

The UK based RCT (Kaura et al. 2019) and 2 comparative studies (US studies: Barrett et al. 2014, Rosenberg et al. 2013) indicated that the use of 14-day Zio XT Service increased diagnostic yield compared with 24-hour Holter monitoring over total wear time. The diagnostic accuracy of Zio XT Service compared with Holter monitoring is unclear, however overall clinical expert opinion suggested that there may be no significant difference in accuracy. A UK study (Eysenck et al. 2019) indicated that Zio XT Service may be more accurate in detecting the presence or absence of AF than the

Novacor R Test (an external event/loop monitor, described as current standard practice) but less accurate than pacemaker data (described as gold standard). Patient compliance for Zio XT Service appears high, with mean wear time ranging from 10.8 days (Rosenberg et al. 2013) to 12.8 days (Eysenck et al. 2019) out of scheduled 14 days in comparative studies. Barrett et al. (2014) provided a comparison of patient experience, reporting that 93.7% participants found the monitoring patch comfortable to wear as opposed to 51.7% for the Holter monitor. A survey into patients from a UK cardiology clinic (Hall et al. 2019, abstract only) found that Zio XT Service was significantly preferred to Holter monitoring in terms of shape, comfort, practicality and returning method.

The company carried out cost modelling in 3 care pathways: for populations of patients with symptomatic palpitations or syncope (cardiology model), patients who have had a stroke or TIA (stroke model), and a third model assessing costs of subsequent stroke treatment of the technology's diagnostic yield in comparison to Holter monitors. The cost analysis found that the use of the Zio XT Service in the 2 patient groups considered results in process cost savings (due to reductions in repeat testing, referrals or cardiology outpatient review, and events in stroke populations) of around £55-£85 per patient, compared to current standard care. The EAC revised the model to address a number of potential limitations including revision of estimated stroke risk and the inclusion of test costs (including repeated test costs) and costs of anticoagulant therapy and its side effects. After developing revised cost models, the EAC concluded that Zio XT Service is unlikely to be cost saving when compared with current practice, however, the estimated increase in cost is small (approximately £20 per patient) and may be offset by benefits of improved diagnosis of AF.

The EAC highlights that there are limitations with the models. Firstly, the value proposition of the technology relies on the increased diagnostic yield of Zio XT Service in comparison with usual practice. The elevated diagnostic yield is well supported by the body of evidence identified by the EAC, however, there is little published evidence investigating its diagnostic accuracy (compared

with 24 hour Holter monitoring against a reference standard). Secondly, there is a lack of clarity around the clinical pathway currently implemented in the NHS. As correctly noted by the company there are a number of different alternatives currently in place. The assumption of no repeat tests with Zio XT Service is plausible but likely to be an underestimate, if only a modest one. The number of repeat tests carried out after an inconclusive/negative test for Holter monitoring has a significant impact on cost, but is unstandardised and varies by local protocol and clinical opinion, therefore the figure for this parameter is unclear. In addition, there are some limitations to the supporting evidence. For example, HES data representing repeat testing incorporates various tests including 24 and 48 hour ECG monitoring, ambulatory ECG monitoring and exercise ECG monitoring (NICE TA593). This may artificially increase the estimated number of repeated Holter tests.

The current evidence would benefit from further research into the diagnostic accuracy of Zio XT Service against standard practice and an appropriate reference standard. In addition, further analysis focusing on technology utilisation and the resultant clinical outcomes would provide greater insight into the clinical response to newly-detected arrhythmia. The evidence supports the case for adoption but there are still several unknowns that should be addressed first.

1 Decision problem

Table 1 Decision Problem

Decision problem	Scope	Proposed variation in company submission	EAC comment
Population	Adults (18 years or older) with suspected cardiac arrhythmia referred for ambulatory ECG monitoring.	None.	
Intervention	Zio ECG monitoring service (Zio Service).	Zio XT ECG monitoring service (Zio XT Service).	Addition of "XT" to name of intervention.
Comparator(s)	Current pathway for ambulatory cardiac arrhythmia detection, which includes Holter and/or event monitoring (external and implantable).	Current pathway for ambulatory cardiac arrhythmia detection, which includes Holter and/or event monitoring.	Company has removed "(external and implantable)". The company states that implantable cardiac monitors are rarely used as a first line of standard care and are not directly comparable. Clinical experts agreed that implantable devices are rarely used as a first line of care. They are more likely used for diagnosis.
Outcomes	Procedure-related outcomes: • Diagnostic yield and accuracy (sensitivity and specificity) • Number of symptomatic and asymptomatic arrhythmia events detected over total wear time • Ability to quantify atrial fibrillation (AF) burden (amount of time spent in AF)	Remove the following: • Health-related quality of life	The company suggests removing "Health-related quality of life" as an outcome as there is no evidence to demonstrate this. The EAC suggests retaining this outcome in case future evidence comes to light.

	• Time to first arrhythmia event and time to first symptomatic event • Time to return device, analysis and report production • Test failure rate • Signal quality Clinical management outcomes: • Time to diagnosis or rule out of cardiac arrhythmia • Time to initiation of preventative treatment • Impact of test results on clinical decision making • Total number of hospital outpatient appointments for testing • Total number of hospital outpatient appointments or admissions for device-related complications • Number of outpatient visits and staff time for undertaking and analysing diagnostic tests • Morbidity (including stroke, thromboembolism, heart failure, and complications associated with preventative treatment)		

	• Mortality Patient outcomes: • Patient compliance (average wear time and analysable wear time) • Ease of use (for patients and healthcare professionals), including training requirements • Device acceptability and patient satisfaction • Health-related quality of life • Device-related adverse events		
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	None.	
Subgroups to be considered	• Adults referred for ambulatory ECG monitoring, who experience asymptomatic arrhythmia events • Adults referred for ambulatory ECG monitoring in primary care • Adults referred for ambulatory ECG monitoring in secondary care	Changes to subgroups: Adults referred for ambulatory ECG monitoring, *with symptoms of arrhythmia* Adults referred for ambulatory ECG monitoring*, without*	The company states that the primary care referral pathway is included within the general medicine pathway as a route to diagnostic services but will not be considered separately within the economic modelling. The company's suggested changes include subgroups with symptomatic or non-

		symptoms of arrhythmia (e.g., patients with cryptogenic stroke or TIA) Adults referred for ambulatory ECG monitoring in secondary care	symptomatic adults. One RCT and 2 non-comparative studies were found in asymptomatic patients. No evidence was found in primary care settings.
Special considerations, including those related to equality	The area of skin in which the Zio XT patch is applied will need shaving if hair is present. Some religions forbid cutting or shaving bodily hair. Zio XT Service is not approved for paediatric use. Religion and age are protected characteristics under the Equality Act. Contraindications are listed the instructions for use for Zio XT Service.	The company notes that traditional approaches to ECG monitoring also require shaving of bodily hair for electrode placement on the body.	The EAC acknowledges this note about the comparators for Zio XT Service.
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristics? No	None.	
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality? No	None.	
	Is there anything specific that needs to be done now to ensure MTAC will have relevant information to consider equality issues when developing guidance? No	None.	

	Cardiac arrhythmias can develop in people of any age but are more common in people over 60 years. Women tend to be at higher risk of certain arrhythmias, including atrioventricular nodal tachycardia, whereas men are 3 times more likely to develop atrial fibrillation at any age. However, of those people who develop atrial fibrillation, women have a much higher incidence of morbidity and mortality. Age and sex are protected characteristics under the Equality Act. People whose first language is not English or who cannot write may not be able to give written information on their symptoms while using the Zio Service.	None.	

2 Overview of the technology

The Zio XT Service (iRhythm Technologies) consists of 3 components: the Zio XT biosensor, the Zio ECG Utilisation Service (ZEUS) system and the Zio XT technical report. The Zio XT biosensor is an adhesive patch with a I-Lead ambulatory electrocardiogram (ECG) recorder. The ZEUS system is a proprietary software platform that is used to store, analyse and sort the recorded ECG data. The Zio XT technical report is a clinically actionable summary of the recorded and analysed data, generated by the ZEUS system and the Zio clinical team.

The Zio XT biosensor is a lightweight and water-resistant patch that has no external leads or wires. The patch is attached to the left upper chest and records a continuous beat-to-beat ECG for up to 14 days. Each patch is intended for single-patient use. Wearers can continue with their usual daily activities during the monitoring period and can press a trigger button on the device when a symptom is felt. This highlights the recording for 45 seconds before and after the button is pressed. A paper-based log should also be kept

by the wearer to record any symptomatic events along with information on what they were doing at the time. This allows for a symptom-rhythm correlation to be included in the Zio technical report.

After the monitoring period, the patch is removed and returned to iRhythm via Freepost through the Royal Mail. The recording is analysed by the artificial-intelligence-led ZEUS system and overseen by Zio's clinical team of accredited cardiac physiologists. It takes between 9-12 months of training for 1 of Zio's cardiac physiologists to become fully competent. A technical report is produced and electronically sent to the wearer's clinician via Zio's secure website. The report contains information regarding arrhythmia episodes, wear and analysis time and events captured by the wearer. If the wearer's clinician has any queries regarding the technical report, they can request more information or amendments to the report via iRhythm's secure website. There are no patient identifiers in or on the Zio XT patch and data cannot be accessed if the patch was to be physically intercepted.

The main innovative aspect is the extended period of continuous monitoring when compared to a standard Holter monitor. A standard Holter monitor is most often used to record for 24 to 48 hours but can be used to record up to 7 days. A Holter monitor is usually worn in a pouch around the waist or neck or carried in a pocket and has external wires. The Zio XT patch can be worn under clothing and so may be more discreet and be less susceptible to noise artefacts. It can also be worn in the bath or shower, allowing the wearer to go about all of their daily activities as normal. The company claims that the Zio XT Patch could improve patient compliance and device wear time.

The device is a Class IIa CE marked device. The device was originally approved on the 2 December 2014 and last amended on 26 November 2019. The CE marking is valid until 26 May 2024.

iRhythm Technologies is registered with the CQC to carry out diagnostic and screening procedures as of 25 July 2018. The CQC have not yet inspected the service.

3 Clinical context

Arrhythmia is described by NHS Choices as the presence of heart rhythm problems, with main types of arrhythmia being:

- atrial fibrillation (AF) – this is the most common type, where the heart beats irregularly and faster than normal
- supraventricular tachycardia – episodes of abnormally fast heart rate at rest
- bradycardia – the heart beats more slowly than normal
- heart block – the heart beats more slowly than normal and can cause people to collapse
- ventricular fibrillation – a rare, rapid and disorganised rhythm of heartbeats that rapidly leads to loss of consciousness and sudden death if not treated immediately

Clinical experts note that it is difficult to compare different types of arrhythmia as most are distinct diseases with distinct pathophysiologies, syndromes and populations. Therefore, the corresponding clinical pathways, severity of condition and clinical outcomes may vary accordingly.

NICE defines AF as atrial tachyarrhythmia characterised by predominantly uncoordinated atrial activation with consequent deterioration of atrial mechanical function.

The NICE guidelines on managing atrial fibrillation and transient loss of consciousness ('blackouts') in over 16s recommend an ECG for the first assessment. If further assessment of possible cardiac arrhythmia is needed, ambulatory ECG monitoring is recommended for 24 or 48 hours. The choice of monitor depends on symptoms and symptom frequency and includes Holter monitoring and external or implantable event recorders.

If the first 24- to 48-hour Holter monitor test does not give a clear diagnosis, people are referred for further investigations. This can include event recording for up to 7 days or admission to hospital for more invasive options, such as fitting an implantable event recorder.

NHS Choices states that the most effective way to detect arrhythmia is using an ECG. If the ECG does not detect arrhythmia, further monitoring may be carried out using a Holter device for 24 hours or longer. Other tests mentioned include:

- cardiac event recorder (CER)
- electrophysiological (EP) study
- echocardiogram

The Holter monitor is the method most commonly used in the NHS for detecting arrhythmia. Holter monitors continuously record the heart rhythm using several electrode patches, which are stuck on the user's chest. The ECG signals are recorded to a portable machine. As with the Zio XT patch, the user can press a button on the front of the recording machine to highlight when they experienced symptoms. Holter monitoring is used for 24 to 48 hours for people who have regular symptoms or can be used for up to 7 days for people with symptoms that happen less often, such as if they only have arrhythmia every 3 to 4 days. Results are analysed by a cardiac physiologist.

Draft NICE guidance (published January 2020, due to be finalised in May 2020) recommends that an implantable cardiac monitor (the Reveal LINQ monitor) should be used to detect AF after cryptogenic stroke if cause of stroke is still unknown after ECG.

Experts also mentioned European Society of Cardiology (ESC) syncope guidelines and ESC Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death guidelines. These guidelines are in line with the NICE guidelines regarding management of arrhythmias.

The company describes 3 clinical pathways for the referral and clinical management for patients undergoing cardiac diagnostic ambulatory monitoring in the Cardiology, Stroke and General Medicine clinical services. The EAC believes that the company has appropriately described the current clinical context as per NHS and NICE guidelines outlined above describing the 24-hour Holter (or if appropriate a longer term 7-day Holter or event

recorder) as the main method of carrying out ambulatory monitoring. The company has validated the pathways described with appropriate UK healthcare professionals. The pathways described are in line with NICE guidelines.

Special considerations, including issues related to equality and improving access

The company notes that applying the Zio Patch may require shaving of body hair, noting that some religions forbid cutting or shaving body hair. The company notes that traditional approaches to ECG monitoring also require shaving of bodily hair for electrode placement.

The company submission states that Zio XT Service may streamline the patient pathway and improve access to ambulatory ECG monitoring among hard-to-reach populations (people living in rural areas and those who have difficulties attending hospital appointments). The biosensor can be placed at the first appointment so patients theoretically would not have to return to have a separate monitor fitting. Patients return the Zio XT biosensor by post, so do not have to return the monitor to the hospital when the monitoring period is over. The extended length of wear time (up to 14 days) and potential increased diagnostic yield may minimise the number of appointments for repeat tests. This issue was discussed within the NICE technical engagement meeting. One clinical expert noted that there was an ongoing UK regional study using the Zio XT Service in a rural population.

Zio XT Service may improve access for populations that are less able to attend hospital appointments, but further published evidence specifically into these populations would be helpful to support this assumption.

4 Clinical and economic evidence selection

4.1 Evidence search strategy and study selection

The EAC considered the company's search strategies to be thorough and appropriate for the topic. However, the EAC ran a new search, which was designed to identify all records relating to the device specifically. The EAC

searched for the name of the device (“Zio” and variants) in a variety of databases and did not limit the results by population, comparator or outcome. There was no separate search for economic evidence; the results from the clinical evidence search were filtered in EndNote and reviewed separately.

The database searches revealed 729 records and following deduplication there were 533 records, in addition to 22 studies from the company’s clinical submission and 9 other studies from the systematic review by Yenikomshian et al. (2019). The titles and abstracts of these records were evaluated by 2 reviewers and sifted for relevance. Following the first sift there were 54 records remaining. The full-text versions of the 54 remaining records were sifted against the inclusion and exclusion criteria and following this second sift, 30 studies were included (including 13 abstracts). The full search strategies and a PRISMA flow diagram is included in Appendix A. The company included studies on a wide range of ambulatory cardiac monitors and was not specific to Zio XT Service. The EAC only included evidence with Zio XT Service as an intervention. Otherwise the EAC considered the company’s inclusion and exclusion criteria to be appropriate given the broad scope.

In its clinical submission, the company included 22 studies that included Zio XT Service as an intervention and were reported as fulltext; the EAC included 16 out of these 22 studies. One further study reported as fulltext was added by the EAC (Rho et al. 2018). The EAC excluded 6 studies from the company’s selection due to population and/or outcomes not being relevant to the decision problem (Camm et al. 2015, Chen et al. 2015, Hannun et al. 2019, Lutsey et al. 2016, Mullis et al. 2019, Muse et al. 2018). The EAC conducted its own search for economic evidence (see Appendix A) to confirm no relevant papers had been missed out. Following application of cost and economic filters, the EAC searches retrieved 36 abstracts related to economic evidence.

4.2 Included and excluded clinical studies

Table 2 Clinical studies selected by the EAC as the evidence base

Comparative, published as fulltext

Study name and location	Design and intervention(s) (including versions)	Participants and setting	Outcomes	EAC Comments
Barrett (2014) US	Prospective within-participant study comparing 14-day Zio XT Service with 24-hour Holter recording Partly funded by company. Zio XT Service 24-hour Holter monitoring	150 adult patients: 146 completed (4 were lost to follow-up, 3 in the Zio XT Service and 1 in the Holter monitoring group) Recruited between April 2012 and July 2012 Patients enrolled for being under evaluation for cardiac arrhythmia (supraventricular tachycardia (>4 beats, not including atrial fibrillation or flutter), atrial fibrillation/flutter (>4 beats), pause >3 seconds, atrioventricular block (Mobitz type II or third-degree atrioventricular block), ventricular tachycardia (>4 beats), or polymorphic ventricular tachycardia/ventricular fibrillation). All patients wore both devices for the first 24 hours and then continued with Zio Patch.	*Primary:* Arrhythmia event detection over total wear time: Zio XT Service: 96 24-hour Holter: 61 ($p < 0.001$) Holter detected 61 arrhythmia events while Zio Patch detected 96. Sixty events were detected by both Holter monitor and Zio Patch. Zio Patch detected 36 events that went undetected by the Holter monitor primarily as a function of prolonged monitoring. *Secondary:* Arrhythmia event detection at 24 hours: Zio Service: 52 24-hour Holter: 61 ($p = 0.013$). Median wear time: Holter monitor 1.0 days (range, 0.9– 1.0) Zio Patch 11.1 days (range, 0.9–14.0)	Some participants had pre-existing arrhythmias and were referred for reasons other than symptomatic arrhythmia. Six types of arrhythmia were included within the study with no breakdown. Calculation by authors suggests study was adequately powered. The company partly funded the study.

		41.8% men, median age 64 years (range 22-94) Single centre (US hospital).	93.7% (134/143) participants found the monitoring patch comfortable to wear as opposed to 51.7% (74/143) for the Holter monitor.	
Eysenck (2019) UK	Prospective within-participant randomised trial comparing 14-day Zio Service (and 3 other external ambulatory ECG monitors) with permanent pacemakers Zio XT Service , Comparators : Novacor R-test[1] (clinical standard) Pacemaker (gold standard) Partly funded by iRhythm	21 Participants with DDDRP PPMs (Dual Chamber Rate Adaptive Permanent Pacemakers) of various brands 18 participants had Paroxysmal AF and 3 had persistent AF 76.2% men, mean age 75 ± 7 years Participants wore 4 devices in random order (all for 14-day period) Minimum of 7-day break between each device Single Centre (UK hospital)	AF burden (R^2 compared with DDDRP PPMs, MSE): R-test: 0.029, 1556.1 Zio: 0.99, 0.24 Detection accuracy (OR, Wald CI, p): Zio vs R-test:12.3, 1.4 to 110.3, p = 0.025 (Zio was superior to the Novacor R Test using pacemakers as the reference standard comparator) Patient Satisfaction: No significant difference between Zio and R-test in discomfort scores (VAS) Mean Patient Time Expenditure (total time spent travelling to and from hospital, attending appointments and waiting for device return):	UK study Small population, high percentage males, high mean age Randomised order of devices. Primary outcome is AF burden, but this is only reported via fit-plots, limited data is reported numerically in the paper. The statistical analyses may not be appropriate. Bland-Altman tests may be more appropriate than R-test analyses. Patients all had pacemakers of varying brands, first study to compare pacemakers to external monitors.

[1] ECG event recorder monitor test, used for 2 weeks. The standard used at the study setting was the Novacor R Test.

	Mean Patient Wear Time: Zio: 307 (95% CI 284.63 to 340.32) hours R-test: 223.6 (95% CI 178.43 to 268.31) hours (p=0.016)		Zio: 26.5 min (95% CI 20.1–36.0) R-test: 53 min (p<0.0001) Total costs: Zio significantly more expensive than R-test (p<0.0001)	This may limit generalisability, due to other cardiac pathology and did not allow assessment of external ambulatory monitors in 'healthy' individuals. Authors note that the Novacor R Test is the current standard practice device for their Trust in AF burden assessment. The company partly funded the study. Definition of AF unclear.
Kaura (2019) UK	RCT comparing 14-day Zio Service with 24-hour Holter recording. Funded by an independent research grant. Company provided support but was not involved in study design or conduct of trial. Zio XT Service	116 randomised adult patients: 90 patients completed 90 days follow up Inclusion: an ischaemic non-lacunar stroke or TIA within the past 72 h by a stroke physician or neurologist Recruited between February 2016 and February 2017 All patients enrolled within 72 hours of TIA or ischemic stroke event	Detection of paroxysmal atrial fibrillation (PAF) with duration ≥ 30s at 90 days: Zio Service: 7 (16.3%) 24-hour Holter: 1 (2.1%) Detection of PAF with duration ≥ 30s at 28 days: Zio Service: 6 (14.0%) 24-hour Holter: 1 (2.1%) Anticoagulation use at 90 days: Zio Service: 7 (16.3%) 24-hour Holter: 1 (2.1%) Second ischaemic stroke or TIA at 90 days: Zio Service: 1 (2.3%)	UK RCT. High participant drop out rate (20%), primarily due to patient refusal for outpatient Holter monitor placement. Experts note that there may be high refusal/drop out for Holter monitoring (although some noted that this rate appears particularly high). It is unclear if this rate is typical of the clinical setting. This study did not directly compare alternative extended monitoring systems like

	24-hour Holter monitoring Mean Zio wear time: 11 days 16 hours (SD ±3.7 days). One UK NHSFT across 2 sites	55 men, 35 women, mean age 70.4 ± 13.2 years	24-hour Holter: 1 (2.1%) Mortality at 90 days: Zio Service: 1 (2.3%) 24-hour Holter: 0 (0) Economic modelling: Zio XT Service would result in 10.8 strokes avoided per year compared with Holter monitoring. Yearly saving in direct medical costs of £113,630, increasing to £162,491 over 5 years.	implantable loop recorders. Authors chose short-duration Holter monitoring as a suitable comparator to the Zio XT Service to reflect current clinical practice and for real-world feasibility. Calculation by authors suggests study was adequately powered, however an independent power calculation by the EAC suggests it was underpowered (0.56) due to high drop out rate.
Rosenberg (2013) US	Prospective within participant study comparing 14-day Zio XT Service with 24-hour Holter recording Partly funded by research grant from company. Zio XT Service 24-hour Holter monitoring	75 adult participants enrolled: 74 completed Inclusion: Patients being managed for AF All patients were taking medication (beta blockers, calcium channel blockers, antiarrhythmic medication) Recruited between April 2011 and May 2012 All patients wore both devices for the first 24 hours and then continued with Zio Patch.	*Agreement during the 24-hour period* All 25 AF episodes recorded on the 24-hour Holter were identified by the Zio XT Service). Mean AF burden: Zio XT Service: 54.7 ± 41.2% Holter: 58.4 ± 42.7% Correlation r = 0.82, p < 0.0001 *Over total wear time:* There was significant agreement between the two devices (kappa 0.49 ± 0.08, P < 0.01).	Pilot study with relatively small sample size. No power calculation reported. The two groups are described as comparable, but statistical significance quoted as p<0.0001 Investigators reading the Zio Patch were blinded to the reports of the 24-hour Holter monitor. Because the study is within participant, the change in AF classification and management solely due to Zio XT Service is

	Single centre (US hospital) Zio mean wear time 10.8 ± 2.8 days	41 men, 33 women, mean age 64.5 ± 8.1 years 	Median time to detection of first event with Zio Patch: 3.7 days. 90% detected by day 7. 28.4% of patients had their management changed as a result of the study: 17.3% had change in their antiarrhythmic medication, 5.3% changed oral anticoagulant use. Mean Zio Patch wear time: 10.8 ± 2.8 days 	unclear. The authors do, however, indicate that 28.4% of patients had a change in their clinical management “as a result of findings from the Zio Patch”. Partly funded by company.

Non-comparative, published as fulltext

Eisenberg (2014) US	Retrospective cohort study No conflicts of interest for the published content Not funded by company Zio XT Service No comparator	524 consecutive patients referred to an academic electrophysiology practice between May 2010 and January 2013 44% men, mean age 56.7 ± 20.2 Patients wore the patch for an average of 7 days (0.33–14, SD 2.6 days). Patients referred for monitoring: most common indication for monitoring was surveillance for any unspecified arrhythmia or palpitations (47%), followed by known or suspected AF (30%), syncope (8%), bradycardia surveillance (4%), tachyarrhythmia surveillance (5%), and chest pain (2%)	Arrhythmia detected in 99.5% of patients: most common was ventricular premature contraction (93%). 57% had significant arrhythmias: most common being supraventricular tachycardia in 231 patients (44%), followed by atrial fibrillation/flutter in 105 patients (20%), and non-sustained ventricular tachycardia in 79 patients (15%). Over one-third of initial arrhythmias were recorded after 48 hours. The majority of AF episodes (62%) were asymptomatic. Patient-reported symptoms did not correlate with arrhythmias, including AF, in half of all symptom recordings.	No comparator. Highly selective population referred for arrhythmia consultation and management. The high yield of arrhythmia detection may not be applicable to a broader population.

Go (2018) US	Retrospective cohort study Study was supported by a research grant from company Zio XT Service No comparator Analysable wear time: 14 [11-14] days	1,965 adults with confirmed PAF 55% men, mean age 69±11.8 October 2011 and October 2016 Two US integrated health care systems	Median burden of AF: 4.4% (IQR,1.1% to 17.23%). AF burden greater than 11.4% led to a more than three-fold increase of stroke or thromboembolism (AF burden calculated: Incidence of thromboembolism while not taking anticoagulants was calculated over 1915 person-years of follow up: 1.51 per 100 person years. This was then stratified by AF burden and adjusted for ATRIA and CHA2DS2VASC score). No association between the duration of the longest AF episode and the risk of stroke.	No comparator. Study sample had confirmed PAF, which may limit generalisability to populations with suspected arrhythmia.

Heckbert (2018) US	Prospective, non-comparative cohort study Funded by research grant Zio XT Service 🟢 No comparator 🔴	1122 participants wore the device for 14 days and 580 wore 2 devices in separate 14-day periods Overall mean age was 75 ± 8 years Mean time between devices was 23 ± 13 days. A subset of participants with atherosclerosis from a study of 6 US centres 🟢	Median monitoring duration was 13.8 days (IQR 13.2–14.0). New AF was detected in 32 (4%) of participants with ≥12 days of monitoring. The agreement for detection vs no detection of AF between 2 monitoring periods was Kappa 0.85 (95% CI: 0.75 – 0.94) 🟡	No comparator. Time between devices could lead to missed arrhythmias.

Reed (2018) UK	Prospective pilot study with a retrospective unmatched cohort Company provided Zio XT Service Zio XT Service 🟢 No comparator 🔴	86 participants aged 16 years or over presenting with unexplained syncope at an emergency department within 6 hours of an episode wore Zio patches for up to 14-days Recruited between November 2015 and June 2017 76 patients returned their Zio patches A retrospective cohort of 603 unmatched patients from a previous study of 1067 people with no obvious diagnosis in the emergency department, followed up for 90 days were also included Single UK emergency department 🟡	90-day diagnostic yield for symptomatic significant arrhythmia was 10.5% in the prospective group vs 2.0% in the comparator group Median time to clinical detection of symptomatic significant arrhythmia was 19 days (IQR 4-30 days) 91% of respondents to a patient questionnaire agreed or strongly agreed that the device was easy to use. 40% indicated that the patch caused skin irritation 🟢	No comparator. Patients aged 16 and 17 included in study Underpowered for secondary outcomes (required 85 patients to reach primary endpoint with 80% power but only 76 patients returned monitors)

Rho (2018) US	Prospective within participant study comparing Zio Service with Carnation Ambulatory Monitoring, CAM Not funded by company Zio XT Service Carnation Ambulatory Monitoring, CAM	30 consecutive adult patients referred to a community cardiology practice were enrolled, 29 completed 66.6% men, mean age 73.1 ± 7.1 years Patients were asked to wear both devices for 7 days	A total of 86.7 ± 0.6 arrhythmias were recorded by Zio-XT and 121.7 ± 2.1 from CAM, p<0.001 The ECG clarity was ranked as high in all 29 CAMs reports (100%) and on 4.5 (16%) of the Zio-XT reports (average of the 2 electrophysiologist reviewers), p<0.001	The patient sample size is small. Comparator is not current pathway. To minimise unintended bias in comparisons, data was independently reviewed the data in separate scrambled sets for each device.

Schreiber (2014) US	Prospective observational study of Zio Service Partly funded by research grant from company. Zio service No comparator	174 adult participants with suspected arrhythmia Recruited between February 2011 and February 2012 All participants wore 14-day Zio Patch 45% men, mean age 52.2 ± 21.0 years Three US emergency departments	98 arrhythmia events detected over 6.9 days (median device wear time) Diagnostic yield (percentage of all patients who had a triggered event without any arrhythmia found or who had a significant symptomatic arrhythmia detected): 63.2% 53.4% of patients who pressed the event button did not have any arrhythmia at the time Median time to first arrhythmia was 1.0 days Median time-to-first symptomatic event was 1.5 days. Median time to event for some types of arrhythmia was 5.8 days.	No comparator. Intervention was only 7 days – relatively short compared with other studies.

Schultz (2019) US	Retrospective cohort study comparing Zio XT Service data from different time periods of use No funding received Zio XT Service No comparator	314 adults with congenital heart disease 39% men, median age 31 (25-41) years June 2013 to May 2016 Mean wear time was 9.5 ± 4.1 days Single centre	156 patients showed a significant arrhythmia, 72 of those (46%) were during the first 48 hours. For total arrhythmias, arrhythmia incidence continued to increase over time: 15% at 1 day, 23% at 2 days, 39% at 5 days, 47% at 7 days, 52% at 10 days, and 62% at 14 days. A clinical management change based on an arrhythmia was made in 49 patients (16%) following Zio XT Service use.	Patients acted as their own controls, comparing the first 48 hours of Zio XT Service to the full 14-day recording. There may have been some selection bias, with standard monitors being used when providers required real-time notification of dangerous arrhythmias. Patient management decisions were made by individual providers so variations in practice may be present.

Steinhubl (2018) US	Prospective matched cohort study Zio XT Service ● Participants were randomised to immediate monitoring with Zio or delayed monitoring 4 months after enrolling ●	1738 adults suspected of having undiagnosed AF were randomised to an immediate or delayed (by 4 months) Zio XT Service intervention group. 3476 matched controls were included in the observational trial Inclusion: aged 75 or older, or male aged 55 or over with 1 or more comorbidities, or female aged 65 or over with 1 or more comorbidities November 2015 to October 2016, follow up until January 2018	New AF detected within 4 months in 3.9% of immediately monitored patients and 0.9% of patients in whom monitoring was delayed (absolute difference, 3.0% [95%CI, 1.8%-4.1%.]) Active monitoring associated with: Increased initiation of anticoagulants (5.7 vs 3.7 per 100 person-years; difference, 2.0 [95% CI, 1.9-2.2]), Outpatient cardiology visits (33.5 vs 26.0 per 100 person years; difference, 7.5 [95% CI, 7.2-7.9), Primary care visits (83.5 vs 82.6 per 100 person-years; difference,0.9 [95% CI,0.4-1.5]) ●	No comparator Limited number of eligible individuals invited successfully enrolled (2.6%). 38% drop out rate. Reasons for drop out unclear. Little information provided about the matched cohort group. Clinical outcome data were not included in this analysis but will be reported when the planned 3-year follow-up is complete.

Solomon (2016) US	Retrospective cohort study Zio Service No comparator Funded by the company Investigators were employees of the company	122,815 Zio recordings from 122,454 patients between November 2011 and December 2013. 53% women, 48.8% < 65 years	Mean Wear Time 9.6 ± 4.0 days 25% of monitors worn for >13.0 days. High risk arrhythmia detected in 20,685 adults (21.7%) Ventricular arrhythmias: 52.5% detected in the first 24 hours and 92.9% were identified by day 7. The differences in diagnostic yield between 2 and 7 days for both ventricular arrhythmias and bradyarrhythmias were statistically significant (p<0.01). Median time-to-first event was between 22 and 74 hours depending on type of arrhythmia	No comparator. Large retrospective population. No follow up on clinical outcomes. A quarter of patients did not wear the patch for the full 7 days, limiting data for analysis. No information if data from this population has been used in any other studies. The population of 122,454 patients is taken from all the Zio XT Service long-term continuous monitors prescribed from November 2011 to December 2013 (N=128,401), so there may be overlap. Company sponsored the study.

Tung (2015) US	Retrospective cohort study Zio XT Service 🟢 No comparator 🔴 Study received grant support from company	1171 reports of patients with a history of stroke or TIA January 2012 to June 2013 55% men, mean age 67.9 years Data from company database 🟡	Mean wear time 10.9 days, analysable time 98.7% Median wear time 13.0 days (IQR 7.2 – 14.0) 66.9% wore the monitor for >10 days. AF present in 5% of all reports at 14 days (4.4% PAF and 0.6% chronic AF). Highest rate of AF detection in the first days of monitoring and a marked decline in the yield of AF detection during the second week. Mean duration before first PAF 1.5 days 14.3% of first PAF occurred after 48 hours 🟡	No comparator No further patient characteristics No record of the number of patients, only reports AF detection is relatively low, authors note that current study likely consisted of a more heterogeneous stroke and TIA population. Variation in monitoring duration may also have contributed to differences in the detection rate of AF.

Turakhia (2013) US	Retrospective cohort study Zio XT Service 🟢 No comparator 🔴 One author is the founder of the company. The study received a grant from the company.	26751 consecutive patients fitted with a Zio XT Patch Data from company database Data from patients receiving their first-time patches were analysed. Data for repeated or subsequent patch monitoring was excluded. January 2011 to December 2011 45.5% men, 60.2 ± 18.7 years 🟡	Mean wear time was 7.6 – 3.6 days Mean time to: first arrhythmia = 1.7±2.2 first symptom-triggered arrhythmias = 3.0±2.9 days respectively 29.9% of first arrhythmias and 51.1% of first symptom-triggered arrhythmias occurred >48 hours after monitoring started. Diagnostic yield: first 48 hours of monitoring versus entire Zio Patch wear duration: - any arrhythmia (43.9% vs 62.2%, p <0.0001) - symptomatic arrhythmia (9.7% vs 4.4%, p <0.0001). Single and multiple arrhythmias were detected in 16,142 (60.3%) of patients. 🟢	No comparator. Large sample size. Some parameters were not analysed statistically, for example, whether the diagnostic yields were different between early and late monitoring. Patients' clinical backgrounds differed. Some of the arrhythmias detected may not have been clinically significant because of their short duration. The company supported the study through a grant. The mean wear time was short compared with other studies, possibly because of clinicians prescribing different monitoring durations.

Turakhia (2015) US	Prospective cohort study Zio Service No comparator Company provided Zio XT Service	79 participants enrolled: 75 completed 100% men, mean age 69 years. Inclusion criteria: age ≥55 years and ≥2 of coronary disease, heart failure, hypertension, diabetes, sleep apnoea. Patients with prior AF, stroke, TIA, implantable pacemaker or defibrillator, or with palpitations or syncope in the previous year were excluded. 75 patients completed the monitoring. Single centre	Overall, any arrhythmia of ≥8 consecutive beats was detected in 36 subjects (48%); 18 subjects (24%) had no arrhythmias. Atrial fibrillation was detected in 4 subjects (5.3%; all with CHADS2≥1 and CHA2DS2-VASc score ≥2). All 4 patients who were detected with AF had ≥1 episode in the first 48 hours, and 3 of 4 experienced the longest episode after the first 48 hours of monitoring. An additional 26 participants (35%) experienced an initial arrhythmia other than AF after the first 48 hours. No subjects reported symptoms during AF episodes.	No comparator. All participants were male, which may limit the generalisability to women. The sample size of this study was underpowered to evaluate individual risk factors or create risk models for detection of AF.

Wineinger (2019) US	Retrospective cohort study Zio Service 🟢 No comparator 🔴	12293 individuals with PAF referred for extended cardiac rhythm evaluation 60% men, average age 69 years Data from company database November 2014 to September 2016 🟡	Median daily rate of paroxysmal AF was 1.21 (IQR 0.31 to 4.95). 13% of patients averaged 1 PAF event every 2 hours, 6.5% averaged at least 1 PAF event each hour and 13.5% experienced only a single event. Average duration was 1.6 minutes (median 2 minutes IQR 54 s to 6.7 minutes). After 24 hours of monitoring, 49.4% of patients with PAF had experienced an event with this increasing to 63.1% after 48 hours of monitoring.	The authors note an inability to relate the subtypes of PAF to meaningful clinical risk factors and outcomes. The lack of clinical data and subsequent follow-up did not allow us to assess differences in stroke occurrence. Clinical validation tied to AF-related outcomes is needed. Data from company's database.

Abstracts

Agarwal (2015)	Retrospective cohort study Zio Service No comparator	237, 69 to 89 years old, 54.9% women The setting was the US national Institutes of Health Atherosclerosis Risk in Communities (ARIC) Study population	Mean (SD) wear time 13.0 (2.3) days. 6% (n=14) had AF (7 with 100% frequency burden, 1 with <1% burden, 6 with 1-3% burden). Nearly all participants had at least one premature atrial complex (PAC) (96.6%, frequency burden - median (IQR) = 0.2% (0.1% to 0.8%), or one PVC (94.5%, frequency burden - median (IQR) = 0.1% (0.0% to 0.5%). Pauses lasting >3 seconds were recorded in 3.8% (n=9), SVTs in 85.3% (n=203), and VTs in 26.9% (n = 64).	Published as abstract, therefore limited information. No comparator. Country of origin unclear.

Chandratheva (2017) UK	Prospective cohort study comparing Zio XT Service with 72-hour Holter monitoring Zio service Apoplex, E Patch and 72-hour Holter monitoring	80 patients, (60%) men, mean age 61.4 years (SD14.4) Twenty had 72-hour Holter, 20 Zio Patch, 20, 3-day E-patch, 20 had in-clinic monitoring using Apoplex. UK hospital	Average time to device placement from clinic (days): Holter 54, Zio Patch 0.2, E-patch1, Apoplex 1. Time to reporting from device placement (days): Holter 13.4, Zio Patch 15.6, E-patch 9.5, Apoplex 1.2. Time to reporting from clinic date in days was significantly shorter for both Zio Patch 15.0 (SD 4.6) and E-Patch 11 (SD8.9) vs Holter 64.3 (SD26.9), p<0.01. AF was detected in four patients, Zio: 1 (5%), E-patch:2(10%), Apoplex:1(5%), Holter 0.	UK study. Published as abstract, therefore limited information. Time wearing Holter monitor was longer than other studies (72 hours)

Ghosh (2018) UK	Prospective cohort study comparing Zio XT Service with 24-hour Holter monitoring Zio service 24-hour Holter monitoring	30 patients with minor stroke or TIA were recruited from a TIA Clinic UK hospital	AF was detected in 1 patient using Zio XT and none on the Holter. Patients waited a median of 59 days for the Holter (range 14-102days). Investigations were completed for 29 patients using Zio XT compared to 18 from Holter. All Zio XT reports were available in clinic compared to 6 from the Holter. Cost of the investigation plus follow up was £367 and £440 for a Holter and Zio XT respectively.	UK study. Sample characteristics (age, sex) unclear. Median wait for Zio XT Service unreported. No statistical analyses were reported. Published as abstract, therefore limited information.

Hall (2019) UK	Prospective cohort study comparing patient experience using Zio XT Service with 24-hour Holter monitoring Zio XT Service Bardy Technomed Holter (Spacelabs) monitoring	250 randomly selected adults from cardiology clinic: 202 completed October 2018 to February 2019 No exclusions were made with regards to age, gender or reason for referral Technomed, Zio and Spacelabs were fitted to 50 patients, and Bardy were fitted to 100	Results demonstrated significant differences between all four devices when comparing the size and shape, comfort, practicality and returning method, $p < 0.0001$ Differences were significant between the Holter monitor and the three patch devices. There were no significant differences between Zio, Bardy and Technomed.	UK study. Published as abstract, therefore limited information.

Keibel (2015) US	Retrospective cohort study Zio XT Service 🟢 No comparator 🔴	68 patients with prior syncopal history, 29% men, mean age 52 (range 16-102). December 2010 to November 2014 Academic cardiology practice 🟡	Average monitoring period was 7d 10hrs (range 2d 9hrs to 14d). 12 arrhythmias were captured in 5 patients (4 patients with 1 arrhythmia, 1 patient with 8). Two hundred and twenty-two triggers (3.3 per patient, range 0-33) and 120 diary entries (1.8 per patient, range 0-8) were recorded. There were 45 diary entries for pre-syncope and none for syncope. None of the triggers or documented symptoms correlated with the captured arrhythmias. 🟡	Published as abstract, therefore limited information. No comparator.

Malhotra (2018) UK	Prospective cohort study Zio XT Service 🟢 No comparator 🔴	119 athletes (112 completed) were instructed to wear a Zio patch following reporting arrhythmia symptoms 79 men, mean age 33.38 +/- 14.78 years) 🟡	Mean period of 11.17+/-3.89 days. 4% of abnormalities were detected within 24 hours, 9% between 24-48 hours and 87% after 48 hours. Of 89 individuals who did not have any abnormities detected in the first 24 hours, 37% had abnormalities detected after 24 hours of monitoring. Of 85 individuals whom did not have any abnormities detected before 48 hours, 41% had abnormalities detected after 48 hours of monitoring 🟡	UK study. Published as abstract, therefore limited information. No comparator. Symptomatic athletes – an atypical study population.

Miller (2014) US	Prospective cohort study comparing patient experience using Zio XT Service with 24-hour Holter monitoring Zio XT Service 🟢 24-hour Holter monitoring 🟢	172 consecutive patients receiving ambulatory ECG monitoring for suspected arrhythmia Age 66 +/- 15 years 86 received Zio, 86 received 24-hour Holter monitoring 2010-2011 🟡	Primary outcome: Frequency of atrial fibrillation (AF) detection was greater with Zio patch monitoring, compared to Holter, in all patients (24.4% vs. 4.7%, P<0.0001) and in subgroups of patients without a history of permanent AF (16.7% vs. 3.5%, P=0.005) or without permanent/persistent AF (14.1% vs. 2.6%, p=0.01). Secondary outcomes: No difference in frequency of medication changes, invasive arrhythmia treatment, repeat monitoring, or hospitalisation 🟢	Published as abstract, therefore limited information. Prospective comparative study. Consecutive sampling. No difference in frequency of medication changes, invasive arrhythmia treatment, repeat monitoring, or hospitalisation at one year. No statistics are reported for this.
Norby 2018 US	Retrospective cohort study Zio XT Service 🟢 No comparator 🔴	2260 adults (mean age, 79 ± 5 years; 58% female) from larger study (into atherosclerosis) Zio XT Patch worn ≥ 2 days and up to 14 days in 2016-2017. AF defined as an irregularly irregular rhythm with absent P waves lasting ≥30 seconds in participants without clinical AF 🟡	Mean analysable wear time: 12.5 days AF was detected in 181 (8.1%) participants using the Zio XT Patch and 82 (3.6%) had subclinical AF 🟡	Published as abstract, therefore limited information.

Salazar 2011 US	Prospective cohort study Zio Service 🟢 No comparator 🔴	48 patients, mean age 54 +/- 18 years and 44% men with the following indications: palpitations/bradycardia/ syncope or surveillance of atrial fibrillation burden post ablation. 🟡	Mean monitoring interval was 4.6 +/- 1.7 days Symptomatic or asymptomatic arrhythmias were reported in 83% of all patients. The average number of patient triggered events was 7 +/- 11 and 66% correlated to an arrhythmia episode. There were an average of 3 +/- 2 diary entries and 48% were associated with an arrhythmia. 🟡	Published as abstract, therefore limited information.
Sattar (2012)	Prospective cohort study Zio Service 🟢 No comparator 🔴	135 patients - 65 males (48%), mean age 48.6 years who presented at an emergency department with suspected arrhythmia February to October 2011 🟡	Average device wear time was 6.1 days (95%CI 5.8-6.4; max 14 days). 51 (38%) had ≥1 significant arrhythmia and 7 (13.7%) were symptomatic at the time. Average time to first arrhythmia episode was 1.8 days (95%CI 1.6-2.0; max 9.8 days) and first symptomatic arrhythmia 2.1 days (95%CI 1.8-2.4; max 8.6 days). 🟢	Published as abstract, therefore limited information.

Su (2014) US	Prospective-retrospective study design Zio service 24-hour Holter monitoring	303 patients: 150 patients using Zio XT Service were compared with a retrospective cohort of 153 patients who had used Holter monitoring US cardiology referral centre	Interim analysis of use of the Zio Patch shows significantly decreased time from appointment to report in hospital information system from 119 days to 29 days	Published as abstract, therefore limited information.

Turakhia (2012) US	Retrospective cohort study Zio Service No comparator	18,236 consecutive patients wearing first-time 14-day ambulatory ECG Zio patch monitors Mean age 60+/-18 years; 46% men. October 2010 to October 2011 National registry of ambulatory ECG data	Mean wear time was 7.1+/-3.3 days Arrhythmias were identified in 64% of patients. After adjustment for age, women compared to men were more likely to have SVT detected (OR 1.30, p<0.001) than any of the other arrhythmias (OR 0.50, p<0.001 for all). Excluding patients with chronic AF, the mean time to first arrhythmia and first symptom-triggered arrhythmia from the start of monitoring was 40+/-51 hours and 66+/-64 hours. 27.6% of first arrhythmias and 41.9% of first symptom-triggered arrhythmias occurred beyond 48 hours from the start of monitoring.	Published as abstract, therefore limited information.

Ullal (2013) US	Prospective cohort study Zio Service No comparator	57 patients (age 68 +/- 7.4 years, 100% men) May 2012 to January 2013 Outpatient clinics in a US health system	AF was detected in 3 patients (5.7%), who had a mean AF burden of 4.2%. Common asymptomatic arrhythmias detected were SVT of >= 4 beats (N=37; 70%), >= 8 beats (N=24; 45%), and >= 60 seconds (N=4, 7.5%). Asymptomatic NSVT of >= 4 beats (N=16; 30%) and >= 8 beats (N=5, 9.4%) were also detected.	

Table 3: Clinical studies (published as fulltext) included by company and excluded by the EAC

Study name and location	Design and intervention(s) (including versions)	Participants	Outcomes	EAC comments
Camm (2015) US	Prospective observational study of Zio XT Service Partly funded by Medtronic Inc Zio XT Service 🟢 No comparator 🔴	42 adult patients: 40 completed Zio Patches applied between April 2013 to May 2013 Participants asked to wear Zio Patch for 7 days Patients with definite or suspected arrhythmogenic right ventricular dysplasia/ cardiomyopathy 🟢	Thirty-seven (93%) ARVD/C patients had an implantable cardioverter defibrillator (ICD) at the time of the study. Median 24-hour premature ventricular contraction (PVC) count was 1,090.5 (IQR=1,711). Difference between maximum and minimum PVC count was highly variable with statistically significant inter-day variance in mean hourly PVC counts in 76% of participants (28/37, 3 cases excluded from analysis due to insufficient data). 🟡	Reported outcomes do not focus on performance or utility of Zio XT Service.
Chen (2015) US	Patients from the ARIC (Atherosclerosis Risk in Communities) study presenting for MRI scans wore a Zio XT Patch monitor for up to 2 weeks. 🟡	325 patients Mean age: 77 years, 47% male. 8% had known AF and 4.6% had a history of stroke. 🟢	Distribution of AF was bimodal: 14% of patients with AF had an AF burden ranging from 1% to 6%, and 12 had an AF burden of 100%. Patients with 100% AF burden had lower executive and verbal cognitive test scores then those without AF. 🔴	Reported outcomes do not focus on performance or utility of Zio XT Service.

Hannun (2019)	A deep neural network (DNN) was designed to classify 12 rhythm classes using ECG data from patients who had worn a Zio XT Patch monitor. The performance of the DNN against the gold standard cardiologist consensus committee was compared.	Training dataset for the DNN consisted of 91,232 ECG records from 53,549 patients. Mean age was 69 years, 57% were male. Test dataset used to validate the DNN consisted of 328 ECG records collected from 328 patients. Mean age was 70 years, 62% were male.	The average F1 score (the harmonic mean of the positive predictive value and sensitivity) for the DNN (0.837) exceeded that of a consensus committee of expert cardiologists (0.780). With specificity fixed at the average specificity achieved by cardiologists, the sensitivity of the DNN exceeded the average cardiologist sensitivity for all rhythm classes.	This study details the development and validation of the newest version of the Zio XT software but does not report outcomes relating to the performance of Zio after the implementation of the new software.
Lutsey (2018) US	Double-blind pilot randomised trial to assess adherence to oral magnesium supplementation (400mg of magnesium oxide daily) and a matching placebo. Patients were asked to wear the Zio XT Patches for 2 weeks after each clinic visit.	59 patients; mean age was 62 years; 27% were male; 1 discontinued intervention. Inclusion: participants aged ≥55 years Exclusion criteria included a prior history of heart disease (coronary heart disease, heart failure, AF), stroke, or known kidney disease.	Zio XT Patch wear time was approximately 13 of the requested 14 days at baseline and follow-up. Two patients did not have data for the Zio XT patch at the end of the study, one where the device malfunctioned and one who dropped out of the study.	Zio XT Service was not the primary intervention.

Mullis (2018) US	Prospective cohort study Funding unclear Zio XT Service No comparator	59 adults with an overall mean PVC burden of ≥5% 81% men, mean age 69 years 2016 to 2018	Mean wear time was 11 days 16 hours (SD 63 days) 43 of 59 patients classified as being in at least 2 of the 3 categories of PVC burden (low, <10%; intermediate, 10% to 20%; or high, >20%) 8 patients were in all 3 categories	Reported outcomes do not focus on performance or utility of Zio XT Service.
Muse (2018) US and Canada	Prospective cohort study Zio XT Service and Holter monitoring were used to detect AF events, but performance was not compared	Inclusion: 40 years of age or older with 1 clinical risk factor for AF, presenting with symptoms of AF, or with a first diagnosis of AF. 934 patients were recruited from an outpatient clinic setting between set dates Mean age: 66.2 (SD 11.8) years; 38% of participants were male.	Of 904 participants with samples for genotyping, 85 manifested AF. Participants in the highest quintile of AF GRS were more likely (odds ratio 3.11; 95% CI 1.27–7.58; p = 0.01) to have had an AF event than participants in the lowest quintile after adjusting for age, sex, smoking status, BMI, hypertension, diabetes mellitus, heart failure, and prior myocardial infarction.	Reported outcomes do not focus on performance or utility of Zio XT Service.

5 Clinical evidence review

5.1 Overview of methodologies of all included clinical studies

Most of the included studies were observational in design and lacked direct comparators or were reported as abstracts. Of the studies reported as fulltext there was 1 UK-based RCT (Kaura et al. 2019), 3 prospective comparative studies (Barrett et al. 2014, Eysenck et al. 2019, Rosenberg et al. 2013) and 13 non-comparative studies (6 prospective: Heckbert et al. 2018, Reed et al. 2018, Rho et al. 2018, Schreiber et al. 2014, Steinhubl et al. 2018, Turakhia et al. 2015 and 7 retrospective: Eisenberg et al. 2014, Go et al. 2018, Schultz et al. 2019, Solomon et al. 2016, Tung et al. 2015, Turakhia et al. 2013, Wineinger et al. 2019). Of the 13 abstracts, 4 were prospective, directly comparative studies (3 UK studies: Chandratheva et al. 2017, Ghosh et al. 2018, Hall et al. 2019 and 1 US study: Miller et al. 2014). Of the remaining 9 non-comparative studies reported as abstracts, 4 were prospective (Malhotra et al. 2018, Salazar et al. 2011, Sattar et al. 2012, Ullal et al. 2013), 4 were retrospective (Agarwal et al. 2015, Keibel et al. 2015, Norby et al. 2018, Turakhia et al. 2012), and 1 was prospective-retrospective comparative (Su et al. 2014).

The highest quality study was a multi-centre UK RCT (Kaura et al. 2019) comparing 14-day Zio Service with 24-hour Holter monitoring in a stroke/TIA population (n = 160). The primary outcome of the RCT was detection of PAF at 90 days. Two comparative studies compared 14-day Zio Service with 24-hour Holter recording in 146 people under evaluation for cardiac arrhythmia (Barrett et al. 2014) and 74 people with diagnosed PAF (Rosenberg et al. 2013). One study assessed Zio XT Service against other external ambulatory ECG monitors in 21 people with pacemakers (Eysenck et al. 2019), using the pacemakers as a gold standard. Barrett et al. (2014), Eysenck et al. (2019) and Rosenberg et al. (2013) were within-subject comparative studies. Diagnostic yield was reported in Barrett et al. (2014), Kaura et al. (2019) and Rosenberg et al. (2013), although studies reported diagnostic yield during differing time durations (number of events detected during a fixed period of time ranged from 24 hours to 90 days). Two studies had information pertaining to diagnostic accuracy: Eysenck et al. (2019) assessed the

diagnostic accuracy of Zio XT Service against the reference standard of a permanent pacemaker (using relative risk calculations) and though Barrett et al. (2014) did not present diagnostic accuracy statistics, the company calculated diagnostic accuracy using data presented in the publication (see section 9 for the EAC's critique of this).

The populations included in the 4 comparative studies were heterogenous, differing in underlying risk factors and co-morbidities (populations included patients with recent stroke or TIA, people with pacemakers or diagnosed AF, people with suspected arrhythmia). Outcomes included arrhythmia event detection over total wear time (diagnostic yield), diagnostic accuracy, AF burden, and agreement between Zio XT Service and Holter monitoring. The study population size ranged between 21 (Eysenck et al. 2019) and 146 people (Barrett et al. 2014). The mean age ranged from 60 to 75 years. Two of the comparative studies (Kaura et al. 2019, Eysenck et al. 2019) were UK based, which may help generalisability of results to the NHS context.

Non-comparative study populations also varied. Studies included populations with suspected arrhythmia (due to various indications), confirmed arrhythmia (including AF, PVC), and also included people with atherosclerosis. The main outcome was diagnostic yield. The populations included in the prospective studies ranged from 30 to 934 people and the retrospective study populations ranged from 314 to 122,454 people. One study (Reed et al. 2018) was set in the UK and included 86 participants from a single emergency department. Other studies were set in the US.

Inclusion criteria varied; some studies (Tung et al. (2015)) included patients with a history of stroke or TIA, while Turakhia et al. (2015) excluded these patients. Schultz et al. (2019) included adult patients with congenital heart disease. Some studies (Go et al. 2018) included patients with confirmed PAF while Schreiber 2014 included patients with suspected arrhythmia. Reed et al. (2018) included patients aged 16 years or over with unexplained syncope (the EAC notes that some of the participants would be out of scope due to their age).

Diagnostic yield and wear time were the most commonly reported outcomes. Diagnostic yield was not always reported fully. Often only the number of patients with a detected arrhythmia was included. Reed et al. (2018) reported a 90-day diagnostic yield for symptomatic significant arrhythmia of 10.5% for Zio XT Service vs 2% for the historical matched cohort. Wear time ranged from 6.9 (median, Schreiber et al. 2014) to 14 (analysable, Go et al. 2018) days.

Patient-related outcomes such as medication use, stroke incidence and mortality were not widely reported. Clinical utility and resource use were similarly absent. Diagnostic accuracy was not clearly derived in any study.

All 4 abstracts describing prospective comparative studies compared Zio XT Service against Holter monitoring. One study (Chandratheva et al. (2017), n = 80) assessed time to device placement and reporting, 1 assessed AF detection and number of completed investigations in 30 people with stroke or TIA (Ghosh et al. 2018), 1 assessed patient experience (Hall et al. 2019, n = 202), and 1 assessed AF detection and changes to treatment (Miller et al. 2014, n=172).

5.2 Critical appraisal of clinical studies and review of company's critical appraisal

The company states that the 4 comparative studies had good methodology, with 3 of the studies considered as having low risk of bias on the Cochrane Risk of Bias 2 Tool. The RCT was subject to some concerns because of the high refusal rate for the Holter monitor from participants but was otherwise deemed to be well designed. The EAC notes that the tool used is specific to RCTs and may not be suitable for non-randomised studies. The EAC carried out a quality assessment of the key studies using the NICE checklist for cohort studies (see Appendix B).

Of 3 key studies directly comparing Zio XT Service with 24-hour Holter monitoring, only 1 was randomised (Kaura et al. 2019). The population in the RCT was people with stroke or TIA and therefore results may not be generalisable to a broader cohort of people with suspected cardiac arrhythmia. Clinical experts were clear that this population was distinct from

other arrhythmias. One expert noted that AF burden may be positively associated with risk of stroke (for example as reported by the Go et al. (2018) study included in this report). There was a high withdrawal rate from both arms of the study due to 20% of participants refusing the use the 24-hour Holter monitor. The authors carried out a power calculation indicating that the study was adequately powered for the primary outcome. The EAC carried out an independent power calculation that found the RCT was underpowered (0.56) due to the high drop out rate. The study is underpowered for the secondary outcomes that included anticoagulation use and mortality. The study was carried out in 2 UK hospitals, which may help generalisability to the NHS.

Barrett et al. (2014) included a broad population from a US hospital which included people referred for ambulatory monitoring for 6 different types of arrhythmia. Some participants had pre-existing arrhythmias and were referred for reasons other than symptomatic arrhythmia. There was no further breakdown of the results. As noted by the experts, different arrhythmias may have varying profiles, therefore it is unclear how generalisable results are. The authors calculated that the study was adequately powered.

The study population in Eysenck et al. (2018) was relatively small (n=21). No power calculation was reported. There was a high percentage of men and therefore, results may not be as generalisable to women. The order of devices was randomised which helps mitigate against order effects. The comparator was not a 24 hour Holter, as with the other 3 comparative studies; the performance of Zio XT service was compared with 3 other ambulatory monitoring devices (1 was an event monitor that was standard care for the authors' Trust) and against a reference standard (pacemaker). The primary outcome was AF burden but was only reported via fit-plots and limited data is reported numerically in the paper. The statistical analyses may not be appropriate for the outcome under study, with Bland-Altman tests potentially being more appropriate than R-test analyses. Patients all had pacemakers of varying brands (brands not detailed in the report), which may bias results. This may limit generalisability, due to the presence of other cardiac pathology

and did not allow assessment of external ambulatory monitors in 'healthy' individuals. The study was carried out in a UK hospital, which may help generalisability to the NHS.

Rosenberg et al. (2013) carried out a study in a US hospital setting where the experts who determined whether the ECG traces showed AF or not were blinded to the source technology. Blinding was not mentioned in the other studies. It is unclear whether the 2 groups within the study were adequately matched. The groups are described as comparable by the study but reported as significantly different ($p<0.0001$). No power calculation was reported.

Many studies were at least in part funded by the company (including the 3 non-randomised comparative studies) which may introduce a source of bias.

The Holter monitor was used as the comparator in most of the included studies, which reflects current clinical practice.

The individual studies were of moderate quality, however results cannot be pooled. The EAC broadly agrees with the company's conclusion that limitations of the evidence base for the Zio XT Service are that the 4 comparative trials were of variable size, with a total of 357 participants, and the populations were heterogeneous, so the number of patients from each population relevant to the decision problem was small.

Several non-pivotal studies may have overlapping populations due to the retrospective nature of the data. The company provided the following table to summarise any possible overlaps.

Table 4 Possible overlaps in population, provided by the company

Study	**Inclusion Criteria**	**Potential Overlap**
Turakhia 2013	All patients who had completed Zio Patch monitoring from January 1, 2011 to December 31, 2011	Eisenberg 2014 Solomon 2016 Go 2018

Tung 2015	Patients who were monitored between January 2012 and June 2013 and whose indication for monitoring was TIA or stroke	Eisenberg 2014 Solomon 2016 Go 2018
Eisenberg 2014	Data reviewed from 524 consecutive patients referred to a five-physician, academic electrophysiology practice between May 28, 2010, and January 11, 2013	Turakhia 2013 Tung 2015 Solomon 2016
Solomon 2016	Over 120,000 patient records between November 2011 and December 2013	Turakhia 2013 Tung 2015 Eisenberg 2014 Go 2018
Go 2018	All Kaiser Permanente patients identified with PAF between October 2011 and October 2016	Solomon 2016 Wineinger 2018
Wineinger 2018	13,293 individuals identified with PAF from November 2014 through September 2016	Go 2018

5.3 Results from the clinical evidence base

Table 5 below details the main outcomes that were reported in the literature. Diagnostic accuracy should compare the performance of Zio XT Service (or competitor technologies) against an appropriate reference standard. Information on diagnostic yield and time-to-event provide information regarding the number of extra arrhythmias that could be picked up by Zio due to the extended wear time. The ability to detect AF burden may have prognostic value and therefore was recorded if studies presented this information. Patient experience and wear time was generally reported to investigate how patient compliance differed between the Zio XT Patch and Holter monitoring.

Table 5 Selected results from evidence available in full-text

Study	Diagnostic accuracy	Diagnostic Yield/arrhythmia detection	Time-to-event	Clinical pathway outcomes	AF Burden	Patient Experience/ Wear Time
Barrett 2014	NR	*Arrhythmia event detection over total wear time:* Zio XT Service: 96 24-hour Holter: 61 ($p < 0.001$) Sixty events were detected by both Holter monitor and Zio Patch. Zio Patch detected 36 events that went undetected by the Holter monitor primarily as a function of prolonged monitoring.	NR	NR	NR	Median: Holter monitor 1.0 days (range, 0.9– 1.0) Zio Patch 11.1 days (range, 0.9–14.0) 93.7% participants found the monitoring patch comfortable to wear as opposed

		Arrhythmia event detection over 24 hours: Zio XT Service: 52 24-hour Holter: 61 (p = 0.013)				to 51.7% for the Holter monitor
Eysenck 2019	Zio XT Service was more likely to detect AF than the Novacor R-Test using pacemakers as the reference standard Zio vs R-test:12.3, 1.4 to 110.3, p = 0.025	NR	NR	NR	R^2 compared with DDDRP PPMs, MSE: R-test: 0.029, 1556.1 Zio: 0.99, 0.24	Mean: Zio: 307 (95% CI 284.63 to 340.32) hours [12.8 days] R-test: 223.6 (95% CI 178.43 to 268.31) hours [9.3 days] (p=0.016)

						Mean patient discomfort score on the same 0 to 5 scale while wearing the Zio XT Patch was 1.86, compared with 2.84 while wearing the Novocor R test, 3.95 for the NUUBO Vest and 0.95 for the Carnation ambulatory monitor.
Kaura 2019	NR	Detection of paroxysmal atrial fibrillation (PAF) with duration ≥ 30s at 90 days: Zio Service: 7 patients (16.3%) 24-hour Holter: 1 patient (2.1%)	NR	Anticoagulation use at 90 days: Zio Service: 7 (16.3%) 24-hour Holter: 1 (2.1%)	NR	Mean Zio wear time: 11 days 16 hours (SD ±3.7 days). Although the Zio XT Patch could not be successfully applied in only 2% of patients in

		Detection of PAF with duration ≥ 30s at 28 days: Zio Service: 6 (14.0%) 24-hour Holter: 1 (2.1%)				the UK-based RCT, 20% of participants refused to have the 24-hour Holter monitor applied, leading to high withdrawal rates (Kaura et al., 2019).
Rosenberg 2013	NR	AF episodes were detected in significantly more patients (18) on the Zio Patch compared with the Holter monitor ($p < 0.0001$).	Median time to detection of first event with Zio Patch: 3.7 days. 90% detected by day 7	21 patients (28.4%) had a change in their clinical management as a result of extended monitoring with the Zio Patch.	Mean: Zio XT Service: 54.7 ± 41.2% Holter: 58.4 ± 42.7% $p<0.0001$	Mean: Zio Patch: 10.8 ± 2.8 days
Eisenberg 2014	NR	Arrhythmia detected in 99.5% of patients: most	Over one-third of initial arrhythmias	NR	NR	NR

		common was ventricular premature beat (93%) 57% had significant arrhythmias	were recorded after 48 hours.			
Go 2018	NR	NR	NR	NR	Median burden of AF: 4.4% (IQR,1.1% to 17.23%). AF burden greater than 11.4% led to a more than three-fold increase of stroke or thromboembolism	NR
Heckbert 2018	NR	New AF was detected in 32 (4%) of participants with ≥12 days of monitoring.	New AF detected in 4% of people with ≥12 days monitoring. 38% first detected	NR	NR	Analysable wear time: 14 [11-14] days

			during days 3 to 12 of monitoring			
Reed 2018	NR	90-day diagnostic yield for symptomatic significant arrhythmia was 10.5% in the prospective group vs 2.0% in the comparator group	Median time to clinical detection of symptomatic significant arrhythmia was 19 days (IQR 4-30 days)	NR	NR	Median monitoring duration was 13.6 days (IQR 11.8–14.0). 91% patients agreed that the device was easy to use. 40% reported skin irritation.
Rho 2018	NR	A total of 86.7 ± 0.6 arrhythmias were recorded by Zio-XT and 121.7 ± 2.1 from CAM, $p<0.001$	NR	NR	NR	NR

Schreiber 2014	NR	98 arrhythmia events detected over 6.9 days	Median time to first arrhythmia was 1.0 days Median time-to-first symptomatic event was 1.5 days Median time to event for some types of arrhythmia was 5.8 days	NR	NR	Median device wear time was 6.9 days
Schultz 2019	NR	156 patients showed a significant arrhythmia	46% of patients who showed arrhythmia did so within the first 48 hours.	A clinical management change based on an arrhythmia was made in 49 patients (16%) following Zio XT Service use.	NR	Mean wear time was 9.5 ± 4.1 days

Steinhubl 2018	NR	New AF detected within 4 months in 3.9% of immediately monitored patients and 0.9% of patients in whom monitoring was delayed (absolute difference, 3.0% [95%CI, 1.8%-4.1%.])	NR	Active monitoring associated with: Increased initiation of anticoagulants (5.7 vs 3.7 per 100 person-years; difference, 2.0 [95% CI, 1.9-2.2]), Outpatient cardiology visits (33.5 vs 26.0 per 100 person years; difference, 7.5 [95% CI, 7.2-7.9), Primary care visits (83.5 vs 82.6 per 100 person-years; difference,0.9 [95% CI,0.4-1.5])	NR	NR

Solomon 2016	NR	High risk arrhythmia detected in 20,685 adults (21.7%) Ventricular arrhythmias: 52.5% detected in the first 24 hours and 92.9% were identified by day 7 The differences in diagnostic yield between 2 and 7 days for both ventricular arrhythmias and bradyarrhythmias were statistically significant (p<0.01).	Ventricular arrhythmias: 52.5% detected in the first 24 hours and 92.9% were identified by day 7. Median time-to-first event was between 22 and 74 hours depending on type of arrhythmia		NR	Mean wear time 9.6 ± 4.0 days 25% of monitors worn for >13.0 days.
Tung 2015	NR	AF present in 5% of all reports at 14 days (4.4% PAF and 0.6% chronic AF).	Highest rate of AF detection occurred in the first days of monitoring and a marked decline in the yield of AF detection	NR	Mean PAF burden was 12.7% of the total monitoring duration	Mean wear time 10.9 days, analysable time 98.7% Median wear time 13.0 days (IQR 7.2 – 14.0)

			during the second week. Mean duration before first PAF 1.5 days 14.3% of first PAF occurred after 48 days			66.9% wore the monitor for >10 days.
Turakhia 2013	NR	Single and multiple arrhythmias were detected in 16,142 (60.3%) of patients. Diagnostic yield: first 48 hours of monitoring versus entire Zio Patch wear duration: any arrhythmia (43.9% vs 62.2%, p <0.0001), symptomatic arrhythmia (9.7% vs 4.4%, p <0.0001)	Mean time to: first arrhythmia = 1.7±2.2 first symptom-triggered arrhythmias = 3.0±2.9 days respectively 29.9% of first arrhythmias and 51.1% of first symptom-triggered arrhythmias occurred >48	NR	NR	Mean wear time was 7.6 – 3.6 days

			hours after monitoring started.			
Turakhia 2015	NR	Overall, any arrhythmia of ≥8 consecutive beats was detected in 36 subjects (48%); 18 subjects (24%) had no arrhythmias.	All 4 patients who were detected with AF had ≥1 episode in the first 48 hours, and 3 of 4 experienced the longest episode after the first 48 hours of monitoring. An additional 26 participants (35%) experienced an initial arrhythmia other than AF after the first 48 hours.	NR	NR	NR

Wineinger 2019	NR	Median daily rate of paroxysmal AF was 1.21 (IQR 0.31 to 4.95).	13% of patients averaged 1 PAF event every 2 hours, 6.5% averaged at least 1 PAF event each hour and 13.5% experienced only a single event.	NR	Median AF Burden was 8.9% (IQR 3.4%–25.2%	NR

6 Ongoing use and data collection

iRhythm review the performance of the Zio XT Service across every customer site globally on a quarterly basis through the Zio XT Service Evaluation Tool. The Zio XT Service Evaluation Tool produces a summary of metrics such as the total diagnostic yield, the most common indications for monitoring, a list of detected arrhythmias, and the average and maximum number of days until a symptomatic arrhythmia is detected. The mean and median patient age is also recorded. Reports can be produced for individual sites, for the UK, or globally.

In addition, iRhythm states that its clinical operations team performs ongoing reviews to ensure the quality of the final Zio XT technical reports and urgent notifications. The company notes that Quality Clinical Managers oversee the Zio Technical Reports produced by the Zio Clinical Team and review 1-3% of all reports on a daily basis. They also review 50% of urgent notifications to the prescribing clinician, 100% of final interpretations completed online by the prescribing clinician and 100% of all reports completed by new Cardiac Physiologists prior to them achieving competency. Further, high-risk ECG outliers, such as a heart rate below 20 beats per minute or over 300 beats per minute, ventricular tachycardia rates under 100 beats per minute and wearers aged over 99 years, are overseen.

Outcomes such as wear time, analysable time and the types of arrhythmia detected are reported in the clinical evidence. Retrospective cohort studies such as Schultz et al. (2019) and Solomon et al. (2016) have made use of such data (also see section 9). There is no data recorded on clinical management of patients or on clinical follow-up including mortality, however.

The EAC believe that iRhythm's methods are sufficient to demonstrate the ongoing acceptability, usage and value of the technology. The ongoing usage data is suitable to generate some of the outcomes reported in the clinical evidence, but further information is required from the patient's clinician and hospital record, plus appropriate follow up.

7 Adverse events

The company identified no relevant reports from the MHRA. The FDA MAUDE site yielded 138 results dating from 2014 (search term: iRhythm Technologies Inc), of which:

- 113 were incidences of contact dermatitis
- 6 were incidences of adhesive failure
- 12 were cases of false negative or incorrect diagnoses being sent to the patient or clinician
- 8 were cases where the device was faulty, or the patient management process failed

A search by the EAC confirmed these results. No other site yielded additional information on adverse events.

In several cases of a false diagnosis being given, iRhythm's narrative suggests either a fault in device hardware or an incorrect interpretation of the technical report. In 1 case it is noted that the incorrect diagnosis did not lead to a delay in treatment and in another it is noted that the patient did not receive any therapy.

As long as the Zio XT Patch reliably records data, the EAC does not forsee significant safety risk of this component of the service. The EAC notes that the main potential factor that may impact the safety of the technology is the accuracy of the detection algorithm and of the actionable report.

8 Evidence synthesis and meta-analysis

The company did not carry out a meta-analysis, stating that the evidence for the efficacy and safety of the Zio XT Service is extremely heterogeneous, in terms of populations, methodology, devices used and outcomes reported. The EAC notes that the study population is a particular source of heterogeneity. In addition, a systematic review of clinical evidence for Zio XT Service (Yenikomshian et al. 2019) also concluded that the heterogeneity found in the studies would confound findings and would preclude conducting a meta-analysis. Yenikomshian et al. (2019) also noted that any advances in the arrhythmia detection algorithm over time may distort comparisons with newer studies. The EAC notes that the company states that there have been no

significant changes to Zio XT Service since 2012. The company also explained that any updates to the algorithm undergo testing before being deployed and need to meet threshold requirements. The company therefore assumes that the accuracy/yield will be equivalent or better than previous versions. The EAC concurs that a meta-analysis carried out with the current clinical evidence would not be robust.

9 Interpretation of clinical evidence

The EAC agreed with the company submission, considering 4 comparative studies pivotal to the decision problem. One UK based RCT was included which meets the requirements for the NICE Evidence Standards Framework best practice standard for digital health technologies with measurable benefits through active monitoring. The EAC notes that Zio XT Service contains an AI component. Any developments to the algorithm may impact the diagnostic accuracy of the device, however the company has noted that that Zio XT Service has not changed significantly in the past 6 years, so study results are generalisable between versions. Two comparative studies were UK based (including an RCT) which supports generalisability to the NHS population.

Experts noted that extended monitoring may be particularly useful in people with infrequent arrhythmias. The most important study aimed to detect PAF in stroke/TIA patients (Kaura et al. 2019) which may be a population that extended monitoring may particularly benefit. Two other studies included people with diagnosed (as opposed to suspected) arrhythmia (Eysenck et al. 2019, Rosenberg et al. 2013), which may be less generalisable. Experts noted that people who have already been diagnosed may be on anticoagulation therapy. Barrett et al. (2014) included a population that had been referred for ambulatory monitoring and included detection for 6 types of arrhythmia. Experts noted that arrhythmia has a broad definition that include any potential problem with heart rhythm and different types of arrhythmia have different pathophysiologies and would include different types of population, therefore this study population may be broad and not necessarily comparable to the other studies that had more specific populations (stroke patients, people with pacemakers, people with diagnosed AF).

Diagnostic accuracy

No studies were found that primarily investigated diagnostic accuracy of Zio XT Service against the standard care of 24 hour Holter monitoring. Eysenck et al. (2019) indicates that Zio XT Service may be more accurate in detecting the presence or absence of AF than the Novacor R Test (an external event/loop monitor, described as current standard practice) but less accurate than pacemaker data (described as gold standard). The company calculated accuracy from data in Barrett et al. (2014), reporting that Zio XT Service had 99% sensitivity, 100% specificity, 98% positive predictive value (PPV) and 98% negative predictive value (NPV) taking the gold standard to be the decision of clinical investigators. This was calculated over total wear time. The EAC notes some potential issues with the calculation: the methodology used for the reference standard comparator (clinician interpretation) is unclear. Experts note that 12 lead ECG is typically considered the gold standard for diagnosing arrhythmia. It is also unclear how false positives were identified. In addition, the EAC notes that the diagnostic accuracy metric is cross-sectional in nature and the calculations in the submission cover different time durations. Barrett et al. (2014) notes that "the adhesive patch monitor detected 36 events that went undetected by the Holter monitor primarily as a function of prolonged monitoring". The Barrett et al. (2014) and Rosenberg et al. (2013) studies carry out some analysis over the same 24 hour period with slightly differing results. Barrett et al. (2014) noted that over a simultaneous 24-hour monitoring period, the Holter monitor had a "performance advantage", detecting more arrhythmia events than the adhesive patch monitor. The Holter monitor detected 11 arrhythmia events not detected by the adhesive patch monitor. The authors explained that 2 were due to an algorithm misclassification and 7 by a processing error by the report reviewer. The authors note that reviewer training and parameters for detection in supraventricular tachycardia were changed as a result. The indication is perhaps that Zio XT Service was not as accurate as Holter monitoring in this specific study, but the authors state that this may have been subsequently corrected for. Rosenberg et al. (2013) notes that in the same 24 hour period, the Zio XT Service recorded all 25 events recorded by the Holter monitor and the authors noted a significant agreement between the 2 technologies.

However it is not clear whether Zio XT Service also recorded additional events to the Holter monitor. Both studies used judgement of a clinical experts as reference standard. The company submitted a study by Hannun et al. (2019) that reported that the Zio deep neural network (DNN) classified a broad range of distinct arrhythmias from single-lead ECGs with high diagnostic performance, similar to that of a committee of cardiologists. The EAC notes that this study was not carried out with the Zio Patch or in a clinical setting and therefore, findings may not be generalisable. The company submission included 1 recent study that assessed the diagnostic accuracy of a continuous ambulatory cardiac monitor (Spyder) versus a loop recorder against ECG recording as reference standard for detecting AF (Mamchur et al. 2019). The company stated that the sensitivity of Spyder was 80.1% and the specificity was 73.1% which is lower than the figures for Zio XT Service reported by Barrett et al (2014) (as calculated by the company). However, the EAC notes that there are potential issues with the calculation of accuracy in the Barrett study (see above) and also that Mamchur (2019) is a very small study (n=32, n=17 for Spyder arm) and therefore, conclusions cannot be drawn on this basis.

Overall, clinical experts suggested that there may be no significant difference in accuracy between Zio XT Service and Holter monitoring. One expert noted that because of the increased number of leads the Holter may, theoretically, be more accurate. Barrett et al. (2014) suggests that, in general, the information provided by additional ECG leads in Holter monitors may be a benefit to both automatic algorithm analysis and clinician interpretation. Specifically, 3-lead recordings allow for the detection of arrhythmia events characterised by a shift in electrical axis that can be missed by single-lead recordings. Another expert, however, noted that Zio may be more accurate for a fixed period of time (24 hours), as there is likely to be less artefact and more analysable rhythm (for example, patients remove the Holter monitors during showers).

Given the expert feedback and study results it may be reasonable to assume there may be little to no significant difference in diagnostic accuracy between Zio XT Service and Holter monitoring, but published evidence levels are low.

Diagnostic yield

The 3 studies comparing arrhythmia detection rates between Zio XT Service and 24-hour Holter monitoring indicate that diagnostic yield is generally higher for patients monitored with Zio XT Service compared with 24 hour Holter monitoring. This was a function of the extended monitoring period. A number of non-comparative studies investigated the time-to-event for Zio XT Service, finding that a significant number of arrhythmias were detected after 48 hours (see further discussion below).

Time-to-event

The utility of extended monitoring may be demonstrated in a number of studies and may be particularly relevant to populations suspected of infrequent arrhythmias. For example, a number of studies found that, though most arrhythmias are detected within the first 48 hours, a significant number of arrhythmias were detected after 48 hours of monitoring, indicating the amount of information that might be missed by a Holter monitor. One large non-comparative study in people with suspected arrhythmia (using cross-sectional data from the company's database) found that Zio XT Service detected an arrhythmia in 60% of patients with over 70% of these rhythms occurring by 48 hours (Turakhia et al. 2013). Over 90% of initial recorded arrhythmias were captured by day 5. Similarly, Eisenberg et al. (2014) found that a third of arrhythmias were recorded after 48 hours. This finding does, however, vary. For example, Schultz et al. (2019) found that 46% of patients who showed arrhythmia did so within the first 48 hours. Reasons for this variation are likely to include heterogeneity in populations referred for testing.

Clinical pathway outcomes

Potential clinical pathway benefits of Zio XT Service (as measured by time to diagnosis and initiation of preventative treatment) were investigated as secondary outcomes in 2 comparative studies (Kaura et al. 2019, Rosenberg et al. 2013). The studies indicate that patients are more likely to be given

medication (if asymptomatic) or have medication switched (if symptomatic) to more appropriate medication, but both are flawed for detecting these outcomes. Kaura et al. (2019) found that a higher proportion of patients randomised to the Zio XT Service were taking anticoagulants at 90 days, 16.3% compared with 2.1% of patients who had 24-hour Holter monitoring. No significant difference was found in clinical outcomes (the authors note there was a short follow up period of 90 days). In a second study, authors stated that 18 patients with PAF had a change in their classification of AF and 21 patients (28.4%) had subsequent medication change as a result of findings from the Zio XT Service, with 17.3% having a change in their antiarrhythmic medication and 5.3% changing oral anticoagulant use (Rosenberg et al. 2013). The EAC notes that this is an overall figure and does not separate the change in clinical management made due to result from solely Zio XT Service. It is assumed that the change is to a more appropriate medication, however, there was no follow up or related clinical outcomes to confirm this. In a non-comparative study, Schultz et al. (2019) reported that a clinical management change based on an arrhythmia was made in 49 patients (16%) following Zio XT Service use. It should be noted that the population in Kaura et al. (2019) was likely to be asymptomatic, whereas the population in Rosenberg et al. (2013) and Schultz et al. (2019) was presumably symptomatic (people with PAF and congenital heart disease, respectively), therefore results are not directly comparable. It is unclear whether patients benefitted from changes in management in these studies.

AF burden

Experts note that there is evidence that AF burden (percentage of time spent in AF) is linked to increased risk of stroke or thromboembolism. Some studies indicate that Zio XT Service may be used for detecting AF burden. Eysenck et al. (2019) reported that Zio XT Service was significantly better at detecting AF burden compared with the Novacor R Test device (which the authors note is standard practice at the Trust where the study was set). Go et al. (2018) reported that AF burden greater than 11.4% led to a more than three-fold increase of stroke or thromboembolism.

Patient experience

Patients appeared to have relatively high levels of acceptance for wearing the Zio Patch (also see section 5). Mean wear time ranged from 10.8 to 12.8 days in the comparative studies (from an intended 14 days). In terms of compliance, in a sample of 21 people Eysenck et al. (2019) found that the Zio XT Patch was worn for longer compared with 3 other continuous cardiac monitors. Barrett et al. (2014) reported that 93.7% participants found the monitoring patch comfortable to wear as opposed to 51.7% for the Holter monitor. In a non-comparative UK study, Reed et al. (2018) reported that 91% of respondents to a patient questionnaire agreed or strongly agreed that the device was easy to use, however 40% indicated that the patch caused skin irritation. A survey into patients of a UK cardiology clinic (Hall et al. 2019, abstract only) found that Zio XT Service was significantly preferred to Holter monitoring in terms of shape, comfort, practicality and returning method.

The Zio Patch includes a function where a user can press a button to report if they feel they are experiencing an event. Studies reported that self-reported events did not correlate with biosensor recorded events (Eisenberg et al. (2014), Schreiber et al. (2014), Turakhia et al. (2015), Keibel et al. (2015) [abstract], Salazar et al. (2011) [abstract]). It is unclear if this function is useful for clinical outcomes.

9.1 Integration into NHS

Three studies available in full-text were carried out in the UK: 1 RCT (Kaura et al. 2019), 1 prospective comparative study, (Eysenck et al. 2018) and 1 non-comparative study (Reed et al. 2018). Two abstracts (Chandratheva et al. (2017) and Ghosh et al. (2018)) also describe studies performed in UK populations. The remaining 2 comparative studies were US based. Inclusion criteria were not the same across studies and the study populations were heterogeneous, ranging from broad inclusion criteria (referral for cardiac monitoring) to more specific (people with pacemakers and a history for AF).

Kaura et al. (2019) recruited patients who had been diagnosed with having had an ischaemic non-lacunar stroke or TIA within the past 72 hours by a stroke clinician or neurologist. Eysenck et al. (2018) recruited patients with in-

situ pacemakers and Reed et al. (2018) recruited patients attending an ED with unexplained syncope. These populations are distinct and heterogenous and expert opinion suggests that usage of Zio XT Service could be used in several distinct populations in NHS practice.

The EAC does not believe that significant changes to IT infrastructure would be required to use Zio XT Service. The clinician is able to access the Zio technical report and add any queries via the Zio secure website. The company states that no extra training is required to interpret the Zio technical report. The EAC does not believe that significant changes to the care pathway would be required to use Zio XT Service. The company claims that the use of Zio XT Service may lead to fewer hospital visits within the pathway as "the monitor is readily available and can be easily fitted at the first appointment". This potential advantage may vary between centres depending on local practice and availability of Holter monitors (clinical experts reported mixed experiences about whether Holter monitors were fitted at first appointment). The company also notes that clinical teams would need to develop symptom referral criteria on the basis of results from Zio XT Service and incorporate this into their cardiac diagnostic ambulatory monitoring pathway in line with clinical guidelines. The company provides some training to clinicians regarding the registration of patient identification details. Minimal training is also required to learn how to apply the Zio XT patch.

9.2 Ongoing studies

The EAC believes that the company's description of ongoing studies is adequate. The table in appendix C outlines the 2 studies in the company submission. The EAC did not retrieve other relevant ongoing studies (see appendix A).

The 2 submitted ongoing studies are RCTs and are expected to be completed in 2019 and 2022-25. Both studies will compare 2 weeks monitoring of the Zio XT Service with standard care. One trial is based in Canada and Germany (NCT02392754: to be completed 2019) and the other is UK based. The UK based study hopes to enroll 2500 total individuals at high-risk for AF, while the other has enrolled 856 participants aged 75 years or over with a history of

hypertension and without known AF. The UK study has a primary endpoint of proportion of participants diagnosed with AF at 2.5 years of follow-up while the other will measure the rate of new diagnosis of AF (or flutter) within 6 months of randomisation.

10 Economic evidence

10.1 Published and unpublished economic evidence

10.1.1 Published and unpublished economic evidence review

The company conducted a literature search of the economic evidence for outpatient cardiac monitoring alongside their search of the clinical evidence. The same search strategy was applied with search terms to capture economic data and the same inclusion criteria for studies were applied. Sixteen published studies were included as part of the economic evidence submission. Additionally, the sponsor conducted hand search in a variety of sources including national and international organisations for cardiology care. The sponsor identified 4 additional references for a total of 20 studies included as part of the evidence base in the economic submission.

The sponsor included 20 references. Only 3 published studies (Kaura et al. 2019, Ghosh et al. 2018 and Chandratheva et al. 2017) and 1 grey literature reference (NICE 2017) assessed Zio XT Service. Therefore, the remaining 17 references presented by the company were excluded by the EAC. The EAC re-ran the search using the strategy for clinical evidence (see section 5 for more information) and applied filters for economic terms. Five publications containing economic data were identified (Steinhubl 2019, Eysenck 2017a, Eysenck 2017b, Eysenck 2018, Eysenck 2019). Three of these, (Eysenck et al. 2017a, Eysenck et al. 2017b, Eysenck et al. 2018), were conference abstracts reporting the study described by Eysenck et al. 2019. Steinhubl et al. 2019 and Eysenck et al. 2019 were included as part of the clinical evidence by the company (but not the economic evidence).

In total, 5 studies were considered to be relevant to inform the decision problem as they analysed patients with suspected AF after either cryptogenic stroke or TIA, a subgroup outlined in the scope of the decision problem. The studies included one economic evaluation (Kaura et al. 2019), two reports containing resource use or costs associated with the technology (Steinhubl et al. 2019; Eysenck et al. 2019) containing cost data only, and two conference abstracts (Ghosh et al. (2018), Chandratheva et al. (2017).

Kaura et al. (2019) reports a randomised non-blinded clinical trial comparing Zio XT Service with a 24-hour Holter monitor and includes a budget impact analysis. The

model estimated the economic savings due to reduction in recurrence of stroke after introduction of Zio XT Service in a population of 1,053 patients treated at King's College Hospital NHS Trust. The methodology of the clinical component of the study is described in detail in the clinical evidence section of this report. The analysis used data from the trial on AF detection rates observed in the Zio XT Service and Holter groups alongside estimates from the literature and assumptions for a number of parameters. The proportion of patients with ischaemic stroke, the proportion of patients requiring outpatient monitoring after TIA, and the proportion of patients requiring outpatient monitoring after ischaemic stroke were retrieved from the Sentinel Stroke National Audit Programme, Putaala et al. (2015) and Amarenco et al. (2016) respectively. The detection rates for the technologies were retrieved from Teo et al. (2017), Jabaudon et al. (2004) and Albers et al. (2016) for Zio, Holter monitor, 5-7-day cardiac external recorder and implantable monitor respectively. Risk of untreated and treated AF were retrieved from Hart et al. (2008). Costs considered in the analysis included medical costs of managing stroke, tests costs, and cost of attending follow-up outpatient visits. Unit costs were retrieved from Xu et al. (2018) and NHS Reference Costs. The analysis applied a time horizon of one year considering medical costs only and five years considering medical and social care costs for managing stroke

Eysenck et al. (2019) is a UK-based study using data from the REMAP-AF trial (see clinical evidence section). The authors compared the use of Zio XT Service, NUUBO Vest and Carnation Ambulatory against the Novacor 'R' monitor in detecting atrial fibrillation. This study reported mean costs derived from the device unit cost, staff costs, patient travel costs and the cost of consumables for the Novacor 'R' test.

Steinhubl et al. (2019) is a prospective matched cohort study that analysed data from patients with suspected AF in the US (see clinical evidence section for further details). The study reported healthcare resource use associated with an active-monitoring strategy based on Zio in comparison to a matched control group over 1 year. Resource use of AF treatment and management AF-related symptoms procedures in both groups were quantified and reported.

Ghosh et al. (2018) and Chandratheva et al. (2017) are conference abstracts presented at the European Stroke Organisation Conference. Ghosh et al. (2018)

reports a comparison of detection rates between Zio XT Service and traditional 24-hour Holter monitor. The authors recruited 30 patients with minor stroke or TIA from Croydon University Hospital in the UK. A cost estimate of the use of the technology was reported consisting of the cost attributed to the investigation and follow-up clinics. Chandratheva et al. (2017) is a comparative study assessing non-invasive cardiac monitoring devices against 72-hour Holter monitor in detecting AF. The study considered Zio XT Service, 3-day E-Patch, and in-clinic Apoplex monitor as the non-invasive monitoring devices. Data from 80 patients from University College London's TIA clinics were considered to estimate cost and time to report for each of the technologies included in the study.

10.1.2 Results from the economic evidence

The results of the relevant economic evidence are summarised in table 6. The results are highly heterogenous due to the variability in the scope and design of each of the studies included in the review. The cost estimates from Eysenck et al. (2019) and Ghosh et al. (2018) suggest the technology is more expensive than alternative technologies. Eysenck (2019) reported a mean cost per patient of £284, £195, £242, and £15 for Zio XT Service, Nuubo Vest, Carnation Ambulatory test, and Novacor 'R' test respectively (derived from figure 3d in the publication). Ghosh et al. (2018) reported a cost of £367 for the 24-hour Holter monitor compared to £440 for the Zio XT Service. In contrast, Chandratheva et al. (2017) concluded the technology is cost-saving when compared with monitoring using 72-hour Holter device. Data reported is scant but indicates cost savings of £269, over £300 and £370 when compared against 72-hour Holter, 3 day E-Patch, and in-clinic monitoring, respectively. All three studies agreed Zio Service is the most efficient in terms of time from clinic to reporting the diagnosis. Kaura et al. (2019) concluded a strategy based on Zio XT Service saves £113,630 and £162,491 of medical costs over 1 and 5 years for a population of 1,053 patients when comparted to Holter-based strategies. After inclusion of social care costs, cost savings rose to £466,598 after five years. Steinhubl et al. (2018) concluded monitoring patients with the technology increases the health care resource use of AF-related therapeutic interventions but decreases all-cause emergency department visits or inpatient stays.

The published economic evidence associated with the use of the technology is scarce and highly heterogeneous. Only 5 studies containing economic data were

available, of which two were conference abstracts. In general, there was very little reporting of any details on methodology to collect and analyse cost data, rendering an appraisal of quality very difficult. Only one study (Kaura 2019) undertakes an economic evaluation, and the details of this are limited to screenshots of an Excel spreadsheet model provided in the appendix. Two studies, including the only economic analysis, concluded the technology is cost saving. Whereas two analyses reported the contrary. Nonetheless, the studies included consistently reported the technology is the most efficient to avoid delays between clinic and diagnosis confirmation. The EAC considers Kaura et al. (2019) to be the most relevant publication. This publication provides evidence to support a conclusion that Zio XT Service is cost saving, but the strength of evidence is weakened by the lack of detailed reporting.

Table 6 Economic Evidence

Author, year and location	Patient population and setting	Intervention and comparators	Unit costs and resource use	Model outcomes and results	EAC Comments
Kaura (2019) UK	Patients with suspected AF after ischaemic stroke or TIA referred to outpatient monitoring UK hospital	Zio XT Service-based monitoring strategy vs 24-Hour Holter- and CER-based monitoring strategies	Medical costs of stroke: 1-year: £13,452 5-year: £17,963 Total costs of stroke: 1-year: £22,429 5-year: £46,039 Unit cost of tests: Zio XT Service: £295 Holter monitor and CER: £133.43 Implantable monitor: £3,583 Unit cost of follow-up outpatient appointment: £79	Number of Strokes prevented using usual care: 2.2 Number of strokes prevented using Zio: 13 Incremental strokes avoided using Zio vs Holter: 10.8 Number of OPD appointments saved using Zio vs Holter: 711 Incremental 1-year medical cost of stroke of Zio vs: -£57,481 Overall (including cost attributable to OPD) 1-year incremental cost of Zio vs Holter: -£113,630 Incremental 5-year medical cost of stroke of Zio vs Holter: -£410,449 Overall (including cost attributable to OPD) 5-year incremental cost of Zio vs Holter: -£466,598	The study was poorly reported; only the results are reported in the main text and little detail is provided in the supplementary documentation. The assumptions made regarding diagnostic accuracy are not clear, nor is the model structure employed. Cost of use or complications related to anticoagulant therapy is not considered in the model.

					The authors did not perform any type of sensitivity analysis.
Eysenck (2019) UK	Patients with suspected AF UK hospital	Zio XT Service, NUUBO vest, Carnation ambulatory monitor, Novacor 'R' test	Mean test cost inclusive of administrative and physiologist staff, cost of patient travel to and from the hospital, and electrode costs for usual practice (Novacor 'R' test)	Mean total cost per patient: Zio XT Service: £284 Nuubo Vest: £195 Carnation Ambulatory test: £242 Novacor 'R' test: £15	**Strengths** The study reflects UK practice **Limitations** The study provides little detail on how total cost per patient were calculated; no information on unit costs and their corresponding sources were provided.
Steinhubl (2018) US	Patients with suspected AF US Hospital	Zio XT Service monitored group vs control group (see table 2 for more information)	AF-related therapeutic interventions Pharmacy fill for anticoagulant for individuals with AF Cardioversion procedures Cardiac ablation Clinical use:	Difference between Zio group and control group of: Pharmacy fill for anticoagulant for individuals with AF: 2.0 (95% CI 1.9 to 2.2) Cardioversion procedures: 1.1 (95% CI 1.0 to 1.2) Cardiac ablation: 0.2 (95% CI 0.18 to 0.24)	**Strengths** The study provides estimates of the consequences in resource use associated with the use of the technology **Limitations**

			Any cause ED visit or inpatient stays Cardiology or primary care visits	Any cause ED visit or inpatient stays: -1.2 (95% CI -1.5 to -0.9) Cardiology or primary care visits: 0.12 (95% CI 0.01 to 0.23)	The study does not reflect UK practice The authors do not provide information on the intervention employed on the matched control group
Ghosh (2018) UK	Patients with suspected AF after minor stroke or TIA UK hospital	Zio XT Service vs 24-hour Holter monitor	Mean cost per patient inclusive of investigation and follow-up clinics	Mean cost per patient: Zio XT Service: £440 24-hour Holter monitor: £367	**Strengths** The study reflects UK practice **Limitations** The study provides little detail on how costs were estimated; the authors only report the aggregated figure
Chandratheva (2017) UK	Patients with suspected AF after TIA UK hospital	Zio XT Service, E-patch, Apoplex in-clinic monitoring vs 72-Hour Holter monitor	Time delays: Time from clinic to device placement Time to reporting from device placement Time to reporting from clinic	Time from clinic to device placement (days): Zio XT Service: 0.2 3-day E-patch: 1 Apoplex AF monitor: 1 72-hour Holter monitor: 54	**Strengths** The study reflects UK practice The authors provide a break-down of the technologies' costs

			Cost per patient inclusive of test unit cost, consumables, and reporting where applicable	Time to reporting from device placement (days): Zio XT Service: 15.6 3-day E-patch: 9.5 Apoplex AF monitor: 1.2 72-hour Holter monitor: 13.4 Time to reporting from clinic (days): Zio XT Service: 15 3-day E-patch: 11 Apoplex AF monitor: NR 72-hour Holter monitor: 64.3 Test cost: Zio XT Service: £300 3-day E-patch: £651 (£600-unit cost, £16 electrode cost, £35 report cost) Apoplex AF monitor: £670 (£650-unit cost and £20 report cost) 72-hour Holter monitor: £569	**Limitations** No information on the sources of the unit costs is provided

10.2 Company de novo cost analysis

10.2.1 Economic model structure

The company submitted a cost analysis over a time horizon of one year based on three separate models.

[redacted] These analyses assessed only costs associated with the diagnostic process from an NHS perspective and therefore did not include any resource use or economic consequence of subsequent treatment. The third analysis assessed the impact on the costs of subsequent stroke treatment of the technology's diagnostic yield in comparison to Holter monitors (hereafter referred as the stroke downstream model). This model extrapolated the economic consequences of the extra risk of recurrent stroke due to delayed or missed diagnosis of AF. All models were validated by clinical experts and the Health Economics team at Imperial College Health Partners.

Patients

The cardiology model considers a population of patients with symptomatic palpitations or syncope referred to cardiology outpatient departments for evaluation. The stroke model considers patients who have experienced ischaemic stroke or TIA without current evidence of AF, referred for identification of paroxysmal AF. The stroke downstream model considers the same population as the stroke model although it estimates the occurrence of further strokes over one year.

Technology

The technology under assessment is Zio XT Service. It consists of 3 components: the 14-day Zio patch, analysis of the ECG by the company and the report generated for clinician review.

Comparators

The comparators are blended strategies based on 24-hour Holter monitor or cardiac event recorder (CER). Both technologies are placed and removed by NHS staff during outpatient visits. Results are reviewed and reported by consultant cardiologists.

Model Structure

All analyses used simple decision trees and undertook an NHS perspective. The cardiology and stroke models estimate the expected cost associated only with the diagnostic process. The time horizon is stated as one year, but encompasses the time required for an investigation of AF to be completed (currently around ten weeks). The downstream stroke model estimates the expected costs of recurrent stroke over a 1-year time horizon. The model structure and the approach undertaken were informed by expert clinical opinion. The EAC considers the model structure and time horizon to be acceptable for each model. The model structures are shown in [redacted] for the cardiology and downstream stroke models, respectively.

The core models do not assess the diagnostic performance (i.e. diagnostic accuracy) of the comparator and the intervention arm. Instead, the models consider test result proportions as estimated from a variety of sources. The possible test results in both models are positive, negative and inconclusive. The cost of an assessment using Holter was estimated from Patient Level Information and Costing System (PLICS) data and Freedom of Information (FOI) requests. The sponsor was unable to retrieve the cost of CER and therefore assumed the same cost as Holter. The cost of Zio was provided by the company. The cost of outpatient visits was based upon NHS Reference Costs 2017/2018.

<u>Cardiology model</u>

The cardiology model (figure 1) considers the current pathway (the comparator arm) assuming a proportion of patients are monitored using 24-hour Holter monitors and the rest are monitored with a 7-day CER. In the intervention arm most patients are monitored with Zio Service, with the remainder receiving a Holter scan. The model assumes that positive and negative results of the first test do not require further testing. Following an inconclusive result, patients may be discharged, undergo a further test (comparator arm only), or undergo placement of an implantable device. If a test is to be repeated, a different technology is used. The sponsor estimated a mean of 1.44 additional tests for patients undergoing additional tests following an inconclusive result.

The cardiology model made the following assumptions:

- The majority of patients undergoing testing with either 24 hour Holter or 7-day CER will receive an inconclusive result. This occurs when a negative scan coincides with the presence of symptoms.
- A small proportion of patients with an inconclusive result will receive an ILR
- Some patient with an inconclusive result will be discharged, others will undergo further tests using the same device
- Negative results incur only the cost of the test
- Positive results incur the test cost and the cost of an outpatient assessment
- Inconclusive results incur the cost of the original test and an outpatient assessment if no further testing is undertaken and the cost of multiple tests, an outpatient assessment and an outpatient follow-up if further testing is undertaken
- The costs of any diagnostic and therapeutic procedures carried out subsequent to rhythm monitoring are not included in the model

The EAC did not consider the inclusion of an 'inconclusive' result to be a useful component of the Cardiology model due to a lack of literature data to inform parameterisation. Consultation and after consultation with the clinical experts also confirmed that they do who did not distinguish an inconclusive result from a negative result. The EAC thought that an outpatient assessment would be required regardless of the result of any test to confirm diagnosis.

Stroke model

As observed in [redacted], the stroke model assumes that current care (the comparator arm) consists of two pathways. The first pathway reflects the monitoring strategies available for confirmed stroke patients. Patients with possible and definite TIA enter the second pathway. Patients with confirmed stroke can be monitored in-clinic, with 24-hour Holter monitor, or with a 7-day CER. Positive results from any of these tests

do not require further testing. Negative results after inpatient monitoring requires the use of a 24-hour Holter monitor. Negative and inconclusive results after either Holter devices or CER require additional monitoring, including implantable monitors as an option. Patients with TIA are monitored with Holter devices or CER only. Zio XT Service entirely replaces the use of Holter monitors and CER in patients with confirmed non-haemorrhagic stroke in the sponsor's stroke model intervention arm. A quarter of patients with possible/definite TIA are still monitored with either Holter devices or CER, with the remaining monitored with Zio. Negative/inconclusive results with Zio XT Service can be further investigated with implantable loop recorders or discharged in case of no significant suspicion.

The stroke model made the following assumptions:

- Patients assessed with any test receive either a positive diagnosis or an inconclusive/negative diagnosis
- A small proportion of patients with an inconclusive/negative result will receive an ILR
- Some patients with an inconclusive/negative result will be discharged, others will undergo further tests
- Inconclusive/negative results with 24 hour Holter or CER which are not repeated incur the cost of the test and an outpatient assessment
- Inconclusive/negative results with Zio Service which are not repeated incur the cost of Zio service only
- Positive results with 24 hour Holter or CER incur the test cost and the cost of an outpatient assessment
- Positive results with Zio XT Service incur the test cost and sometimes incur the cost of an outpatient assessment
- Inconclusive results with 24 hour Holter or CER may be repeated. The repeat test may be a 24 hour Holter or CER. Where a different test is chosen for the

second test it is used once. Where the same test is chosen it is used more than once (but less than twice on average).

The EAC regarded the stroke model as acceptable. The EAC thought that an outpatient visit would be required regardless of the outcome of any test.

Downstream stroke model

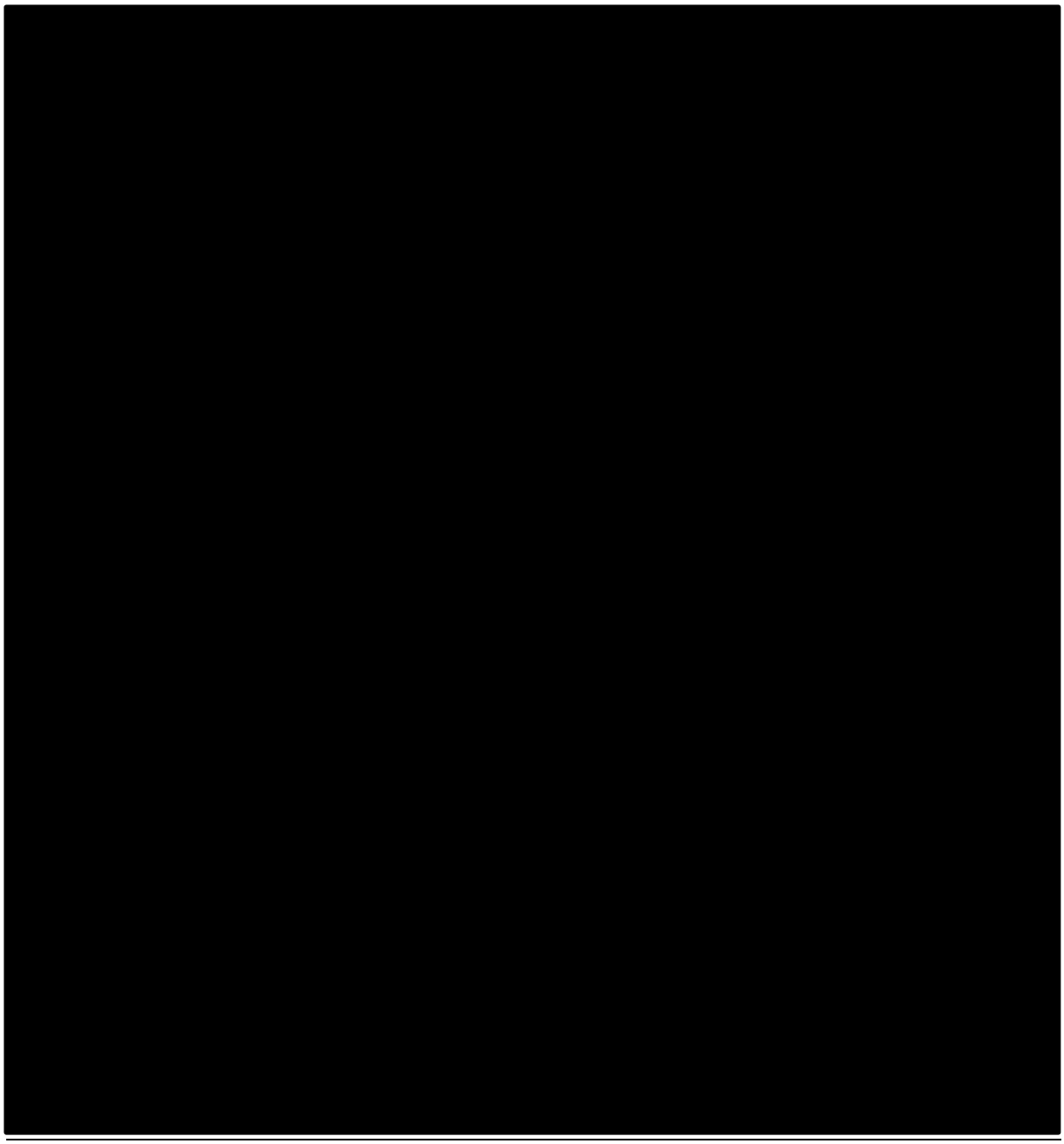
[redacted] The model uses an estimate of the true prevalence of AF in this population based upon the CRYSTAL-AF study results (Sanna 2014). The sensitivity of the technologies is assumed equal to their positive diagnostic yield (i.e. perfect diagnostic accuracy). Therefore, there is no risk of false positives. Due to the lack of supporting published evidence, this assumption was validated by clinical advice. A second detection pass is specified for Holter devices and CERs in case of negative results on the first detection pass. The diagnostic accuracy of the second pass was assumed to be independent from the first pass. In case of test positive results, anticoagulant therapy is prescribed. Undetected AF (false negatives) is associated with a higher risk of stroke. Patients with AF were assumed to be untreated with anticoagulant therapy and hence at higher risk of stroke during the delay between initiation of testing and the follow-up outpatient visit. These data on this delay from Holter and CER was taken from company's analysis of HES data and Freedom of Information requests. For Zio XT Service the delay was assumed to be 19 days, 70 days for Holter monitor and 88 days for CER. The company considered the 1-year health care cost for managing stroke from Xu et al. (2018). This cost was not adjusted to consider the timing of the stroke over the one-year horizon of the model.

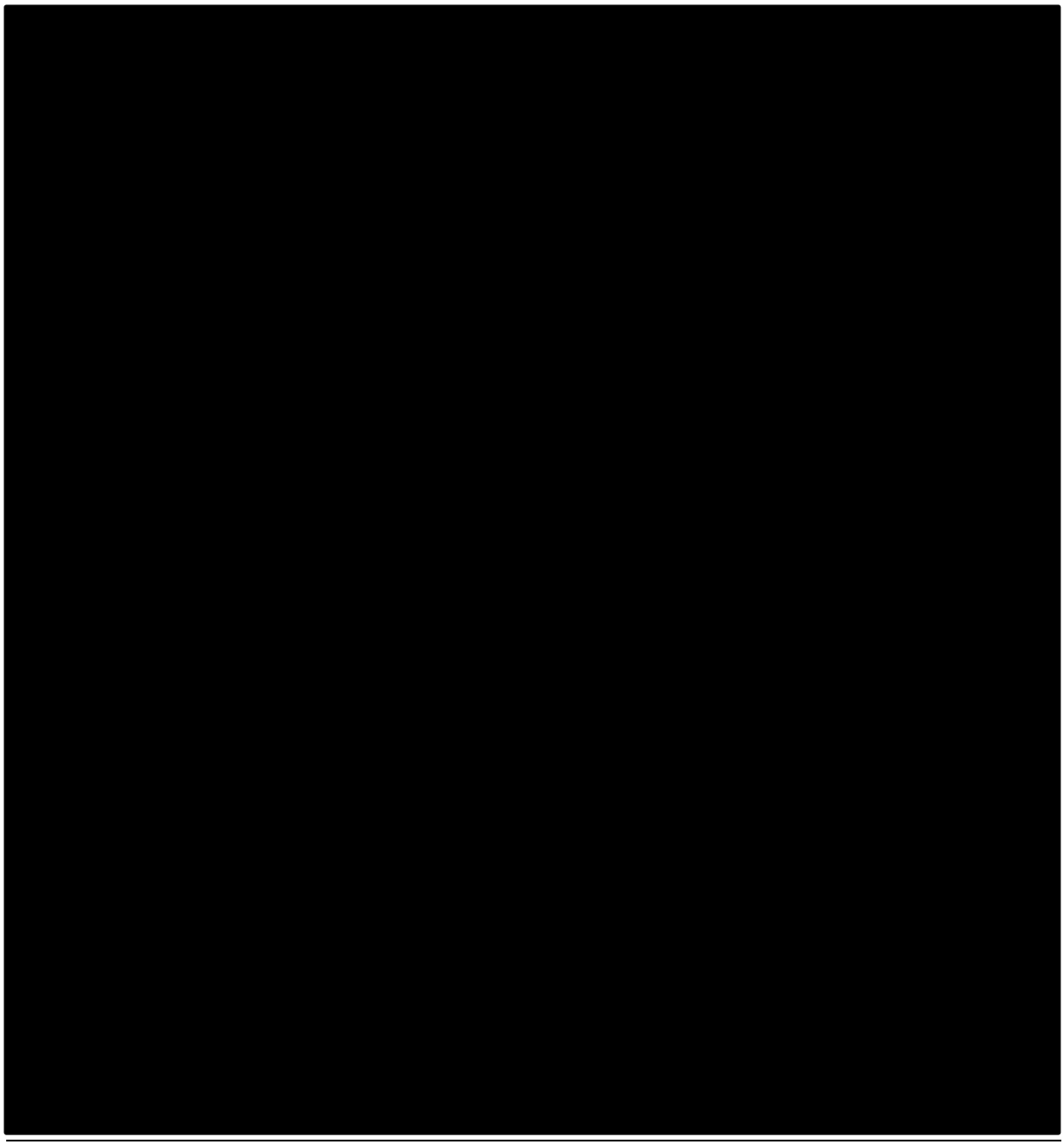
The downstream stroke model made the following assumptions:

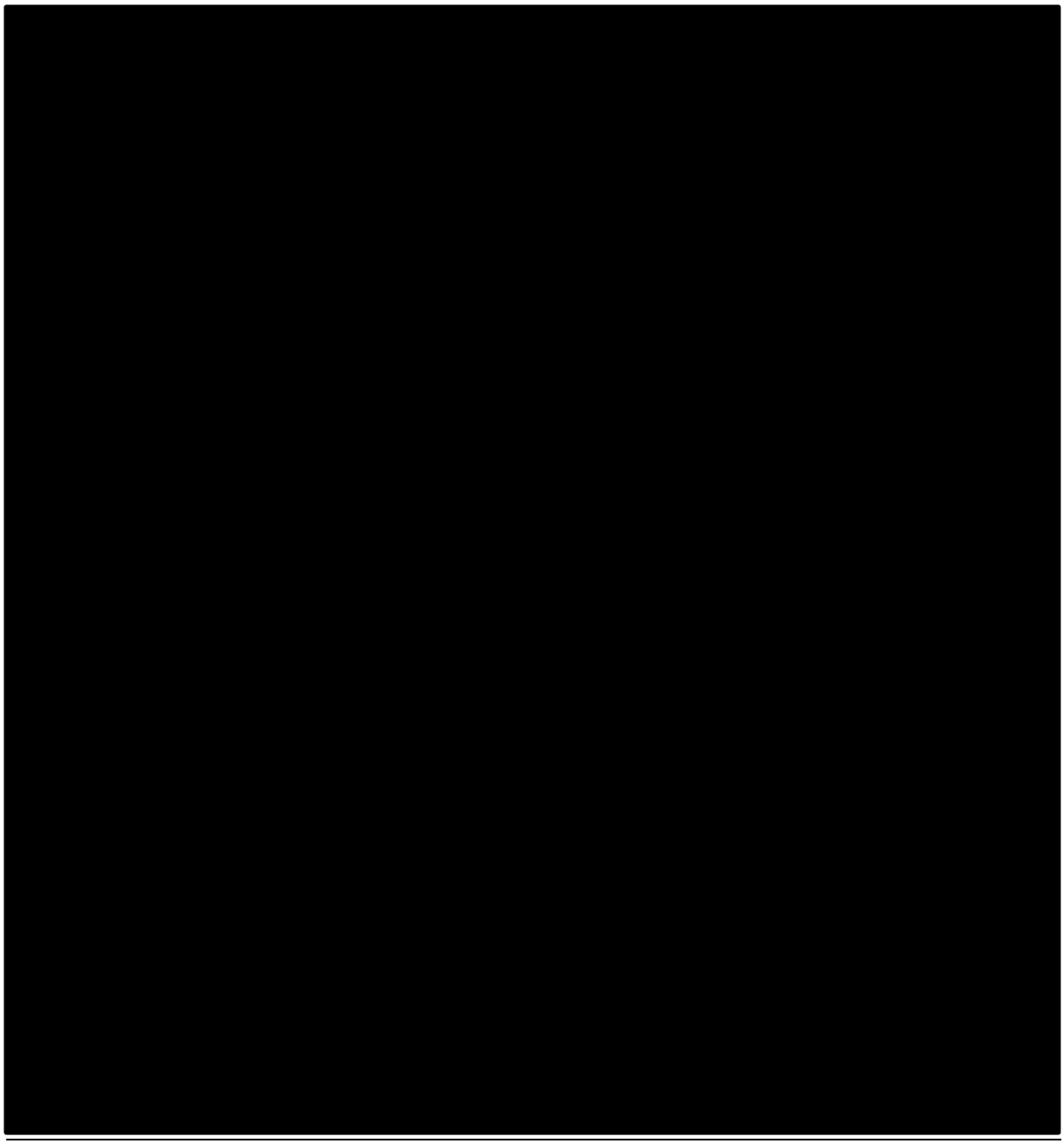
- Testing results in two outcomes: AF detected or AF not detected
- The specificity of all tests is 100%.
- A negative test with 24 hour Holter or CER leads to a second test using the same technology; a negative test with Zio Service is not repeated

- The yield of the second 24 hour Holter or CER test is the same as the first test used.
- Patients receive and adhere to anticoagulation therapy after a positive test
- Patients with AF are at heightened risk of recurrent stroke until they receive anticoagulation therapy

The EAC thought the overall structure of the downstream model was acceptable. However, the EAC believes that the downstream model has omitted important considerations in stroke care. The company's model does not include the cost associated with the use of anticoagulant therapy and the potential complications arising from it, including the risk and cost of intracranial bleeding and other clinical events. Additionally, the EAC considers it appropriate to include diagnostic costs as well as the cost of stroke treatment. The EAC believes it is unlikely that all negative monitoring test would be repeated. In the absence of definitive data, the EAC assumed a mean of 1.389 tests per patient in accordance with the HES data provided by the company.







10.2.2 Economic model parameters

Cardiology and stroke models

Alongside the cost of Zio XT Service and the cost of the Holter and CER tests, the parameters that drive the overall results in the cardiology and stroke models are the probability of inconclusive tests and the probability of test repetition. The probability of an inconclusive test influences the likelihood of utilising an implantable loop

recorder (ILR). ILRs are the costliest monitoring option considered in the analysis (£3,221). The probability of test repetition is used in both cardiology and stroke models. It was estimated using analysis of HES data conducted by the company. The company's model estimated a mean of 1.44 additional tests performed in the group of patients who undergo test repetition. From the HES data provided by the company, the EAC calculates 1.465 additional tests for the 27% of patients who undergo more than one test within 12 months. The EAC has some reservations regarding an assumption that an average of 1.389 tests are undertaken per patient for symptomatic patients in the cardiology model or for patients in the stroke models. The HES data provided by the company refers to a group of procedures including exercise stress tests. The HES data presenting repeat testing incorporates various tests including 24 and 48 hour ECG monitoring, ambulatory ECG monitoring and exercise ECG monitoring (NICE TA593). This may artificially increase the estimated number of repeated Holter tests, for example according to the NICE CG109 people who have experienced syncope during exercise, need to undergo exercise ECG monitoring as part of their diagnostic routine. The EAC was unable to source a more reliable estimate of the number of repeat tests but believes the true figure may be lower than a mean of 1.389 investigations per patient.

In the cardiology model, the probability of inconclusive test for Holter devices and CERs was estimated as the remaining probability of the sum of the positive and negative diagnostic yield. The company was unable to identify a reliable negative yield estimate for Holter or CER. Therefore, they used the positive diagnostic yields reported in Tsang (2014) for Holter and CER and the positive to negative ratio of Zio and of CER from Barnelli (2003) to calculate the negative yields for Holter and CER respectively. The EAC revised the cardiology model to combine inconclusive and negative results for 24 hour Holter and CER, negating the need to estimate the probability of a negative result.

Downstream stroke model

The company's downstream stroke cost model is mainly driven by the difference in risk of stroke and its subsequent management cost. The company considered a 1-year stroke risk of 12.3% for untreated patients with underlying AF. An absolute risk difference of 8.4% was applied to treated patients. Both values were based upon the

EAFT study. The company considered a 1-year risk of stroke of 9.9% for patients without underlying AF. This parameter was calculated using the probability of stroke in AF untreated patients and an odds ratio of patients with AF in comparison to patients free of AF of 1.24 based on Burn et al. (1994). The EAC had concerns about these values. The EAC contacted clinical experts to enquire on the suitability of these references. The clinical experts suggested they may be appropriate. They considered the population analysed in this study to be substantially different to the population in the decision problem. For example, more than 70% of the patients suffered in the EAFT study suffered from chronic AF and up to 25% suffered multiple strokes in the year prior to randomisation. Additionally, this study was conducted before aspirin and oral anticoagulants where implemented as standard practice to reduce risk of stroke. The EAC considered the data in Diamantopoulos 2016 to be more relevant to the decision problem. The EAC estimated the risk of stroke for patients with untreated AF, treated AF and without AF from data in Diamantopoulos 2016.

The company considered the impact of the delay between initiating investigation and diagnosis confirmation on stroke risk. Specifically, patients were assumed to be untreated and at higher risk of stroke during this delay. The sponsor company conducted their own analysis of HES data and retrospective data to estimate these parameters. The EAC believes that the estimate from HES data is likely to be representative of clinical practice but notes that the company's analysis has not been published or peer reviewed and the EAC has only been provided with summary results that don't allow methodological quality assessment.

10.2.3 Clinical parameters and variables

Tables 7, 8 and 9 summarise the clinical parameters and variables of the company's cardiology, stroke and downstream cost models, respectively.

Table 7 Clinical parameters used in the company's cardiology model

Variable	Company value	Source	EAC value	EAC comment
Probability of Holter monitor yielding a positive result	24.2%	Tsang (2014)	24.2%	The EAC considers this appropriate

Probability of Holter monitor yielding a negative result	11.4%	Extrapolated from clinical evidence using the observed positive: negative results ratio of Zio in company's retrospective data and Tsang et al (2014)	75.8%	The EAC combined the inconclusive and negative results into a single category.
Probability of CER monitor yielding a positive result	23%	Tsang (2014)	23%	The EAC considers this appropriate
Probability of CER monitor yielding a negative result	18.5%	Extrapolated from clinical evidence using the observed positive: negative results ratio of CER reported in Balmelli (2013) and positive yield from Tsang et al (2014)	77%	The EAC combined the inconclusive and negative results into a single category.
Probability of Zio yielding a positive result	63.5%	Company's retrospective audit data	63.5%	The EAC accepts the value provided by the company
Probability of Zio monitor yielding a negative result	29.9%	Company's retrospective audit data	29.9%	The EAC accepts the value provided by the company
Probability of not progressing to repeat monitoring given inconclusive results in Holter devices and CERs	73%	Company's analysis on HES data	73%	Estimate derived from data on all patients undergoing electrocardiogram monitoring or stress testing. The EAC has some concerns regarding the applicability of this data to the population in the company's models.
Probability of fitting implantable device given inconclusive results in all tests	2%	Clinical advice	2%	Company value based on reasonable assumption
Proportion of patients monitored with CER in current route	15%	Clinical advice	15%	Company value based on reasonable assumption
Proportion of patients who would have had a Holter monitor switched to Zio	80%	Clinical advice	80%	Company value based on reasonable assumption

Table 8 Clinical parameters used in the company's stroke model

Variable	Company value	Source	EAC value	EAC comment
Proportion of stroke patients undergoing monitoring as in-patient	50%	Clinical advice	50%	Company value based on reasonable assumption
Proportion of patients with positive diagnosis monitored in clinic	5.6%	SSNAP (2019)	5.6%	The EAC considers this appropriate
Proportion of patients with non-haemorrhagic stroke	57.6%	Calculated as product of patients with new stroke or TIA 66% (Giles 2007), and 87.3% proportion of non-haemorrhagic stroke 87.3% (SSNAP 2019)	57.6%	The EAC considers this appropriate
Proportion of patients with stroke/TIA monitored with Holter in current route arm	50%	Clinical advice	50%	Company value based on acceptable sources
Proportion of patients with TIA monitored with Zio in intervention arm	75%	Clinical advice	75%	Company value based on reasonable assumption
Probability of CER yielding a positive result	7.4%	Gladstone (2014)	7.4%	The EAC considers this appropriate
Probability of Holter yielding a positive result	2.1%	Kaura (2019)	2.1%	The EAC considers this appropriate
Probability of Zio yielding a positive result	16.1%	Kaura (2019)	16.1%	The EAC considers this appropriate
Probability of not progressing to repeat monitoring given negative results in Holter devices and CERs	73%	Company's analysis on HES data	73%	Estimate derived from data on all patients undergoing electrocardiogram monitoring or stress testing. The EAC has some concerns regarding the applicability of this data to the population in the company's models.

Table 9 Clinical parameters used in the company's downstream stroke model

Variable	Company value	Source	EAC value	EAC comment
True prevalence of AF in	30%	Sanna (2014) (CRYSTAL AF study)	30%	The EAC considers this appropriate

selected population				
Probability of yielding a positive result with Holter	2.1%	Kaura (2019)	2.1%	The EAC considers this appropriate
Probability of yielding a positive result with CER	7.4%	Gladstone (2014)	7.4%	The EAC considers this appropriate
Probability of yielding a positive result with Zio	16.1%	Kaura (2019)	16.1%	The EAC considers this appropriate
Risk of stroke in AF free patients	9.9%	Calculated from clinical evidence using the risk of stroke in patients with untreated AF of12.3% (EAFT 1993) and odds ratio of 1.24 for stroke with AF from Burn (1994)	5.28%	The EAC considered the estimates retrieved from the EAFT study are not valid as the population considered in such study is fundamentally different to the one outlined in the decision problem. The EAC applied the estimates for these parameters from Diamantopoulos (2016) as they are more representative of the population under consideration
Risk of stroke in undetected AF patients	12.3%	EAFT (1993)	7.85%	
Risk of stroke in detected AF patients	3.9%	EAFT (1993)	3.1%	
Time to make a diagnosis for Holter	70 days	Company's analysis on HES data and FOI requests	70 days	Company value based on acceptable sources
Time to make a diagnosis for CER	88 days	Company's analysis on HES data and FOI requests	88 days	Company value based on acceptable sources
Time to make a diagnosis for Zio	19 days	Company's retrospective data	19 days	Company value based on acceptable sources

10.2.4 Resource identification, measurement and valuation

10.2.4.1 Price of the technology

The company provided a cost of £310 per patient attributed to the use of the technology. This figure includes the device, the cost of analysing and reporting.

10.2.4.2 NHS and unit costs

The company provided unit cost estimates for 24-hour Holter monitor, cardiology outpatient visits, implantation of implantable loop recorder, based on PLICS data from 2016/17 and NHS reference costs. The unit cost of CERs was assumed to be the same as the Holter monitor given the lack of evidence on this parameter.

The company used PLICS data and Freedom of Information Request to estimate the unit cost of 24-Hour Holter monitors. The cost estimate of the Holter monitor use in their model is £185. It is inclusive of the device fitting/removal, reporting, (£158) and hardware and maintenance components (£27). The company justified the use of PLICS data after noting the variation in reference cost data across different specialties for EY51Z: Electrocardiogram monitoring or stress testing. The EAC notes that over two thirds of procedures across all specialties were conducted in cardiology in the year 2017/18. The EAC believes the NHS reference cost for 2017/18 for cardiology services of £141 is a more suitable source. The PLICS data from 2016/17 is based on information gathered voluntarily in a limited number of NHS Trusts. The NHS reference cost is representative of national practice. The EAC accepts that the reference cost may exclude hardware and maintenance costs. The EAC notes that the category EY51Z, used for both the cost estimate from NHS reference costs and PLICS data, includes a number of different procedures including exercise stress tests. The EAC was unable to source a better estimate of the cost of ambulatory electrocardiogram monitoring in the NHS. Hence uncertainty remains regarding the true cost of 24-hr Holter monitoring or 7-day CER.

The company was unable to find a cost of CER and assumed the cost was the same as a 24 hour Holter assessment. The EAC undertook its own search for the cost of CER. The available evidence was very limited. An Italian report estimated the cost of 7-day CER at €39 compared to €62 for 24 hour Holter monitoring (Scalvini 2005). Details of the cost calculations are lacking. A study from Portugal of the financial impact of introducing ILR for the diagnosis of syncope provided a cost of €43.70 for ambulatory ECG monitoring and €47.30 for external loop recording, derived from Portuguese NHS reimbursement tariffs (Providencia 2014). These studies may not accurately reflect cost differences between the two technologies in the UK but would indicate an assumption of similar cost is reasonable.

The cost of a cardiology outpatient visit was derived from NHS reference costs 2017/2018. All the sponsor's models applied a value of £142. The EAC considers this value is appropriate. It was applied only as a consequence of positive or inconclusive results in the cardiology model. In the stroke model, the cost was not included for patients using Zio Service except where an ILR was used. The EAC

revised each model to include an outpatient assessment following testing regardless of the result or technology.

The unit cost of implantable loop recorders (£3221) was based upon National Reference Costs 2017/2018 and the cost reported in the Medtech Innovation Briefing 141 - the Reveal LINQ insertable cardiac monitor (NICE 2018). This figure consists of the cost of the implantation procedure (£308), the unit cost of the device (£1,800), and an extrapolation of the daily cost of continuous monitoring (£3.05) over 1 year. The EAC considers this value to be appropriate.

10.2.4.3 Resource use

The company estimated an average resource use of 1.44 additional tests for the group of patients who undergo test repetition. This value was estimated on analysis of HES data carried out by the company. The EAC calculated this parameter to be 1.465 from the HES data provided by the company. The EAC notes that this parameter is derived from data on all patients undergoing electrocardiogram monitoring or exercise stress tests in the NHS. The EAC was unable to find an estimate that better matched the population in the company's models, but the EAC believes the data may overestimate the number of repeat tests in the cardiology and stroke populations.

Data on the resource use and associated cost of anticoagulation therapy was not applied to the downstream stroke cost model by the company. The EAC considers this element should be incorporated as this an important element in the consequences of having a confirmed diagnosis of AF.

10.2.4.4 Adverse events

The company's cardiology and stroke models do not consider adverse events as they only focus on the cost of the diagnostic process. The downstream stroke model considers the health care costs of managing stroke over 1-year. The value used in the company's model is £13,452 and was retrieved from the analysis conducted by Xu (2018) of data from the Sentinel Stroke National Audit Programme. This value has a perspective of the NHS only. The EAC considers this source and figure is appropriate

The EAC believes the cost of anticoagulant therapy including the cost of increased incidence of major bleeds should be included in the model. The EAC considers the cost projections in the NICE costing report accompanying the Clinical guideline on the management of atrial fibrillation [CG180] to be the most appropriate source of data since the guidelines consider oral anticoagulants as well as warfarin and the proportion of patients given no therapy.

10.2.4.5 Miscellaneous costs, savings, resources and capacity changes

No miscellaneous costs, savings, resources or capacity changes were considered in the company's analysis.

10.2.4.6 Total costs

Table 10 summarises the costs employed in the company and the EAC's base-cases.

Table 10 Base Case Costs

Parameter	Company base-case	EAC base-case	Source
Cost of Zio XT Service	£310	£310	Company
24-hour Holter use cost	£185.12	£168.12	NHS Reference Costs 2017/2018 and FOI request
CER use cost	£185.12	£168.12	Assumed to be equal to Holter device cost
Implantable loop recorder cost	£3,221	£3,221	NHS Reference Costs 2017/2018 + MIB 141 – Reveal LINQ insertable cardiac monitor (NICE)
Cardiology outpatient visit	£142	£142	NHS Reference Costs 2017/2018
Mean number of additional tests if repetition is decided	1.44	1.465	Data from HES
Cost of stroke	£13,452	£13,452	Xu (2018)
Cost of anticoagulation therapy including cost of bleeds	Not included	£452	NICE Clinical Guideline CG180 Atrial fibrillation: management.

			Costing report uprated to 2017/18 prices

10.2.6 Scenario and sensitivity analysis

The company conducted deterministic one-way sensitivity analysis on all parameters in their models, with values varied over the range +/- 20%. The company justified the range chosen on account of limited availability of evidence on uncertainty for most parameters. The company's downstream stroke model described in previous sections was considered as scenario analysis; the EAC considered it as part of the company's base-case analysis.

10.3 Results from the economic modelling

10.3.1 Base case results

Table 11 Summary of base case results

	Company's results			EAC's results		
	Intervention arm	**Comparator arm**	**Cost saving per patient**	**Technology**	**Comparator**	**Cost saving per patient**
Cardiology model	£431.33	£516.59	£84.76	£466.78	£465.96	-£0.82
Stroke model	£382.69	£437.97	£55.28	£493.94	£423.13	-£70.81
Downstream stroke model	£1,256.15	£1,332.65	£76.50	£1237.45	£1216.62*	-£20.83

*Results for CER comparator, Holter comparator is more expensive

The company estimates a cost saving from the use of Zio XT Service in each of the 3 models. The EAC estimates a very modest cost increase in the revised cardiology model and cost increases in the stroke and downstream stroke models. In the company's cardiology model 40.3% of patients underwent repeat testing after a 24 hour Holter test. In the company's stroke model 25.9% of patients underwent repeat testing with 24 hour Holter or CER. The EAC corrected both the stroke and cardiology models submitted by the company to ensure that 27% of patients underwent further testing after a 24 hour Holter test (in accordance with the HES

data). This change will have reduced the cost of the comparator in the cardiology model and very slightly increased it in the stroke model. The EAC replaced the cost estimate for a 24-hour Holter assessment from PLICS data of £165 with an estimate from NHS reference costs of £141. This change reduced the cost of the comparator in the stroke and cardiology models. The EAC included an outpatient assessment cost after all test results and regardless of the technology used. The inclusion of an outpatient assessment prior to discharge following a negative test result in the cardiology model increased the costs of the technology more than the comparator since Zio Service produces more negative results. The inclusion of an outpatient assessment after all Zio results in the stroke model increased the costs of the technology.

The downstream stroke model was revised to include the costs of anticoagulant treatment including side-effects. This increased the cost of Zio Service more than the comparators. The EAC amended parameters on the risk of stroke. The EAC estimates were lower than those used by the company. This decreased costs in all three arms (Zio XT Service, 24-hour Holter and CER) but had the biggest impact on the comparator arms where more patients have undiagnosed AF. However, the biggest change the EAC made to the downstream stroke model was the inclusion of additional test costs. This increased the cost of both arms but had a larger impact on the cost of testing with Zio Service. The company's model assumed that a negative test with 24-hr Holter or 7-day CER is repeated (but not a negative test with Zio XT Service). The EAC assumed that negative investigations with either 24-hr Holter or 7-day CER are sometimes repeated and that investigations with Zio Service are not repeated. The EAC assumed 1.389 tests with either 24-hr Holter or CER on average per patient, in line with the data from HES submitted by the company. The overall impact of these changes is that EAC estimates a modest cost increase with Zio Service in the downstream stroke model compared to either 24-hr Holter monitoring or 7-day CER.

10.3.2 Scenario and sensitivity analysis results

The company's one-way sensitivity analysis of the cardiology model showed that inference that Zio XT Service is cost saving was robust to all parameters varied over a range of +/-20%. The company's one-way sensitivity analysis of the stroke model showed that inference that Zio Service is cost saving was sensitive to variation in the

probability of a repeat 24 hour Holter or CER after a negative/inconclusive scan. At the upper limit of the values tested for this parameter, Zio service was slightly more expensive than current care. The company did not undertake sensitivity analysis of the downstream stroke model.

The EAC undertook one-way sensitivity analysis for each of the 3 models. The figures (3 to 5) below provide the Tornado plots for each of the three models. The inference from the cardiology model that Zio XT Service is cost incurring is sensitive to the majority of parameters. This is unsurprising given the small difference in costs observed in the base case. The results are most sensitive to uncertainty in the costs of Zio XT Service followed by the costs of 24 hour Holter monitoring and then the probability of testing with an ILR. Cost differences are not sensitive to the proportion of patients still using 24 hour Holter in the Zio arm, the proportion of patients receiving CER under current care or the probability of a positive diagnosis using Zio Service (when it is assumed that the probability of an inconclusive Zio XT Service report is fixed). In contrast, inference from the EAC's stroke model that Zio Service is cost incurring was robust to parameter uncertainty in one-way sensitivity analysis of all parameters except the cost of Zio XT Service. The breakeven point for the cost of Zio XT Service is £229.

The main reason for the difference in sensitivity of inference from the EAC's revised cardiology and stroke models is simply the magnitude of the cost difference in the base case, which is much larger in the stroke model. Whilst there are differences in the two models, the impact of changes in parameters on the overall costs of Zio Service and current care were similar across the two models.

The inference from the EAC's downstream stroke model that Zio service is cost incurring was sensitive to the costs of Zio Service, the probability that a negative test is repeated, the costs of 7-day CER, the costs of treating stroke and the probability of a stroke with untreated AF in one-way sensitivity analysis comparing Zio Service with 7-day CER. The cost of Zio Service was almost identical to the cost of 24 hour Holter monitoring in the base case rendering the result sensitive to the majority of model parameters.

The findings from the revised downstream stroke model are dependent on the assumption that conventional testing is repeated for negative tests with a mean of 1.389 tests per patient, whereas Zio XT Service is not repeated after an inconclusive/negative result. The EAC undertook a scenario analysis in which it assumed that all monitoring is repeated after a negative test. In this scenario Zio Service was cost incurring. Costs were £1604 for Zio Service compared to £1395 for CER and £1422 for Holter monitoring. If all first negative Zio Service tests are repeated the impact on costs for Zio Service is substantial. In a second scenario analysis the EAC assumed that monitoring with 24-hr Holter or 7-day CER is repeated if a negative test is obtained for the first test, but Zio Service is not repeated. In this scenario Zio XT Service, at £1237 was considerably cheaper than either 24 hour Holter (£1422) or 7-day CER (£1395).

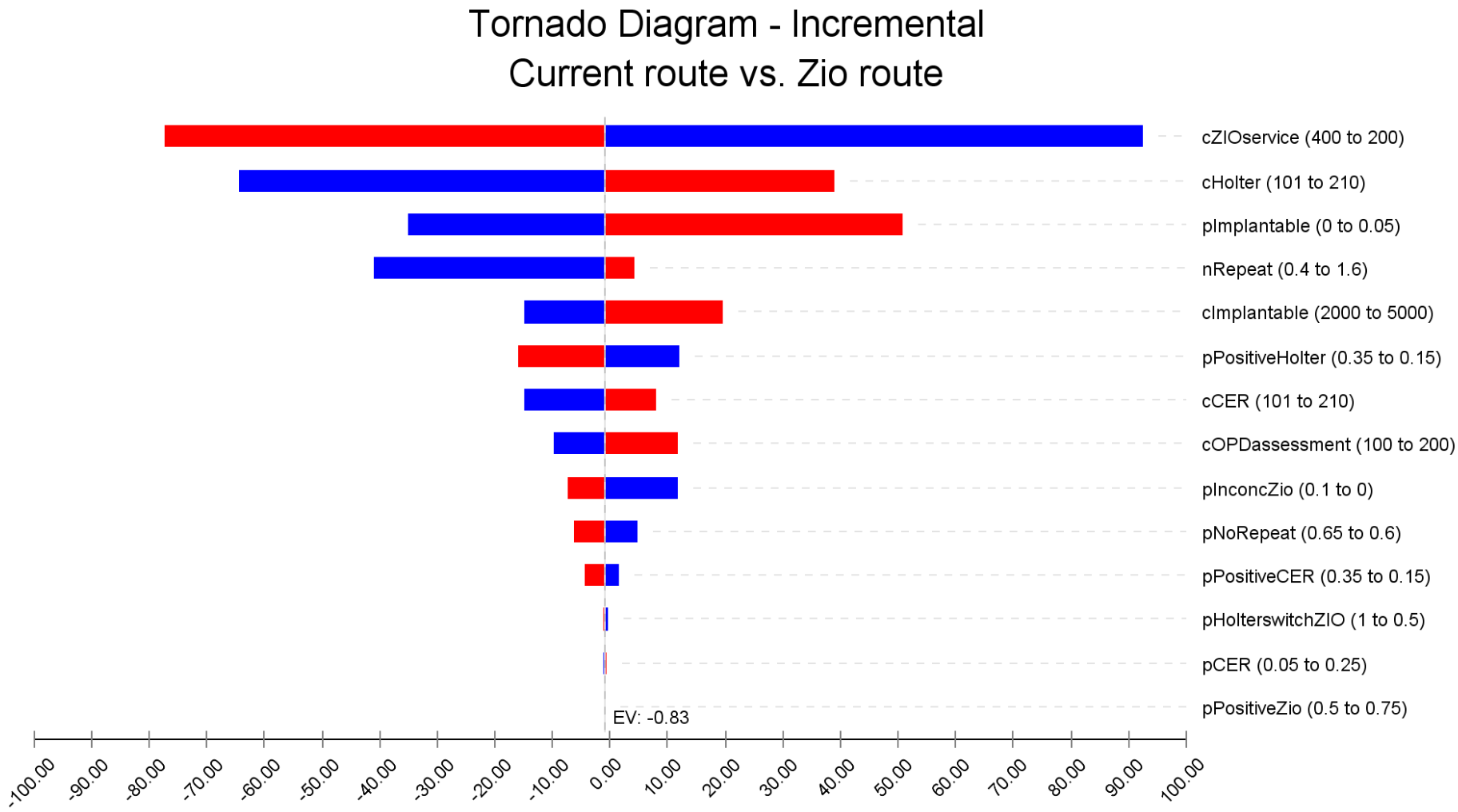


Figure 4 Tornado plot showing one-way sensitivity analysis for the EAC's cardiology model.

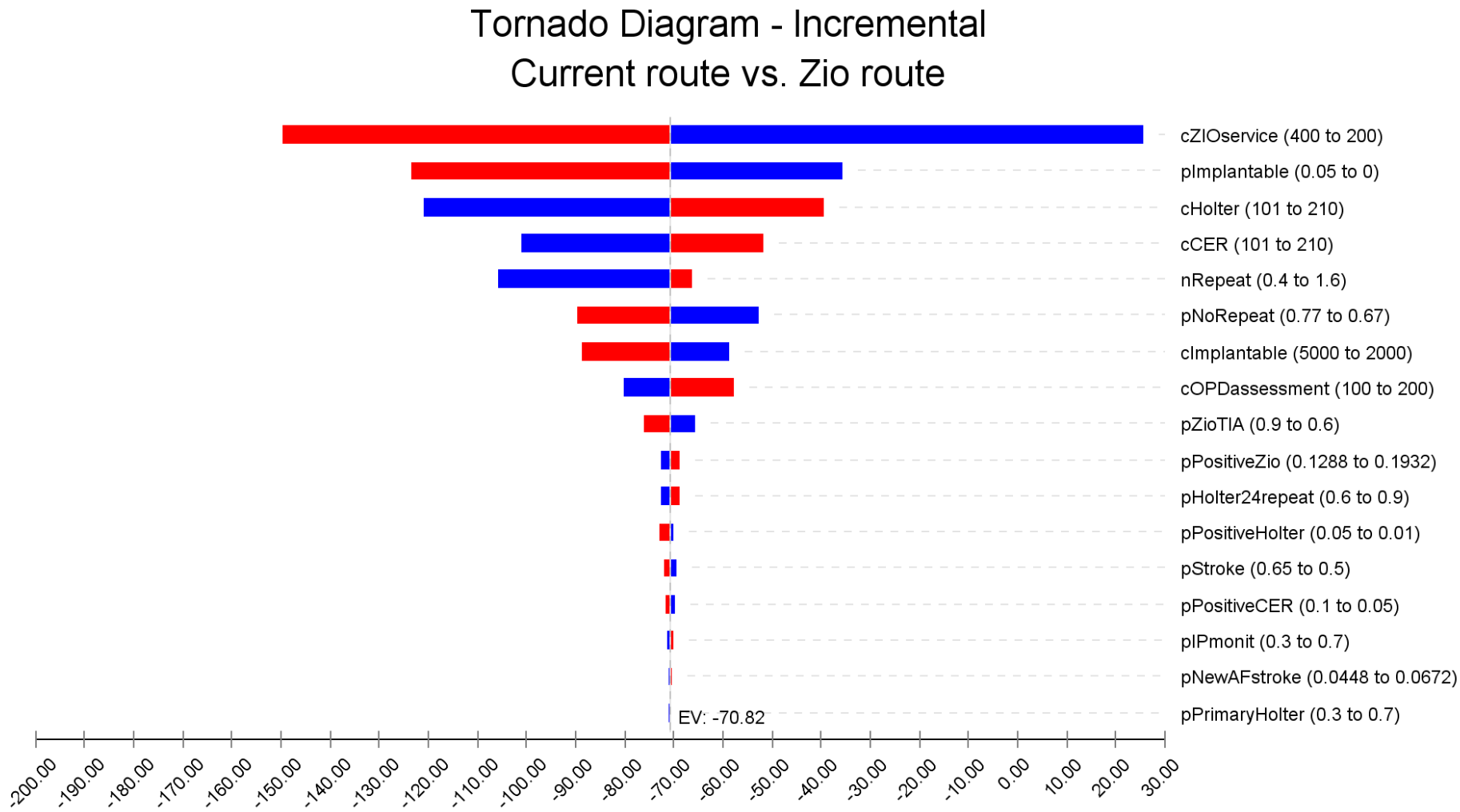


Figure 5 Tornado plot showing one-way sensitivity analysis for the EAC's stroke model.

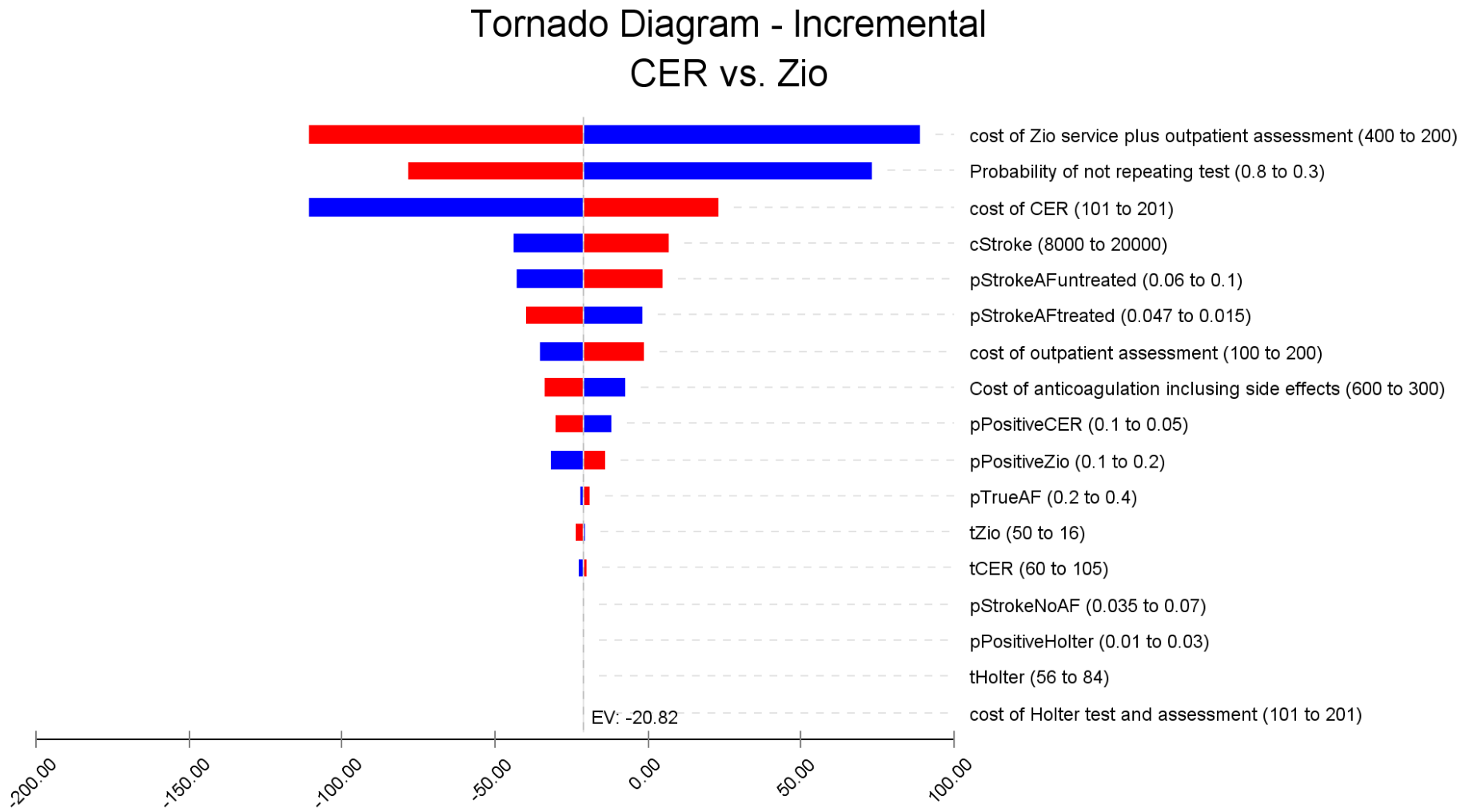


Figure 6 Tornado plot showing one-way sensitivity analysis for the EAC's downstream stroke model comparing Zio service with CER.

10.3.3 Additional results

No additional sub-group analysis was carried out.

10.4 EAC Interpretation of economic evidence

Briefly summarise how the EAC have revised the company's economic model.

The EAC made changes to the cost of monitoring with 24-hour Holter or CER in each of the company's models. The EAC considered an estimate of the cost of £142 derived from the NHS reference cost for electrocardiogram or stress testing in a cardiology department to be more likely to represent the true cost than the estimate derived from analysis of PLICs data from 2016/17 since PLICs data was not universally reported during this period. The EAC applied the cost of an outpatient visit to the cost of monitoring for all patient regardless of the monitoring technology or result. This cost had been applied more selectively in the company's cardiology and stroke models.

The EAC made amendments to the cardiology model submitted by the company to combine inconclusive and negative results into a single outcome 'inconclusive/negative' after a 24 hour Holter or CER test. The EAC made amendments to the parameters in the cardiology and stroke models governing the number of patients not undergoing a further test after an inconclusive result for monitoring with 24 hour Holter or CER. These changes ensured that 73% of the patients did not receive a second test, in line with the supporting HES data provided by the company. The change was marginal for the stroke model, but significantly reduced the number of repeat tests in the cardiology model. The EAC revised the parameter governing the number of repeat tests to match the HES data provided by the company. The change made was a very modest increase in the value of the parameter (from 1.44 to 1.465 tests).

The overall impact of these changes was to decrease the cost of current care in the cardiology model and to increase the cost of Zio service in the stroke model. The amended cardiology and stroke models indicated the diagnostic costs of Zio Service are greater than those under current care, albeit the difference was minimal for the cardiology model. The drivers of diagnostic

cost are clearly the test cost and the number of test repeats. The company provided evidence from HES data on the number of repeat tests in the current pathway. The EAC has some concerns that the data may overestimate the number of tests undertaken in the cardiology and stroke models. The assumption of no repeat tests with Zio Service is plausible but likely to be an underestimate, if only a modest one. The current cost of Zio Service is known; there is uncertainty in the cost of the comparator. The EAC applied a cost from NHS reference costs for cardiology services which is lower than the value the company derived from analysis of PLICS data.

The EAC amendments to the downstream stroke model increased the cost for Zio Service when compared to current care. The main change was the inclusion of test costs. These costs are highly dependent on the number of repeat tests undertaken in current practice. The EAC assumed a mean of 1.389 tests per patient but notes that the data upon which this estimate is made may overestimate the number of repeat tests for the population in the downstream stroke model. An assumption of 1.389 tests under current care generates lower diagnostic costs under the current pathway than those under Zio Service. The additional costs of Zio Service are offset by the avoidance of stroke through earlier detection and improved diagnostic yield with Zio Service. The impact of this is mitigated in the EAC's model by the inclusion of anticoagulant therapy costs.

The EAC regards the downstream model as the most informative model after inclusion of diagnostic costs. The EAC considers diagnostic costs, treatment costs for AF and the costs of stroke are all relevant costs and should be included in the analysis. Hence the EAC thinks that the results from the downstream stroke model should be given most prominence. However, the EAC notes that the findings of the downstream model are sensitive to assumptions regarding the number of repeat tests under the current care pathway. The EAC base its base case on the HES data provided by the company but has some reservations that these data may have overestimated the parameter.

Does the EAC think the results of the economic modelling support the case for adoption of the technology? Are the system benefits claimed by the company justified?

On the basis of the revised models, the EAC concludes that Zio XT Service is unlikely to be cost saving when compared with current practice. The EAC places most weight on the revised downstream stroke model which incorporates both diagnostic costs and treatment costs for stoke prevention and stroke. That analysis indicated a modest cost increase of around £20 per patient through the introduction of Zio XT Service. The EAC notes that a time horizon of one year may provide a conservative estimate of the cost savings from the avoidance of stroke. Set against this is a concern that the HES data may overestimate the number of repeat tests undertaken in the current care pathway. The potential benefits to patients of improved diagnosis of AF are evidently significant. An additional cost of £20 per patient is modest when set against these benefits. However, there is no available evidence to support that an increased diagnostic yield with Zio XT Service improves clinical outcomes.

11 Conclusions

11.1 Conclusions on the clinical evidence

The clinical evidence for Zio XT Service comprises 1 RCT, 3 prospective comparative studies, and 13 non-comparative studies. There were 13 studies reported as abstracts. The EAC has focused on the 4 comparative studies that were reported as fulltext publications. The UK based RCT (Kaura et al. 2019) and 2 comparative studies (US studies: Barrett et al. 2014, Rosenberg et al. 2013) indicated that the use of 14-day Zio XT Service increased diagnostic yield compared with 24-hour Holter monitoring over total wear time.

The diagnostic accuracy of Zio XT Service compared with Holter monitoring is unclear. The Barrett et al. (2014) and Rosenberg et al. (2013) studies carry out some analysis over the same 24 hour period with slightly differing results. Holter monitoring had a “performance advantage” in Barrett et al. (2014) due to algorithm misclassification and report reviewer processing errors (the authors note that the service was subsequently corrected). Rosenberg et al. (2013) reported significant agreement in event detection between Zio XT

Service and Holter monitoring. Both studies used judgement of a clinical experts as reference standard. Overall, clinical experts suggested that there may be no significant difference in accuracy between Holter monitoring and Zio XT Service. However, 1 expert also noted that because Holter monitors make use of more leads, they may be more accurate. Barrett et al. (2014) suggests that in general, the information provided by additional ECG leads in Holter monitors may benefit both automatic algorithm analysis and clinician interpretation. Specifically, 3-lead recordings allow for the detection of arrhythmia events characterised by a shift in electrical axis that can be missed by single-lead recordings. Therefore, the diagnostic accuracy of Zio XT Service may vary by type of arrhythmia. One expert noted that Zio XT Service may be more accurate for a fixed period of time (24 hours), as there is likely to be less artefact and more analysable rhythm (for example, patients remove the Holter monitors during showers).

Experts noted that extended monitoring would be particularly useful for populations suspected of infrequent arrhythmias by increasing diagnostic yield. It is unclear how increased diagnostic yield may affect clinical outcomes. Kaura et al. (2019) reported that a significantly higher proportion of patients randomised to the Zio XT Service arm were taking anticoagulants at 90 days, 16.3% compared with 2.1% of patients who only had 24-hour Holter monitoring. The study was, however, underpowered for these outcomes and did not report the effect of increased anticoagulation use to clinical outcomes. Rosenberg et al. (2013) stated that 18 patients with PAF had a change in their classification of AF and 21 patients (28.4%) had subsequent medication change “as a result of findings from the Zio Patch”, with 17.3% having a change in their antiarrhythmic medication and 5.3% changing oral anticoagulant use. This was attributed to longer monitoring time compared to 24 hour Holter monitoring. Without more information about diagnostic accuracy or resulting clinical outcomes, it is unclear how appropriate these changes to patient management were.

The EAC agrees with the company’s statement that compliance for Zio XT Service appears high, with mean wear time ranging from 10.8 days

(Rosenberg et al. 2013) to 12.8 days (Eysenck et al. 2019) out of scheduled 14 days in comparative studies. Barrett et al. (2014) provided a comparison of patient experience, reporting that 93.7% participants found the monitoring patch comfortable to wear as opposed to 51.7% for the Holter monitor. A survey into patients of a UK cardiology clinic (Hall et al. 2019, abstract only) found that Zio XT Service was significantly preferred to Holter monitoring in terms of shape, comfort, practicality and returning method.

Various outcomes were reported by the non-comparative studies (arrhythmia prevalence, type of arrhythmia) but the lack of a control group makes it impossible to draw any conclusions about the efficacy of Zio XT Service.

- **Does the evidence present an unbiased estimate of the technology's treatment effect?**

The biggest potential source of bias is the heterogeneity of the study populations. Population and type of arrhythmia varied, therefore no meta-analysis was carried out by the EAC or the company. Despite the heterogeneity, results consistently indicate that 14-day Zio XT Service has increased diagnostic yield compared with 24-hour Holter monitor over total wear time.

- **Was the treatment effect relevant to the population, intervention, comparators and outcomes in the decision problem?**

The scope included a broad population (all adults with suspected cardiac arrhythmia referred for ambulatory ECG monitoring) and outcomes (including procedural, clinical management and patient). A relatively large number of studies were found that investigated Zio XT Service as an intervention, but this was constrained by the lack of relevant within-study comparators in the evidence.

- **Is there evidence on any important subgroups?**

Kaura et al. (2019) provided evidence in patients who had an ischaemic stroke or TIA in the previous 72 hours. These patients were presumably asymptomatic (although this was not made explicit).

Two non-comparative studies (Turakhia 2015, Tung 2015) provided evidence in asymptomatic patients.

- **Are there any other important uncertainties in the clinical evidence?**

As mentioned, more information about diagnostic accuracy, and analysis for different types of arrhythmia in different populations would help inform conclusions about Zio XT Service's clinical efficacy. Further comparative evidence about how Zio XT Service impacts clinical management or patient outcomes would be helpful.

11.2 Conclusions on the economic evidence

The EAC made a number of amendments to the company's cardiology and stroke models. Firstly, the percentage of patients receiving repeat Holter tests after 24 hour Holter monitoring was amended to 27.0% (as per the HES data sent by the company) rather than the 40.3% in the company's cardiology model and 25.9% in the stroke model. This change reduced the cost of the comparator in the cardiology model and very slightly increased it in the stroke model. Secondly, the EAC used NHS reference costs rather than PLICS data for Holter assessment. The EAC believes the NHS reference cost is a more suitable source as PLICS data is based on information gathered voluntarily in a limited number of NHS Trusts. The NHS reference cost is deemed more representative of national practice. This change reduced the cost of the comparator in the stroke and cardiology models. Thirdly, the EAC included outpatient assessment prior to discharge in the costs which increased the cost of the technology.

For the downstream stroke model, the EAC revised the company model to include the cost of anticoagulant therapy, to lower the estimated stroke risk, and, most significantly, to include repeated diagnostic test costs. The overall impact of these changes is that EAC estimates a modest cost increase with Zio XT Service in the compared to either 24-hr Holter monitoring or 7-day CER. However, the EAC notes that the findings of the downstream model are sensitive to assumptions regarding the number of repeat tests under the current care pathway.

The EAC regards the downstream model as the most informative model after inclusion of diagnostic costs. The EAC believes that diagnostic costs, treatment costs for AF and the costs of stroke should be included in the analysis. Hence the EAC suggests that the results from the downstream stroke model should be given most prominence.

On the basis of the revised models, the EAC concludes that Zio XT Service is unlikely to be cost saving when compared with current practice. The revised downstream stroke model incorporates both diagnostic and treatment costs for stroke prevention and stroke. That analysis indicated a modest cost increase of around £20 per patient through the introduction of Zio XT Service (per the downstream stroke model). However, the potential benefits to patients of improved diagnosis of AF are evidently significant and a small additional cost per patient may be justified when set against these benefits.

Key uncertainties remain around the cost evidence. Firstly, the value proposition of the technology relies on the increased diagnostic yield of Zio XT Service in comparison with usual practice. The elevated diagnostic yield is well supported by the body of evidence identified by the EAC, however, there is little published evidence investigating its diagnostic accuracy (compared with 24 hour Holter monitoring against a reference standard). Secondly, there is a lack of clarity around the clinical pathway currently implemented in the NHS. As correctly noted by the company there are a number of different alternatives currently in place. The assumption of no repeat tests with Zio XT Service is plausible but likely to be an underestimate, if only a modest one. The number of repeat tests carried out after an inconclusive/negative test for Holter monitoring has a significant impact on cost but is unstandardised and varies by local protocol and clinical opinion, therefore the figure for this parameter is unclear. In addition, there are some limitations to the supporting evidence. For example, HES data representing repeat testing incorporates various tests including 24 and 48 hour ECG monitoring, ambulatory ECG monitoring and exercise ECG monitoring (NICE TA593). This may artificially increase the estimated number of repeated Holter tests. In addition, the HES

data are not published or peer reviewed and the EAC has only been provided with summary results that don't allow methodological quality assessment.

12 Summary of the combined clinical and economic sections

The clinical evidence consists of 30 studies – only 4 of which are considered pivotal as they are comparative and compare 14 day Zio XT Service with 24 hour Holter monitoring or other standard event monitoring devices. The individual studies are of moderate quality (with some significant flaws), however the populations are heterogenous and therefore results cannot be combined. There is adequate evidence to suggest Zio XT Service increases diagnostic yield compared with 24 hour Holter monitoring. However, there are gaps in evidence regarding its diagnostic accuracy and clinical outcomes.

In total, 5 studies were considered to be relevant to inform the decision problem as they analysed patients with suspected AF after either cryptogenic stroke or TIA, a subgroup outlined in the scope of the decision problem. The studies included 1 economic evaluation (Kaura et al 2019), 2 reports containing resource use or costs associated with the technology (Steinhubl et al 2019; Eysenck et al 2019) containing cost data only, and 2 conference abstracts (Ghosh et al (2018), Chandratheva (2017). On the basis of the revised models, the EAC concludes that Zio XT Service is unlikely to be cost saving when compared with current practice. The downstream stroke model estimates an increased cost of £20 per patient. However, the potential benefits to patients of improved diagnosis of AF are evidently significant and a small additional cost per patient may be justified when set against these benefits.

13 Implications for research

The main gaps in the current evidence would benefit from research into:

- Better understanding of the diagnostic accuracy of Zio XT Service against an appropriate reference standard.
- A better understanding of the clinical pathway for people referred for ambulatory cardiac monitoring.

- Technology utilisation and resulting clinical outcomes to provide greater insight into clinical response to newly-detected arrhythmia.

14 References

Agarwal SK, Chen L, Alonso A, Lopez F, Soliman E, Ndumele C, et al. Arrhythmia burden among community dwelling elderly using two weeks of ambulatory ECG recordings. Journal of the American College of Cardiology. 2015;1):A300.

Barrett PM, Komatireddy R, Haaser S, Topol S, Sheard J, Encinas J, et al. Comparison of 24-hour Holter monitoring with 14-day novel adhesive patch electrocardiographic monitoring. Am J Med. 2014;127(1):95.e11-95.e9.5E17.

Chandratheva A, Pleming J, Dados A, Simister R. New versus conventional noninvasive cadiac monitoring for atrial fibrillation detection in TIA clinic. European Stroke Journal. 2017;2(1_Suppl):117.

Eisenberg E, Steven K. Carlson M, Rahul N. Doshi M, Jerold S. Shinbane M, Philip M. Chang M, Leslie A. Saxon M. Chronic Ambulatory Monitoring: Results of a Large Single-Center Experience. The Journal of Innovations in Cardiac Rhythm Management. 2014;5:1818-23.

Eysenck W, Freemantle N, Sulke N. A randomized trial evaluating the accuracy of AF detection by four external ambulatory ECG monitors compared to permanent pacemaker AF detection. Journal of Interventional Cardiac Electrophysiology. 2019.

Eysenck W, Freemantle N, Waller O, Veasey R, Furniss S, Sulke N. A randomised controlled trial analysing novel ECMS in AF monitoring: The remap-AF trial. Journal of Interventional Cardiac Electrophysiology. 2018;51 (1 Supplement 1):S77.

Eysenck W, Sulke N, Waller O, Shunmugam R, Veasey R, Furniss S. How good are new external loop recorders in AF monitoring? the REMAP-AF trial. Journal of Interventional Cardiac Electrophysiology. 2017;48 (Supplement 1):S79-S80.

Eysenck WJT, Sulke AN, Waller O, Shunmugam SR, Veasey RA, Furniss SS. How good are newelrs in AF monitoring? Europace. 2017;19 (Supplement 1):i29.

Ghosh M, Lochrie N, Mahmood S, Lawrence E, Kee YYK. Improving detection of atrial fibrillation after transient ischaemic attack and stroke. European Stroke Journal. 2018;3 (1 Supplement 1):228.

Go AS, Reynolds K, Yang J, Gupta N, Lenane J, Sung SH, et al. Association of Burden of Atrial Fibrillation With Risk of Ischemic Stroke in Adults With Paroxysmal Atrial Fibrillation: The KP-RHYTHM Study. JAMA Cardiology. 2018;3(7):601-8.

Hall R, John S, Monkhouse C, Rowland E, Chow A, Lowe M, et al. A patient centred evaluation of innovative ambulatory ECG monitoring. Heart. 2019;105 (Supplement 6):A37-A8.

Hannun, A. Y. Pranav, R., Masoumeh, H. et al. (2019). "Cardiologist-level arrhythmia detection and classification in ambulatory electrocardiograms using a deep neural network." Nature Medicine 25(1): 65-69.

Heckbert SR, Austin TR, Jensen PN, Floyd JS, Psaty BM, Soliman EZ, et al. Yield and consistency of arrhythmia detection with patch electrocardiographic monitoring: The Multi-Ethnic Study of Atherosclerosis. Journal of Electrocardiology. 2018;51(6):997-1002.

Kaura A, Sztriha L, Chan FK, Aeron-Thomas J, Gall N, Piechowski-Jozwiak B, et al. Early prolonged ambulatory cardiac monitoring in stroke (EPACS): an open-label randomised controlled trial. Eur J Med Res. 2019;24(1):25-.

Keibel A, Carlson S, Saxon L, Chang P, Doshi R, Shinbane J, et al. Diagnostic yield of a 14 day ambulatory ECG recorder in patients with suspected syncope. Journal of Cardiac Failure. 2015;1):S43.

Mamchur, S.E., Khomenko, E.A., Chichkova, T.Y., et al. (2019). "Noninvasive long-term ECG monitoring vs. loop recorder implantation for the atrial fibrillation management." Annals of Noninvasive Electrocardiology.

Malhotra A, Tahir A, Bulleros P, Fanton Z, Potterton A, Sharma S. The efficacy of the Ziopatch patch- novel leadless prolonged ECG monitoring in athletes. European Journal of Preventive Cardiology. 2018;25 (2 Supplement 1):S94.

Miller JD, Hoang D, Perino A, Azarbal F, Ullal A, Than C, et al. Comparative effectiveness of 14-day Zio patchbased versus 24-hour holter ambulatory ECG monitoring for atrial fibrillation: Insights from an interrupted time series analysis. Heart Rhythm. 2014;1):S230.

Mullis AH, Ayoub K, Shah J, Butt M, Suffredini J, Czarapata M, et al. Fluctuations in premature ventricular contraction burden can affect medical assessment and management. Heart Rhythm. 2019.

Reed MJ, Grubb NR, Lang CC, Gray AJ, Simpson K, MacRaild A, et al. Diagnostic yield of an ambulatory patch monitor in patients with unexplained

syncope after initial evaluation in the emergency department: the PATCH-ED study. Emergency Medicine Journal. 2018;35(8):477.

Rho R, Vossler M, Blancher S, Poole JE. Comparison of 2 ambulatory patch ECG monitors: The benefit of the P-wave and signal clarity. American Heart Journal. 2018;203:109-17.

Rosenberg MA, Samuel M, Thosani A, Zimetbaum PJ. Use of a noninvasive continuous monitoring device in the management of atrial fibrillation: a pilot study. Pacing Clin Electrophysiol. 2013;36(3):328-33.

Salazar MA, Riva G, Shinbane JS, Cesario DA, Cao M, Saxon LA. Efficacy of leadless patch for ambulatory monitoring. Heart Rhythm. 2011;1):S436.

Sattar A, Drigalla D, Higgins S, Schreiber D. Prevalence of arrhythmias in ED patients discharged using a novel ambulatory cardiac monitor. Journal of the American College of Cardiology. 2012;1):E642.

Schreiber D, Sattar A, Drigalla D, Higgins S. Ambulatory cardiac monitoring for discharged emergency department patients with possible cardiac arrhythmias. West J Emerg Med. 2014;15(2):194-8.

Schultz KE, Lui GK, McElhinney DB, Long J, Balasubramanian V, Sakarovitch C, et al. Extended cardiac ambulatory rhythm monitoring in adults with congenital heart disease: Arrhythmia detection and impact of extended monitoring. Congenital Heart Disease. 2019;14(3):410-8.

Solomon MD, Yang J, Sung SH, Livingston ML, Sarlas G, Lenane JC, et al. Incidence and timing of potentially high-risk arrhythmias detected through long term continuous ambulatory electrocardiographic monitoring. BMC Cardiovascular Disorders. 2016;16(1):35.

Steinhubl SR, Waalen J, Edwards AM, Ariniello LM, Mehta RR, Ebner GS, et al. Effect of a Home-Based Wearable Continuous ECG Monitoring Patch on Detection of Undiagnosed Atrial Fibrillation: The mSToPS Randomized Clinical Trial. JAMA. 2018;320(2):146-55.

Su G. Impact of a novel ambulatory ecg monitoring technology in an urban safety net hospital. Heart Rhythm. 2014;1):S262.

Tung CE, Su D, Turakhia MP, Lansberg MG. Diagnostic Yield of Extended Cardiac Patch Monitoring in Patients with Stroke or TIA. Front Neurol. 2015;5:266-.

Turakhia M, Hoang D, Zimetbaum P, Yang F, Froelicher V, Heidenreich P. Clinical experience and diagnostic yield from a national registry of 14-day

ambulatory ECG patch monitoring. Journal of the American College of Cardiology. 2012;1):E646.

Turakhia MP, Hoang DD, Zimetbaum P, Miller JD, Froelicher VF, Kumar UN, et al. Diagnostic Utility of a Novel Leadless Arrhythmia Monitoring Device. American Journal of Cardiology. 2013;112(4):520-4.

Turakhia MP, Ullal AJ, Hoang DD, Than CT, Miller JD, Friday KJ, et al. Feasibility of extended ambulatory electrocardiogram monitoring to identify silent atrial fibrillation in high-risk patients: the Screening Study for Undiagnosed Atrial Fibrillation (STUDY-AF). Clinical Cardiology. 2015;38(5):285-92.

Ullal AJ, Hoang DD, Than C, Heidenreich PA, Miller JD, Friday K, et al. Feasibility of outpatient ambulatory ECG monitoring to screen for silent atrial fibrillation: Pilot findings from screening trial for undiagnosed atrial fibrillation (study-AF). Circulation: Cardiovascular Quality and Outcomes Conference: American Heart Association's Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke. 2013;6(3 SUPPL. 1).

Wineinger NE, Barrett PM, Zhang Y, Irfanullah I, Muse ED, Steinhubl SR, et al. Identification of paroxysmal atrial fibrillation subtypes in over 13,000 individuals. Heart Rhythm. 2019;16(1):26-30.

Yenikomshian M, Jarvis J, Patton C, Yee C, Mortimer R, Birnbaum H, et al. Cardiac arrhythmia detection outcomes among patients monitored with the Zio patch system: a systematic literature review. Current Medical Research & Opinion. 2019;35(10):1659-70.

15 Appendices

15.1 Appendix A

- Clinical and economic evidence

Total records retrieved: 729

Total following deduplication: 533

- 22 records from the company submission
- 9 records, not also in the submission, from the systematic review by Yenikomshian et al (2019)

- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to September 24, 2019
- Search date: 26th September 2019

1	(zio or ziotm or zior or ziopatch or zioxt or (zeus and zio)).mp.	172
2	irhythm*.af.	19
3	1 or 2	185
4	animals/ not (animals/ and humans/)	4585749
5	3 not 4	92
6	(editorial or letter or case report or comment or news).pt.	1947408
7	**5 not 6**	**91**

- Embase 1974 to 2019 Week 38
- Search date: 26th September 2019

1	(zio or ziotm or zior or ziopatch or zioxt or (zeus and zio)).mp.	328
2	irhythm*.af.	84
3	1 or 2	354
4	(animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not ((animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) and exp human/)	5861503
5	3 not 4	273
6	(editorial or letter or case report or comment or news).pt.	1720851
7	5 not 6	267
8	**limit 7 to conference abstract status**	**112**
9	**7 not 8**	**155**

- Cochrane (CDSR and CENTRAL)
- Search date: 26th September 2019

ID	Search	Hits
#1	(zio or ziotm or zior or ziopatch or zioxt or (zeus and zio))	26
#2	irhythm*	8
#3	**#1 or #2**	**27**

- PubMed
- Search date: 26th September 2019

Search	Query	Items found
#19	**Search (#15 or #16 or #17) Filters: Humans Sort by: [pubsolr12]**	**54**
#18	Search (#15 or #16 or #17)	170
#17	Search irhythm*	19
#16	Search (zio[Title/Abstract] AND zeus[Title/Abstract])	1
#15	Search (zio[Title/Abstract] OR ziotm[Title/Abstract] OR zior[Title/Abstract] OR ziopatch[Title/Abstract] OR zioxt[Title/Abstract])	157

- Web of Science
- Search date: 26th September 2019

# 6	**187**	(#1 or #2) not #5 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
# 5	**72**	#3 or #4 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
# 4	31	(#1 or #2) *AND* **DOCUMENT TYPES:** (Proceedings Paper) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
# 3	41	(#1 or #2) *AND* **DOCUMENT TYPES:** (Meeting Abstract) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
# 2	4	TS=(irhythm*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
# 1	258	TS=(zio or ziotm or zior or ziopatch or zioxt or (zeus and zio)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

- ## Ongoing studies

Total records retrieved: 78

Total following deduplication: 50

- 7 records extracting from the CENTRAL results
- 2 records relevant to currently ongoing studies

- ClinicalTrials.gov
- Search date: 26th September 2019

Search string (expert search)

39 Studies found for (**zio OR ziotm OR zior OR ziopatch OR zioxt OR irhythm)**

- WHO ICTRP
- Search date: 26th September 2019

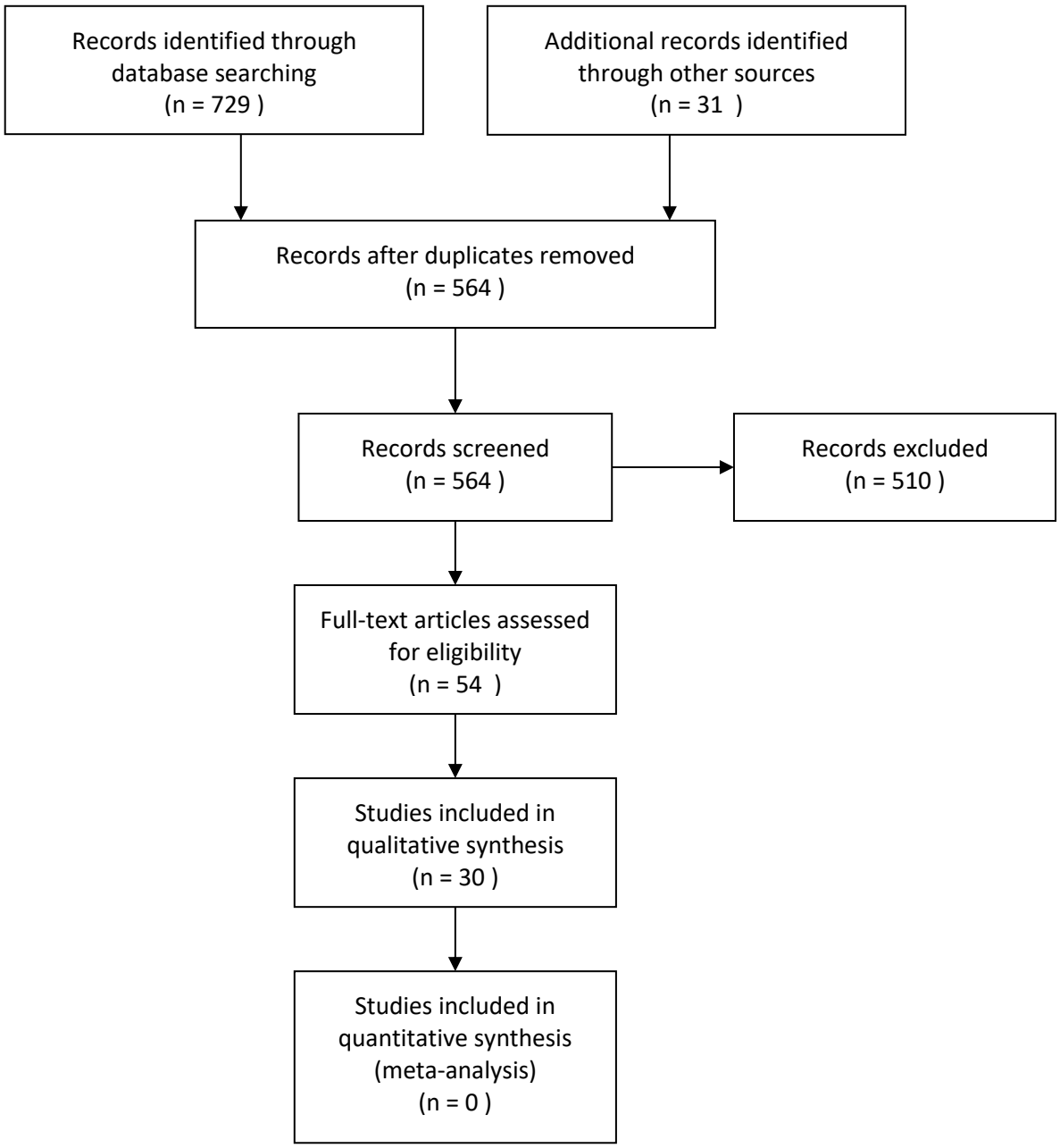
Search string (default search)

32 Studies found for (**zio OR ziotm OR zior OR ziopatch OR zioxt OR irhythm)**

- PROSPERO
- Search date: 26th September 2019

Line	Search for	Hits
#1	zio	0
#2	ziotm	0
#3	zior	0
#4	ziopatch	0
#5	zioxt	0
#6	irhythm	0

PRISMA 2009 Flow Diagram



15.2 Appendix B

Table 12 Methodologies of company and EAC included studies available in full-text

Study and type	population	intervention	comparator	outcomes	Other (follow-up, setting, versions of device etc.)	EAC comment
Comparative						
Barrett 2014 Prospective within subject study	US: 150 Adult Patients: 146 completed April 2012 – July 2012 41.8% men, median age 64 years	Zio XT Service, 14 days	Holter monitor, 24 hours	Arrhythmia event detection over total wear time Arrhythmia event detection at 24 hours Median Wear Time	Some participants had pre-existing arrhythmias and were referred for reasons other than symptomatic arrhythmia. Calculation by authors suggests study was adequately powered. The company partly funded the study. Pre-2018 version of ZEUS system	Comparative Company included EAC included
Eysenck 2019 Prospective within-subject randomised trial	21 UK NHS Participants with DDDRP PPMs 76.2% men, mean age 75 years	Zio XT Service	Nuubo vest Carnation Ambulatory Monitor (CAM) Novacor R-test	AF Burden Detection Accuracy Patient satisfaction Mean Wear Time	No data on when patients were recruited. Patients all had pacemakers of varying brands, first study to compare pacemakers to external monitors.	Comparative Company included EAC included

Study and type	population	intervention	comparator	outcomes	Other (follow-up, setting, versions of device etc.)	EAC comment
Kaura 2019 RCT	UK 116 NHS randomised adult patients: 90 patients completed 90 days follow up February 2016 – February 2017 55 men, 35 women, mean age 70.4 years	Zio XT Service, 14 days	Holter Monitor, 24 hours	Detection of PAF duration ≥ 30s at 90 days Detection of PAF with duration ≥ 30s at 28 days Anticoagulation use at 90 days Second ischaemic stroke or TIA at 90 days Mortailty at 90 days	High participant drop out rate (20%), primarily due to patient refusal for outpatient Holter monitor placement.	Comparative Company included EAC included
Rosenberg 2013 Prospective within subject study	US 75 adult participants with PAF: 74 completed 41 men, 33 women, mean age 64.5	Zio XT Service, 14 days	Holter Monitor, 24 hours	Mean AF burden Agreement during first 24 hours Median time to detection	Pilot study with relatively small sample size. The two groups are described as comparable, but statistical significance quoted as p<0.0001 Investigators reading the Zio Patch wereblinded to the reports of the 24-hour Holter	Comparative Company included EAC included

Study and type	population	intervention	comparator	outcomes	Other (follow-up, setting, versions of device etc.)	EAC comment
				Mean Zio Patch wear time Agreement between devices	monitor. Partly funded by company.	
Non-Comparative						
Camm 2014 Prospective non-comparative observational study	42 adult patients April 2013 to May 2013	Zio XT Service	None	Median 24-hour premature ventricular contraction (PVC) count was 1,090.5 (IQR=1,711). Difference between maximum and minimum PVC count was highly variable with statistically significant inter-day variance in mean hourly PVC counts in		Non-comparative Company Included EAC excluded

Study and type	population	intervention	comparator	outcomes	Other (follow-up, setting, versions of device etc.)	EAC comment
				76% of participants (28/37, 3 cases excluded from analysis due to insufficient data).		
Chen 2015 Prospective cohort study	325 patients were included with mean age of 77 years and 47% were male. 8% had known AF and 4.6% had a history of stroke.	Zio XT Patch monitor	None	Distribution of AF was bimodal: 14% of patients with AF had an AF burden ranging from 1% to 6%, and 12 had an AF burden of 100% (i.e., persistent). Patients with 100% AF burden, but not those with 1% to 6% burden, had lower executive and verbal cognitive test scores then those without AF.		Non-comparative Company Included EAC excluded

Study and type	population	intervention	comparator	outcomes	Other (follow-up, setting, versions of device etc.)	EAC comment
Eisenberg 2014 Retrospective cohort study	524 consecutive US patients May 2010 – January 2013 44% men, mean age 56.7	Zio XT Service	None	Detection of arrhythmias		Non-comparative Company included EAC included
Go 2018 Retrospective cohort study	1965 US adults with PAF	Zio XT Service	None	Analysable wear time Median burden of AF		Non-comparative Company included EAC included
Hannun 2019 Retrospective pilot study	91,232 ECG records from 53,549 patients. Mean age was 69 years, 57% were male.	Zio XT Service	None	The average F1 score, which is the harmonic mean of the positive predictive value and sensitivity, for the DNN (0.837) exceeded that of a consensus committee of expert		Non-comparative Company Included EAC excluded

Study and type	population	intervention	comparator	outcomes	Other (follow-up, setting, versions of device etc.)	EAC comment
				cardiologists (0.780). With specificity fixed at the average specificity achieved by cardiologists, the sensitivity of the DNN exceeded the average cardiologist sensitivity for all rhythm classes.		
Heckbert 2018 Prospective, non-comparative cohort study	1122 US participants wore 1 device for 14 days 580 wore 2 devices for 2 separate 14 day periods	Zio XT Service	None	Median monitoring duration New AF detection Detection agreement between monitoring periods		Non-comparative Company included EAC included
Lutsey 2016	59 patients were randomised ; mean age	Zio XT Patch monitor	None	Zio XT Patch wear time was approximately 13 of the		Non-comparative Company included

Study and type	population	intervention	comparator	outcomes	Other (follow-up, setting, versions of device etc.)	EAC comment
Double-blind pilot randomised trial	was 62 years; 27% were male; 1 discontinued intervention due to side effects and dropped out of study.			requested 14 days at baseline and follow-up. More than 90% of patients wore the patch for ≥ 12 days. 2 patients did not have data for the Zio XT patch at the end of the study, one where the device malfunctioned and one who dropped out of the study.		EAC excluded
Mullis 2018 Prospective cohort study	59 adults with an overall mean PVC burden of ≥5% 81% men, mean age 69 years	Zio XT Service	None	Mean wear time Number of patients in PVC categories		Non-comparative Company included EAC included

Study and type	population	intervention	comparator	outcomes	Other (follow-up, setting, versions of device etc.)	EAC comment
	2016 to 2018					
Muse 2018 Prospective multicenter cohort study	934 patients were recruited from an outpatient clinic setting between set dates. Eligible patients were ≥40 years, able to provide a blood sample, have ≥ 1 clinical risk factor for AF and either present with symptoms of AF or with the first diagnosis of AF on ECG. 30 patients	Zio XT Patch monitor or long-term Holter cardiac rhythm monitor	None	Of 904 participants with samples for genotyping, 85 manifested AF. Participants in the highest quintile of AF GRS were more likely (odds ratio 3.11; 95% CI 1.27–7.58; p = 0.01) to have had an AF event than participants in the lowest quintile after adjusting for age, sex, smoking status, BMI, hypertension, diabetes mellitus, heart failure, and prior myocardial infarction.		Non-comparative Company included EAC excluded

Study and type	population	intervention	comparator	outcomes	Other (follow-up, setting, versions of device etc.)	EAC comment
	were excluded from the final analysis. The mean age for participants with AF (68.5 years [SD 11.2]) was greater than for participants without AF (65.9 years [SD 11.8], p=0.046). Men made up most of the participants with AF (52%) and the minority of participants without AF (36%).					

Study and type	population	intervention	comparator	outcomes	Other (follow-up, setting, versions of device etc.)	EAC comment
Reed 2018 Prospective pilot study Retrospective unmatched cohort	86 UK NHS participants aged 16 years or over presenting with unexplained syncope	Zio XT Service	None	90-day diagnostic yield Median time to clinical detection Patient reported ease of use Patient reported incidence of skin irritation		Non-comparative Company included EAC included
Rho 2018 Prospective within participant study	30 consecutive US patients 66.6% Men, mean age 73.1	Zio XT Service	Carnation Ambulatory Monitoring (CAM)	Total arrhythmias recorded Physiologist reported clarity of ECG		Comparative, but not with Holter Company not included EAC included
Schreiber 2014 Prospective observational study	174 US Adults with suspected arrhythmia February 2011 – February 2012	Zio XT Service	None	median device wear time Diagnostic yield Median time to first arrhythmia Median time-to-first		Non-comparative Company included EAC included

Study and type	population	intervention	comparator	outcomes	Other (follow-up, setting, versions of device etc.)	EAC comment
	45% men, mean age 52.2			symptomatic event		
Schultz 2019 Retrospective cohort study	314 US adults with congenital heart disease 39% men, median age 31 June 2013 – May 2016	Zio XT Service	None	Incidence of significant arrhythmia Number of clinical management changes		Non-comparative Company included EAC included
Steinhubl 2018 Randomised Cohort Trial with an observational matched cohort	1738 US adults suspected of having undiagnose d AF and 3476 matched controls Mean age 72.4 years, 38.6% female	Zio XT Service	None	New AF detected within 4 months		Non-comparative Company included EAC included

Study and type	population	intervention	comparator	outcomes	Other (follow-up, setting, versions of device etc.)	EAC comment
	November 2015 – October 2016					
Solomon 2016 Retrospective cohort study	122,815 Zio recordings from 122,454 patients between November 2011 and December 2013. 53% women, 48.8% < 65 years	Zio XT Service	None	Wear Time Rate of high-risk arrhythmia detection Rate of ventricular arrhythmia detection Diagnostic yield Time-to-first-event		Non-comparative Company included EAC included
Tung 2015 Retrospective cohort study	1171 US reports from patients with history of stroke or TIA January 2012 to June 2013	Zio XT Service	None	Mean wear time Median wear time AF detection Mean duration before first PAF		Non-comparative Company included EAC included

Study and type	population	intervention	comparator	outcomes	Other (follow-up, setting, versions of device etc.)	EAC comment
	55% men, mean age 67.9 years					
Turakhia 2013 Retrospective cohort study	26751 consecutive US patients January 2011 – December 2011 45.5% men mean age 60.2 years	Zio XT Service	None	Mean wear time Mean time to first arrhythmia Diagnostic yield		Non-comparative Company included EAC included
Turakhia 2015 Prospective cohort study	79 US patients enrolled, 75 completed 100% men, mean age 69 years	Zio XT Service	None	Arrhythmias detected AF detected		Non-comparative Company included EAC included
Wineinger 2019 Retrospective cohort study	12993 US individuals with PAF 60% men, mean age 69 years	Zio XT Service	None	Rate of PAF Average duration of PAF		Non-comparative Company included EAC included

Table 13 Summary of the strengths and weaknesses of the trial incorporating internal and external validity

Kaura 2019		
	Strengths	**Weaknesses**
Study design	Prospective Randomised controlled trial	Open-label
Patient selection	UK NHS population	Specific patient group (ischaemic non-lacunar stroke or TIA within the past 72 h), limits generalisability
Randomisation	Generally well matched baseline patient characteristics	-
Blinding	-	No blinding - not feasible to blind patients or treating/assessing clinicians. Moderate to high risk of performance bias.
Patient attrition	Reasons for patient withdrawal documented.	High drop-out rate (20%) Moderate risk of attrition bias.
Reporting of outcomes	Detection of PAF was measured at multiple time points An economic evaluation is reported	No patient-related outcomes were reported No details of clinical utility or resource use Economic evaluation is based on a large number of assumptions
Statistical analysis	Power calculation for sample size for primary outcome performed.	The study is underpowered.
Study company	Funded by an investigator-led research grant	-

Study identification **Kaura 2019**					
Guideline topic: Zio XT Service	**Review question no: DHT 005**				
Checklist completed by: JE					
		Circle or highlight one option for each question:			
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors	Yes	~~No~~	~~Unclear~~	Randomly assigned in 1:1 ratio using a computerised black randomisation generator
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	~~No~~	~~Unclear~~	Randomisation generator was stratified for age, gender and history of hypertension
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	~~No~~	~~Unclear~~	Baseline characteristics were comparable between patients with different treatments from companies
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	~~Unclear/unknown risk~~	~~High risk of bias~~			
Likely direction of effect: N/A					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	~~Yes~~	~~No~~	Unclear	No information is given regarding patient care
B2	Participants receiving care were kept 'blind' to treatment allocation	~~Yes~~	No	~~Unclear~~	Not feasible to blind participants
B3	Individuals administering care were kept 'blind' to treatment allocation	~~Yes~~	No	~~Unclear~~	Not feasible to blind those administering care

Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect? Paper does not report this detail.					
~~Low risk of bias~~	~~Unclear/unknown risk~~	High risk of bias			
Likely direction of effect: not known.					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	~~No~~	~~Unclear~~	Patients in both study arms were followed up for 90 days, without direct contact by the research team.
C2	**a. How many participants did not complete treatment in each group?** 13 in treatment group, 13 in the comparator group				
	b. The groups were comparable for treatment completion	Yes	~~No~~	~~Unclear~~	N/A
C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data	Yes	~~No~~	~~Unclear~~	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	~~No~~	~~Unclear~~	90 days
D2	The study used a precise definition of outcome	~~Yes~~	~~No~~	Unclear	Definition of PAF unclear
D3	A valid and reliable method was used to determine the outcome	~~Yes~~	~~No~~	Unclear	Not reported
D4	Investigators were kept 'blind' to participants' exposure to the intervention	~~Yes~~	No	~~Unclear~~	No blinding.

D5	Investigators were kept 'blind' to other important confounding and prognostic factors	~~Yes~~	~~No~~	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					

Study identification **Barrett (2014)**					
Guideline topic: Zio XT Service	**Review question no: DHT 005**				
Checklist completed by: KG					
		Circle or highlight one option for each question:			
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors	Yes	~~No~~	~~Unclear~~	Each participant acted as their own control subject. Wore both Holter and Zio XT Service.
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	~~No~~	~~Unclear~~	Each participant acted as their own control subject. Wore both Holter and Zio XT Service.
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	~~No~~	~~Unclear~~	Each participant acted as their own control subject. Wore both Holter and Zio XT Service.
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					

Low risk of bias	~~Unclear/unknown risk~~	~~High risk of bias~~			
Likely direction of effect: N/A					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	~~No~~	~~Unclear~~	Each participant acted as their own control subject. Wore both Holter and Zio XT Service.
B2	Participants receiving care were kept 'blind' to treatment allocation	~~Yes~~	No	~~Unclear~~	Not feasible to blind participants
B3	Individuals administering care were kept 'blind' to treatment allocation	~~Yes~~	No	~~Unclear~~	Not feasible to blind those administering care
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect? Paper does not report this detail.					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	~~No~~	~~Unclear~~	Total wear time (24 hours and 14 days)
C2	**a. How many participants did not complete treatment in each group?** 150 patients were enrolled, and 4 were lost to follow-up, 3 in the adhesive monitoring patch group and 1 in the Holter monitoring group				
	b. The groups were comparable for treatment completion	Yes	~~No~~	~~Unclear~~	N/A
C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data	Yes	~~No~~	~~Unclear~~	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	~~Unclear/unknown risk~~	~~High risk of bias~~			

Likely direction of effect: not known.					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	~~No~~	~~Unclear~~	Total wear time (24 hours and 14 days)
D2	The study used a precise definition of outcome	Yes	~~No~~	~~Unclear~~	Arrhythmia events were defined as detection of any 1 of 6 arrhythmias
D3	A valid and reliable method was used to determine the outcome	~~Yes~~	~~No~~	Unclear	Not reported
D4	Investigators were kept 'blind' to participants' exposure to the intervention	~~Yes~~	No	~~Unclear~~	No blinding.
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	~~Yes~~	~~No~~	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					

Study identification **Eysenck 2019**					
Guideline topic: Zio XT Service	**Review question no: DHT 005**				
Checklist completed by: KG					
		Circle or highlight one option for each question:			
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors	Yes	~~No~~	~~Unclear~~	All participants received all interventions/comparators.

A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	~~No~~	~~Unclear~~	Each participant acted as their own control subject, wore every ECM for 2 weeks in randomised order.
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	~~No~~	~~Unclear~~	Each participant acted as their own control subject, wore every ECM for 2 weeks in randomised order.
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	~~Unclear/unknown risk~~	~~High risk of bias~~			
Likely direction of effect: N/A					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	~~No~~	~~Unclear~~	Each participant acted as their own control subject, wore every ECM for 2 weeks in randomised order.
B2	Participants receiving care were kept 'blind' to treatment allocation	~~Yes~~	No	~~Unclear~~	Not feasible to blind participants
B3	Individuals administering care were kept 'blind' to treatment allocation	~~Yes~~	No	~~Unclear~~	Not feasible to blind those administering care
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect? Paper does not report this detail.					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	~~No~~	~~Unclear~~	Each participant acted as their own control subject. Mean study duration 77 days.
C2	**a. How many participants did not complete treatment in each group?** None.				
	b. The groups were comparable for treatment completion	Yes	~~No~~	~~Unclear~~	N/A

C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data	Yes	~~No~~	~~Unclear~~	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	~~Unclear/unknown risk~~	~~High risk of bias~~			
Likely direction of effect: not known.					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	~~No~~	~~Unclear~~	Mean 77 days
D2	The study used a precise definition of outcome	~~Yes~~	~~No~~	Unclear	Definition of AF unclear
D3	A valid and reliable method was used to determine the outcome	~~Yes~~	~~No~~	Unclear	Not reported
D4	Investigators were kept 'blind' to participants' exposure to the intervention	~~Yes~~	No	~~Unclear~~	No blinding.
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	~~Yes~~	~~No~~	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					

Study identification

Rosenberg (2013)					
Guideline topic: Zio XT Service	**Review question no: DHT 005**				
Checklist completed by: KG					
		Circle or highlight one option for each question:			
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors	Yes	~~No~~	~~Unclear~~	Each participant acted as their own control subject. Wore both Holter and Zio XT Service.
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	~~No~~	~~Unclear~~	Each participant acted as their own control subject. Wore both Holter and Zio XT Service.
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	~~No~~	~~Unclear~~	Each participant acted as their own control subject. Wore both Holter and Zio XT Service.
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	~~Unclear/unknown risk~~	~~High risk of bias~~			
Likely direction of effect: N/A					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	~~No~~	~~Unclear~~	Each participant acted as their own control subject. Wore both Holter and Zio XT Service.
B2	Participants receiving care were kept 'blind' to treatment allocation	~~Yes~~	No	~~Unclear~~	Not feasible to blind participants
B3	Individuals administering care were kept 'blind' to treatment allocation	~~Yes~~	No	~~Unclear~~	Not feasible to blind those administering care
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect? Paper does not report this detail.					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			

Likely direction of effect: not known.					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	~~No~~	~~Unclear~~	Total wear time (24 hours and 14 days)
C2	**a. How many participants did not complete treatment in each group?** 1 of 75 people				
	b. The groups were comparable for treatment completion	Yes	~~No~~	~~Unclear~~	N/A
C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data	Yes	~~No~~	~~Unclear~~	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	~~No~~	~~Unclear~~	Total wear time (24 hours and 14 days)
D2	The study used a precise definition of outcome	~~Yes~~	~~No~~	Unclear	Definition of AF unclear
D3	A valid and reliable method was used to determine the outcome	~~Yes~~	~~No~~	Unclear	Not reported
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	~~No~~	~~Unclear~~	Investigators reading the Zio Patch were blinded to the reports of the 24-hour Holter monitor.
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	~~Yes~~	~~No~~	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					

~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~
Likely direction of effect: not known.		

15.3 Appendix C

Table 14 Ongoing Studies

Principal investigator, and location	Year (expected completion date)	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention (and version(s))	Comparator(s)	Outcomes
Louise Bowman, Professor of Medicine and Clinical Trials, and Honorary Consultant Physician (Lipidology), University of Oxford [www.amalfitrial.org]	Primary outcome will be analysed 2.5 years after randomization (approx. mid-2022) and the secondary outcome will be analysed 5 years post-randomization (approx. end of 2024/early 2025).	Randomised controlled trial	High risk individuals with a CHA2DS2-VASc score ≥ 3 (men) or ≥ 4 (women), aged ≥ 65 years without known atrial fibrillation (AF) identified from primary care records. Enrolling 2500; including 1250 randomized to the Zio XT Patch and 1250 in the control arm.	The intervention group will receive 2 weeks of continuous non-invasive ECG monitoring using the Zio XT Patch compared to usual care on rates and time diagnosed with AF over a follow up period of 5 years.	Usual care	Proportion of participants diagnosed with AF compared to usual care at 2.5 years of follow up.
David J. Gladstone, MD PhD FRCPC, Sunnybrook	2019	SCREEN-AF is an investigator-	The trial targets patients aged 75	Eligible participants will	The control group will receive	New diagnosis of ECG-confirmed atrial fibrillation or

Research Institute, University of Toronto [NCT02392754]		initiated, multicentre, open-label, two-group randomised controlled trial investigating non-invasive, home-based AF screening. Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Screening	years or older with a history of hypertension and without known AF who would be potential anticoagulant candidates if AF were detected. Eligible participants will be recruited from primary care practices. 856 study participants enrolled.	be randomly allocated (1:1) to one of two groups: control or intervention. The intervention group will undergo ambulatory screening for AF with a 2-week continuous ECG patch monitor (Zio XT Service) worn at baseline and again at 3 months, in addition to standard care for 6 months (including a pulse check and heart auscultation by a physician at baseline and 6 months). The intervention group will also	standard care for 6 months (including a pulse check and heart auscultation by a physician at baseline and 6 months).	flutter within 6 months post randomisation, defined as at least one episode of continuous AF >5 minutes (or AF documented on 2 separate 12-lead ECGs >5 minutes apart).

				receive a home BP monitor with automatic AF detection capability to be used twice daily for 2 weeks during the ECG monitoring blocks.		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

Zio XT Service for detecting cardiac arrhythmias

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company submission of evidence and with the EAC assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This report contains information that has been supplied in confidence and will be redacted before publication. This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- Appendix D: Decision problem and claimed benefits

1 The technology

Zio XT ECG monitoring service (Zio XT Service, iRhythm Technologies) is a remote cardiac monitoring system used to detect cardiac arrhythmias. It is comprised of 3 components:

- Zio XT biosensor: a wearable single lead ambulatory electrocardiogram (ECG)
- ZEUS: a proprietary, regulated software platform and online portal that stores, analyses and sorts the ECG data to generate a report of the findings
- Zio XT technical report: a clinically actionable summary of the recorded ECG data

The Zio XT Service is intended to replace or enhance the current assessment pathway for cardiac arrhythmia detection in people with palpitations, fainting (syncope) and suspected cardiac arrhythmia. The adhesive Zio XT biosensor is placed on the person's left upper chest and records a continuous beat-to-beat ECG for up to 14 days. The device is designed to facilitate patient compliance and thereby improve data collection. Without external leads or wires, noise artefacts are reduced in the data and the wearer may go about normal daily activities, including light exercise or showering, without required monitor maintenance. Each Zio XT biosensor is intended for single-patient use. After the monitoring period is completed, the wearer removes the biosensor and sends it to the company by freepost. The ECG recordings are analysed using the artificial intelligence led algorithm within ZEUS and overseen by accredited cardiac physiologists. A technical report is produced, containing information regarding arrhythmia episodes, wear and analysis time and patient-captured events, and is sent to the prescribing clinician for final analysis and interpretation. There are no patient identifiers in or on the Zio XT Patch and data cannot be accessed if the Zio XT Patch were to be physically intercepted.

For the Evidence Standards Framework for digital health technologies, Zio XT Service is classified as an active monitoring technology and so has a tier 3b evidence level.

The device is a Class IIa CE marked device. The device was originally approved on the on 2 December 2014 and last amended on 26 November 2019. The CE marking is valid until May 2024. iRhythm Technologies is also registered with the CQC since July 2018.

2 Proposed use of the technology

2.1 Disease or condition

Cardiac arrythmia covers a number of conditions in which the heartbeat is irregular, too fast or too slow. Types of arrythmias are categorised by where they originate in the heart (atria or ventricles) and whether they increase (tachycardia) or decrease the heart rate (bradycardia). Important examples of cardiac arrythmia include atrial fibrillation, supraventricular tachycardia, bradycardia, heart block and ventricular fibrillation (NHS, 2018).

2.2 Patient group

Zio Service is intended for use in people suspected of having cardiac arrhythmia, specifically those with symptoms or suspected arrhythmic episodes more than 24 hours apart. Common symptoms include palpitations, dizziness or light-headedness (presyncope) and fainting (syncope) and are known to account for a large number of emergency presentations each year in the UK

2.3 Current management

NICE's guidelines on transient loss of consciousness ('blackouts') in over 16s and guidelines on managing atrial fibrillation provide recommendations on current methods of arrhythmia detection.

The NICE guideline on transient loss of consciousness ('blackouts') in over 16s, recommends recording a 12-lead ECG using automated interpretation as

the initial assessment. All people with transient loss of consciousness (TLoC) should be referred for specialist cardiovascular assessment, except those with a firm diagnosis after initial assessment of uncomplicated faint, situational syncope or orthostatic hypotension, or people whose presentation is strongly suggestive of epileptic seizure. For people with a suspected cardiac arrhythmic cause of syncope, the guideline recommends offering an ambulatory ECG. The type of device should be chosen on the basis of the patient's history and frequency of TLoC. Holter monitoring (up to 48 hours if necessary) is recommended in people who have TLoC at least several times a week. In those with TLoC every 1 to 2 weeks an external event recorder should be offered. An implantable event recorder should be offered to people with infrequent TLoC (less than once every 2 weeks).

The NICE guideline on managing atrial fibrillation recommends performing manual pulse palpation to assess for the presence of an irregular pulse in people presenting with any of the following:

- breathlessness/dyspnoea
- palpitations
- syncope/dizziness
- chest discomfort
- stroke/transient ischaemic attack

It is recommended that an ECG be performed in all people, whether symptomatic or not, in whom atrial fibrillation is suspected because an irregular pulse has been detected. Arrhythmias may be missed by a 12-lead ECG in people with paroxysmal AF (that is, intermittent atrial fibrillation) because of the occasional nature of the arrhythmic episodes. If arrhythmia is not detected on the initial 12-lead ECG and further assessment of suspected paroxysmal atrial fibrillation is needed, ambulatory ECG monitoring is recommended. The choice of monitor used depends on symptoms and symptom frequency. The guideline recommends the following:

- use a 24-hour ambulatory ECG monitor (such as a Holter monitor) in people with suspected asymptomatic episodes or symptomatic episodes less than 24 hours apart
- use an event recorder ECG (which can be external or implantable) in people with symptomatic episodes more than 24 hours apart.

2.4 Proposed management with new technology

Zio Service would be used for monitoring up to a 14-day period in place of current methods of cardiac event detection, such as Holter monitoring or event recording (external or implantable) in people suspected of having cardiac arrhythmia. The use of the Zio Service would be prescribed by a clinician, most often a cardiologist or GP, in primary, secondary or tertiary care. It may also be prescribed by a stroke clinician or neurologist.

3 Company claimed benefits and the decision problem

Details of the company's claimed benefits and the decision problem are described in Appendix D. The company submission proposed some variations to the decision problem, including minor changes to the comparator, subgroups to be considered and outcomes. The company preferred the technology to be referred to as the Zio XT Service. The proposed variations to the decision problem are described in table 1 of the assessment report (page 9), along with the EAC's views of these variations. The EAC agreed with the company removing implantable cardiac monitors as a comparator because they are rarely used as first line monitors. It also agreed with the company that traditional ECG monitors require shaving for electrode placement, similar to that required for Zio XT service.

4 The evidence

4.1 Summary of evidence of clinical benefit

The company presented 22 full text studies (4 comparative and 18 non-comparative) with Zio XT Service as an intervention. The company included

several other studies in their submission however these were not considered by the EAC as they were on a wide range of ambulatory cardiac monitors and were not specific to Zio XT Service.

The EAC undertook their own literature search and identified 30 relevant clinical studies. This comprised of 16 of the 22 studies submitted by the company, as well as an additional full text study and 13 conference abstracts (see table 1 for details). The rationale for the selection of these studies is in section 4.1 and 4.2 of the EAC assessment report.

Table 1 Included studies and excluded studies

Studies included by both EAC and company	
Publication and study design	16 studies included by both: • 1 UK-based RCT (Kaura et al. 2019) • 3 prospective within-subject comparative studies (Barrett et al. 2014, Eysenck et al. 2019, Rosenberg et al. 2013) • 5 prospective non-comparative studies (Heckbert et al. 2018, Reed et al. 2018, Schreiber et al. 2014, Steinhubl et al. 2018, Turakhia et al. 2015) • 7 retrospective non-comparative studies (Eisenberg et al. 2014, Go et al. 2018, Schultz et al. 2019, Solomon et al. 2016, Tung et al. 2015, Turakhia et al. 2013, Wineinger et al. 2019)
Studies in submission excluded by EAC	
Publication and study design	6 studies were excluded by the EAC due to the population and/or outcomes not being relevant to the decision problem: • 1 randomised trial (Lutsey et al. 2018) • 1 validation study (Hannun et al. 2019) • 1 prospective observational study (Camm et al. 2015) • 3 prospective cohort studies (Chen et al. 2015, Mullis et al. 2019, Muse et al. 2018)
Studies not in submission included by EAC	
Publication and study design	• Prospective within participant study (Rho et al. 2018) • 13 abstracts (Agarwal et al. 2015, Chandratheva et al. 2017, Ghosh et al. 2018, Hall et al. 2019, Keibel, et al. 2015, Malhotra et al. 2018, Miller et al. 2014, Norby et al. 2018, Salazar et al. 2011, Sattar et al.

	2012, Su et al. 2014, Turakhia et al. 2012, Ullal et al. 2013)

The EAC considered the 4 comparative studies to be pivotal to the decision problem (see table 2 for details). A multi-centre UK RCT (Kaura et al. 2019) was considered to be the highest quality study. The study compared the diagnostic yield of 14-day Zio XT Service with 24-hour Holter monitoring in a stroke/TIA population (n = 160). There was a high withdrawal rate because of 20% of the participants refusing to have the 24-hour Holter monitor applied, and this may have biased results. Calculation by authors suggests the study was adequately powered for the primary outcome. However, the EAC carried out an independent power analysis and found the RCT likely to underpowered (0.56) because of the high withdrawal rate. The EAC judged the other 3 comparative studies to be of adequate quality. Neither the company or the EAC did a meta-analysis because they considered the evidence to be heterogeneous in terms of populations, methodology, comparators, and outcomes reported.

The EAC did not consider that the non-comparative observational studies or those reported as abstracts provided sufficient information to draw conclusions about the effectiveness of Zio XT Service. The EAC also reviewed the ongoing data collection available from the Zio XT Service Evaluation. It judged that this data are sufficient to demonstrate the ongoing acceptability, usage and value of the technology however further information is required from the patient's clinician and hospital record plus appropriate follow-up.

Three of the 4 comparative studies compared 14-day Zio XT Service with 24-hour Holter monitor (Barrett et al. 2014, Kaura et al. 2019, Rosenberg et al. 2013) and 1 compared it with an external loop recorder (Novacor R-test; Eysenck et al. 2019). The populations in these studies were heterogenous, differing in underlying risk factors and co-morbidities. Study populations included patients with recent stroke or TIA, people with pacemakers or diagnosed atrial fibrillation, and people with suspected arrhythmia. However,

despite the heterogeneity, results consistently indicated that 14-day Zio XT Service has increased diagnostic yield compared with 24-hour Holter monitor over total wear time. Two of the studies were conducted in the UK (Kaura et al. 2019 and Eysenck et al. 2019). The EAC noted that patient compliance for Zio XT Service appears high, with median wear time ranging from 10.8 days (Rosenberg et al. 2013) to 12.8 days (Eysenck et al. 2019) out of a scheduled 14 days. Only Barrett et al. (2014) provided a comparison of patient experience, reporting that 93.7% participants found the monitoring patch comfortable to wear compared with 51.7% for the Holter monitor.

In conclusion the EAC considered that there is adequate evidence to suggest Zio XT Service increases diagnostic yield compared with 24-hour Holter monitoring. However it considered that there are gaps in evidence regarding its diagnostic accuracy and clinical outcomes. Clinical expert opinion suggested that there may be no significant difference in accuracy between Zio XT Service and Holter monitoring.

NICE developed a patient survey to gather patient experience using Zio XT Service. There were 26 respondents (mean age: 56.7 years, 58% female and 42% male) and the results are summarised in the patient survey report. The results showed a mixed response regarding the comfort of wearing the patch, however 85% wore the patch for the full time it was prescribed (usually 14 days) and the majority of the responders stated that wearing the Zio patch did not prevent them taking part in normal activities. The majority of respondents did not experience side effects from using the device (with the exception of 4 respondents who experiencing skin irritation). Most responders found the patch easy to apply and remove, and many felt that posting the patch back to the company was straightforward.

Table 2 Summary of key studies

Study name, design and funding	Participants/ population	Intervention & comparator	Outcome measures and follow up	Results	EAC Comments
Kaura et al. (2019) RCT, UK Funded by a research grant. Company provided support but was not involved in study design or conduct of trial.	116 randomised adult patients with an ischaemic non-lacunar stroke or TIA within the past 72 h: 90 patients completed 90 days follow up 55 men, 35 women, mean age 70.4 ± 13.2 years	Intervention: 14-day Zio Service Comparator: 24-hour Holter recording.	Detection of paroxysmal atrial fibrillation (PAF) with duration ≥ 30s at 90 days, Detection of PAF with duration ≥ 30s at 28 days, Anticoagulation use at 90 days, Second ischaemic stroke or TIA at 90 days, mortality at 90 days, economic modelling	Detection of PAF with duration ≥ 30s at 90 days: • Zio Service: 7 (16.3%) • 24-hour Holter: 1 (2.1%) Detection of PAF with duration ≥ 30s at 28 days: • Zio Service: 6 (14.0%) • 24-hour Holter: 1 (2.1%) Anticoagulation use at 90 days: • Zio Service: 7 (16.3%) • 24-hour Holter: 1 (2.1%) Second ischaemic stroke or TIA at 90 days: • Zio Service: 1 (2.3%) • 24-hour Holter: 1 (2.1%) Mortality at 90 days: • Zio Service: 1 (2.3%) • 24-hour Holter: 0 (0) Economic modelling: Zio XT Service would result in 10.8 strokes avoided per year compared with	High participant drop out rate (20%), primarily due to patient refusal for outpatient Holter monitor placement. Experts note that there may be high refusal/drop out for Holter monitoring (although some noted that this rate appears particularly high). It is unclear if this rate is typical of the clinical setting. This study did not directly compare alternative extended monitoring systems like implantable loop recorders. Authors chose short-duration Holter monitoring as a suitable comparator to

				Holter monitoring. Yearly saving in direct medical costs of £113,630, increasing to £162,491 over 5 years.	the Zio XT Service to reflect current clinical practice and for real-world feasibility. The EAC did an independent power calculation and suggests it was underpowered (0.56) due to high drop out rate.
Eysenck et al. (2019) Single centre, prospective study, UK Partly funded by the company	21 participants with DDDRP permanent pacemakers of various brands. 18 participants had Paroxysmal AF and 3 had persistent AF 76.2% men, mean age 75 ± 7 years	14-day Zio XT Service (and 3 other external ambulatory ECG monitors) Comparators: Novacor R-test (clinical standard) Pacemaker (gold standard) Participants wore 4 devices in a randomised order (all for 14-day period), with a minimum of 7-day break between each device.	AF burden, Detection accuracy, Patient satisfaction, Mean patient time expenditure, Total costs.	<u>AF burden (correlation compared with DDDRP permanent pacemakers [R^2], MSE):</u> R-test: 0.029, 1556.1 Zio: 0.99, 0.24 <u>Detection accuracy (OR, Wald CI, p):</u> Zio vs R-test:12.3, 1.4 to 110.3, p = 0.025 (Zio was superior to the Novacor R Test using pacemakers as the reference standard comparator) <u>Patient Satisfaction:</u>	UK study Small population, high percentage males, high mean age Randomised order of devices. Primary outcome is AF burden, but this is only reported via fit-plots, limited data is reported numerically in the paper. The statistical analyses may not be appropriate. Bland-Altman tests may

		Mean patient wear time: • Zio: 307 (95% CI 284.63 to 340.32) hours • R-test: 223.6 (95% CI 178.43 to 268.31) hours (p=0.016)		No significant difference between Zio and R-test in discomfort scores (VAS) Mean Patient Time Expenditure (total time spent travelling to and from hospital, attending appointments and waiting for device return): Zio: 26.5 min (95% CI 20.1–36.0) R-test: 53 min (p<0.0001) Total costs: Zio significantly more expensive than R-test (p<0.0001)	be more appropriate than R-test analyses. Patients all had pacemakers of varying brands, first study to compare pacemakers to external monitors.
Barrett et al. (2014) Single centre, prospective within-participant study, US. Partly funded by company	150 adult patients were enrolled for an evaluation of cardiac arrhythmia: 146 completed (3 in the Zio XT Service group and 1 in the Holter group did not complete). 41.8% men, median age 64 years (range 22-94)	Intervention: 14-day Zio XT Service Comparator: 24-hour Holter recording. All patients wore both devices for the first 24 hours and then continued with Zio Patch.	Arrhythmia event detection over total wear time (primary outcome), arrhythmia event detection at 24 hours, median wear time, patient preference.	Arrhythmia event detection over total wear time (primary outcome): • Zio XT Service: 96 • 24-hour Holter: 61 (p < 0.001) Sixty events were detected by both Holter monitor and Zio Patch. Arrhythmia event detection at 24 hours: • Zio Service: 52 • 24-hour Holter: 61 (p = 0.013).	Some participants had pre-existing arrhythmias and were referred for reasons other than symptomatic arrhythmia. Six types of arrhythmia were included within the study with no breakdown.

				Median wear time: Holter monitor 1.0 days (range, 0.9– 1.0) Zio Patch 11.1 days (range, 0.9–14.0) Patient preference 93.7% (134/143) participants found the monitoring patch comfortable to wear as opposed to 51.7% (74/143) for the Holter monitor.	Calculation by authors suggests study was adequately powered. The company partly funded the study.
Rosenberg et al. (2013) Single centre, prospective within participant study, US Partly funded by the company	75 adult participants enrolled: 74 completed Inclusion: Patients being managed for AF All patients were taking medication (beta blockers, calcium channel blockers, antiarrhymic medication)	14-day Zio XT Service compared with 24-hour Holter recording All patients wore both devices for the first 24 hours and then continued with Zio Patch. Zio mean wear time 10.8 ± 2.8 days	Agreement during the 24-hour period, mean AF burden, changes in clinical classification of the AF over total wear time, median time to detection of first event, mean wear time	Agreement during the 24-hour period All 25 AF episodes recorded on the 24-hour Holter were identified by the Zio Service). Mean AF burden: Zio XT Service: 54.7 ± 41.2% Holter: 58.4 ± 42.7% p<0.0001 *Over total wear time:* Clinical classification of the AF pattern changed as a result of	Pilot study with relatively small sample size. No power calculation reported. The two groups are described as comparable, but statistical significance quoted as p<0.0001 Investigators reading the Zio Patch were blinded to the reports of the 24-hour Holter monitor.

	Recruited between April 2011 and May 2012 41 men, 33 women, mean age 64.5 ± 8.1 years			wearing the Zio Patch in 21 patients There was significant agreement between the two devices (kappa 0.49 ± 0.08, P < 0.01). Median time to detection of first event with Zio Patch: 3.7 days. 90% detected by day 7. Mean Zio Patch wear time: 10.8 ± 2.8 days	Partly funded by company.
Abbreviations: AF, atrial fibrillation; DDDRP, Dual Chamber Rate Adaptive Pacemaker; MSE, mean squared error; PAF, paroxysmal atrial fibrillation; TIA, transient ischemic attack.					

4.2 Summary of economic evidence

The company submission identified a total of 20 economic studies. The EAC excluded 17 of these studies because they did not assess Zio XT Service specifically. The EAC identified 2 additional studies through their own literature search. In total, the EAC considered 5 economic studies to be relevant to the decision problem. These studies analysed patients with suspected AF after either cryptogenic stroke or TIA, a subgroup outlined in the scope of the decision problem. The economic evidence base consisted of:

- 3 published studies containing: a budget impact analysis (Kaura et al. 2019), resource use data (Steinhubl et al. 2019) and cost data only (Eysenck et al. 2019), and
- 2 conference abstracts (Ghosh et al.2018, Chandratheva et al. 2017).

The results of the relevant economic evidence are summarised in section 10.1.2 (table 6) of the EAC assessment report.

The EAC noted that study results were highly heterogenous because of the variability in the design of each of the studies. Cost estimates from 2 of the studies (Eysenck et al. 2019 and Ghosh et al. 2018) suggest the technology is not cost saving among selected comparators (including Holter monitoring). Chandratheva et al. (2017) however, concluded the technology is cost-saving when compared with 72-hour Holter, 3-day E-Patch, and in-clinic monitoring. All 3 studies concluded that Zio XT Service is the most efficient in terms of time from clinic to diagnosis reporting. Kaura et al. (2019) concluded that Zio XT Service is cost-saving against Holter-based strategies when considering the risk of stroke in 1,053 untreated AF patients (a saving of £113,630 in one year and after inclusion of social care costs, cost savings, rose to £466,598 after five years). Steinhubl et al. (2018) found that Zio XT Service increases the health care resource use of AF-related therapeutic interventions but decreases all-cause emergency department visits or inpatient stays. The EAC noted that, although relevant to the decision problem, none of the estimates

from the evidence base were used to populate the company's economic model.

De novo analysis

The company presented 2 separate base-case economic models ('cardiology model' and 'stroke model'). The cardiology model considered a population of patients with symptomatic palpitations or syncope referred to cardiology outpatients for evaluation. The stroke model considered patients who had experienced ischaemic stroke or TIA without current evidence of AF, referred for identification of paroxysmal AF. Both models were cost-minimisation analyses comparing 14-day Zio XT Service with blended strategies based on 24-hour Holter monitor or cardiac event recorder. The models assessed the costs associated with the diagnostic process only. They did not assess the diagnostic performance of the technologies nor consider the resource use or assess the economic consequence of subsequent treatment. The company presented a third model as a scenario analysis which assessed the consequences of the technology's diagnostic yield in comparison to Holter monitors ('stroke downstream model'). It used the same population as the stroke model but extrapolated the economic consequences of the extra risk of recurrent stroke because of delayed or missed diagnosis of AF.

All analyses used a decision tree structure, undertook an NHS perspective and had a time horizon of 1 year. The model structures are shown in [redacted] in section 10.2.1 of the EAC assessment report. The company used clinical opinion to validate the model structure and the approach undertaken. The EAC considered the model structure and time horizon to be acceptable for each model. However, the EAC considered the downstream stroke model to be part of the base-case analysis for the technology, not a scenario analysis.

The company models make a number of assumptions which are discussed in section 10.2.1 of the assessment report. The EAC agreed with most of the assumptions in the cardiology model but it did not consider that an inconclusive result differed from a negative result. The EAC also considered

that an outpatient assessment is required regardless of the results. The EAC accepted all the assumptions in the stroke model except it considered that an outpatient assessment is required regardless of the results. The EAC also revised the downstream stroke model to include the costs associated with the use of anticoagulant therapy and the potential complications associated with their use, and to include repeated diagnostic test costs.

Model clinical parameters

The main clinical parameters driving the company's base case models are the probabilities of each of the devices yielding a positive, negative or inconclusive result and the probability of test repetition. The clinical parameters for the models were either sourced from available literature, extrapolated from clinical evidence or informed by expert advice. A full description of the parameters is outlined in section 10.2.3 of the EAC assessment report.

The company's model estimated a mean of 1.44 additional tests in patients who undergo test repetition. The EAC reviewed the HES data used by the company and calculated that 1.465 additional tests would be used for the 27% of patients who have more than 1 test in 12 months. With the limited data available and using advice from expert advisers about current clinical practice, the EAC also revised the cardiology model to merge negative and inconclusive results.

The EAC agreed with most of the clinical parameters values and sources used by the company for the downstream stroke model. However, the EAC considered that the risk of stroke estimates taken from the EAFT study were not appropriate for the population defined in the decision problem and applied estimates from Diamantopoulos et al. (2016). The EAC also noted that it was unable to assess the methodological quality of the company's analysis of HES data for the impact on stroke risk of the delay between initiating investigation and diagnosis confirmation from the summary provided.

Costs and resource use

The cost parameters of the company base case models include device use costs and the cost of outpatient visits. The base case cost values and sources are shown in table 10 of the EAC assessment report. The EAC agreed with most of the sources used to inform the cost parameters and resource use, with the following exceptions:

- That NHS reference costs for 2017/2018 are a more appropriate source for the cost estimate of Holter use than estimates derived from PLICS and FOI data (£168 instead of £185).

- The EAC included an outpatient assessment after the results from all tests, regardless of the result or technology.

- In the downstream stroke model, the health care costs of managing stroke over 1 year was £13,452, taken from Xu et al. (2018). The EAC agreed with the cost of stroke taken from Xu et al. (2018) however it considered the costs related to the use of anticoagulation therapy and its potential complications should be included. Table 4 summarises the parameters and values used by the EAC.

- ***Table 4 Base case costs***

Parameter	Company base-case	EAC base-case	Source
Cost of Zio XT Service	£310	£310	Company
24-hour Holter use cost	£185.12	£168.12	NHS Reference Costs 2017/2018 and FOI request
CER use cost	£185.12	£168.12	Assumed to be equal to Holter device cost
Implantable loop recorder cost	£3,221	£3,221	NHS Reference Costs 2017/2018 + MIB 141 – Reveal LINQ insertable cardiac monitor (NICE)

Cardiology outpatient visit	£142	£142	NHS Reference Costs 2017/2018
Mean number of additional tests if repetition is decided	1.44	1.465	Data from HES
Cost of stroke	£13,452	£13,452	Xu (2018)
Cost of anticoagulation therapy including cost of bleeds	Not included	£452	NICE Clinical Guideline CG180 Atrial fibrillation: management. Costing report uprated to 2017/18 prices

Results

The company estimates a cost saving from the use of Zio XT Service in each of the 3 models. The EAC estimates a modest cost increase in the revised cardiology model and cost increases in the stroke and downstream stroke models. The company and EAC base case results are presented in table 5.

Table 5 company and EAC base case results

	Company's results			**EAC's results**		
	Intervention arm	**Comparator arm**	**Cost saving per patient**	**Technology**	**Comparator**	**Cost saving per patient**
Cardiology model	£431.33	£516.59	£84.76	£466.78	£465.96	-£0.82
Stroke model	£382.69	£437.97	£55.28	£493.94	£423.13	-£70.81
Downstream stroke model	£1,256.15	£1,332.65	£76.50	£1237.45	£1216.62*	-£20.83

*Results for CER comparator, Holter comparator is more expensive

Sensitivity analysis

The company's one-way sensitivity analysis of the cardiology model showed that Zio XT Service is cost saving was robust to all parameters varied over a range of +/-20% and Zio XT Service is cost saving was sensitive to variation

in the probability of a repeat 24hr Holter or CER after a negative/inconclusive scan.

The EAC undertook one-way sensitivity analysis for each of the 3 models. For the cardiology model, the results are sensitive to the majority of parameters especially the costs of Zio XT Service, the costs of 24hr Holter monitoring and the probability of testing with an implantable loop recorder (ILR). In contrast, the results from the stroke model were robust to parameter uncertainty in one-way sensitivity analysis for all parameters except the cost of Zio service. The breakeven point for the cost of Zio Service is £229.

For the downstream stroke model, the cost of Zio XT Service was almost identical to the cost of 24hr Holter monitoring so the results are sensitive to the majority of model parameters. For the comparison with 7-day CER, the results are sensitive to the costs of Zio Service, the probability that a negative test is repeated, the costs of 7-day CER, the costs of treating stroke and the probability of a stroke with untreated AF.

Scenario analysis

The EAC undertook a scenario analysis for the downstream stroke model in which it assumed that all monitoring is repeated after a negative test. In this scenario, Zio XT Service was cost incurring. Costs were £1,604 for Zio Service compared to £1,395 for CER and £1,422 for Holter monitoring. This scenario shows the substantial impact on costs if all first negative Zio XT Service tests are repeated.

In a second scenario analysis the EAC assumed that monitoring with 24-hr Holter or 7-day CER tests are repeated when a negative test is obtained for the first test, but Zio Service is not repeated. In this scenario Zio Service was cost-savings compared with either 24-her Holter (£1,237 vs £1,422) or 7-day CER (£1,237 vs £1,395).

Additional analyses (see the addendum to the assessment report)

In preparation for the committee meeting, the EAC assumptions used in the modelling were discussed with some of the clinical experts. For the base case analysis, the EAC assumed that all monitoring tests would be followed up with an outpatient visit regardless of findings. Advice from clinical experts regarding follow-up appointments was that variation in practice exists across England, with most centres inform patients and their GPs of negative findings by letter following a negative result from the Zio XT service. In order to test different assumptions regarding outpatient visits following monitoring, the EAC undertook additional sensitivity analysis on all 3 of the EAC revised models. Full details of the assumptions and the results are described in the addendum to the assessment report.

In scenarios in which follow-up outpatient appointments were included for standard care but not for Zio XT Service, Zio XT Service was cost saving across all 3 of the EAC's revised models. However, in scenarios in which outpatient appointments were included or excluded regardless of the type of monitoring, Zio XT Service was frequently, but not always, cost incurring.

5 Ongoing research

The company and EAC identified 2 ongoing studies. Both studies are RCTs which will compare 2 weeks monitoring of the Zio XT Service with standard care (opportunistic screening or pulse check and heart auscultation by a physician). One study is based in Canada and Germany and has enrolled 856 participants aged 75 years or over with a history of hypertension and without known AF. The primary endpoint is the rate of new diagnosis of AF (or flutter) within 6 months of randomisation and is expected to be completed in 2019. The other is a UK-based study which plans to enroll 2,500 people at high-risk for AF. It has a primary endpoint of proportion of participants diagnosed with AF after 2.5 years of follow-up (see section 9.2 of the EAC assessment report for further information).

6 Issues for consideration by the Committee

Clinical evidence

The EAC considered the diagnostic accuracy of Zio XT Service compared with Holter monitoring is unclear. It noted that Rosenberg et al. (2013) reported significant agreement in event detection between Zio XT Service and Holter monitoring. However Holter monitoring had a "performance advantage" in Barrett et al. (2014) due to algorithm misclassification and report reviewer processing errors (the authors note that the service was subsequently corrected). Overall, clinical experts suggested that there may be no significant difference in accuracy between Holter monitoring and Zio XT Service. However, 1 expert also noted that because Holter monitors make use of more leads, they may be more accurate. At technical engagement the company stated that Zio XT is a diagnostic service not device, and that it is the clinician who makes the final diagnosis and so it believes that diagnostic yield is a more relevant measure of effectiveness

It is unclear from the available evidence whether an increase in diagnostic yield with Zio XT Service is associated with improved clinical outcomes. Kaura et al. (2019) reported that a significantly higher proportion of patients in the Zio XT Service arm were taking anticoagulants at 90 days (16.3% vs 2.1% with 24-hour Holter monitoring). The study was, however, underpowered for these outcomes. In Rosenberg (2013) 28.4% of patients had a change in classification of their AF and had their management changed as a result of using the Zio XT Service, with 17.3% having a change in their antiarrhythmic medication and 5.3% changing oral anticoagulant use. The EAC considered that without more information about diagnostic accuracy, it is unclear how appropriate these changes to patient management were. At technical engagement the company stated that, based on results from Kaura et al. (2019), 8 times as many post-stroke patients with AF will be appropriately treated as a result of monitoring with the Zio Service than would be following monitoring with Holter. The company believe that the incremental clinical gain

from treatment is indisputable, given that treating AF in these patients is known to reduce the risk of further stroke/TIA by 60-70%.

The comparative study populations are heterogenous and so no meta-analysis has been possible. The EAC considers the specific populations of some of the studies may limit the generalisability of the results to the broader population of people being referred for ambulatory monitoring in the NHS. In their response to technical engagement the company state that despite the heterogenous nature of the populations studied, there is considerable consistency across the studies in terms of diagnostic yield, and that this suggests results are likely to be generalisable.

Cost evidence

There are uncertainties around the cost evidence. The main areas of uncertainty include:

- The value proposition of Zio XT Service relies on an increased diagnostic yield which is supported by the clinical evidence, however, there is little published evidence investigating the diagnostic accuracy of Zio XT Service compared with 24-hour Holter monitoring against a reference standard.

- There is a lack of certainty around the clinical pathway and variations in clinical practice.

- The assumption of no repeat tests with Zio XT Service is plausible but likely to be an underestimate. The number of repeat tests carried out after an inconclusive/negative test for Holter monitoring has a significant impact on cost. This is unstandardised and appears to vary by local protocol and clinical opinion, making the figure for this parameter unclear. Also, the HES data used for this parameter incorporates various tests (including 24- and 48-hour ECG monitoring, ambulatory ECG monitoring and exercise ECG monitoring [NICE TA593]), so the figure may be an overestimate of the number of repeated Holter tests in the current care pathway.

- The revised downstream stroke model results are dependent on the assumption that conventional testing is repeated for negative tests with a mean of 1.389 tests per patient, whereas Zio XT Service is not repeated after an inconclusive/negative result. The EAC undertook a scenario analysis to explore the impact of this.

- Clinical advice is that outpatient visits are not usually required following a negative result from Zio XT service. The EAC undertook additional analysis to explore the impact of this.

7 Authors

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NICE Medical Technologies Evaluation Programme

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Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- Chalkidou A, Erskine J, Goddard K, et al. Zio XT Service for detecting cardiac arrhythmias, December 2019

B Submissions from the following sponsors:

- iRhythm Technologies Inc

C Related NICE guidance:

Published:

- Atrial fibrillation: management. NICE Clinical guideline CG180 (2014).
- Lead-I ECG devices for detecting symptomatic atrial fibrillation using single time point testing in primary care. NICE diagnostics assessment guidance DG35 (2019).

Under development:

- Atrial fibrillation: management. NICE guideline. Publication expected September 2020.
- Implantable cardiac monitors to detect atrial fibrillation after cryptogenic stroke. NICE diagnostics assessment guidance. Publication expected TBC.

D References

Agarwal SK, Chen L, Alonso A, Lopez F, Soliman E, Ndumele C, et al. Arrhythmia burden among community dwelling elderly using two weeks of ambulatory ECG recordings. Journal of the American College of Cardiology. 2015;1):A300.

Barrett PM, Komatireddy R, Haaser S, Topol S, Sheard J, Encinas J, et al. Comparison of 24-hour Holter monitoring with 14-day novel adhesive patch electrocardiographic monitoring. Am J Med. 2014;127(1):95.e11-95.e9.5E17.

Chandratheva A, Pleming J, Dados A, Simister R. New versus conventional noninvasive cadiac monitoring for atrial fibrillation detection in TIA clinic. European Stroke Journal. 2017;2(1_Suppl):117.

Eisenberg E, Steven K. Carlson M, Rahul N. Doshi M, Jerold S. Shinbane M, Philip M. Chang M, Leslie A. Saxon M. Chronic Ambulatory Monitoring: Results of a Large Single-Center Experience. The Journal of Innovations in Cardiac Rhythm Management. 2014;5:1818-23.

Eysenck W, Freemantle N, Sulke N. A randomized trial evaluating the accuracy of AF detection by four external ambulatory ECG monitors compared to permanent pacemaker AF detection. Journal of Interventional Cardiac Electrophysiology. 2019.

Ghosh M, Lochrie N, Mahmood S, Lawrence E, Kee YYK. Improving detection of atrial fibrillation after transient ischaemic attack and stroke. European Stroke Journal. 2018;3 (1 Supplement 1):228.

Go AS, Reynolds K, Yang J, Gupta N, Lenane J, Sung SH, et al. Association of Burden of Atrial Fibrillation With Risk of Ischemic Stroke in Adults With Paroxysmal Atrial Fibrillation: The KP-RHYTHM Study. JAMA Cardiology. 2018;3(7):601-8.

Hall R, John S, Monkhouse C, Rowland E, Chow A, Lowe M, et al. A patient centred evaluation of innovative ambulatory ECG monitoring. Heart. 2019;105 (Supplement 6):A37-A8.

Heckbert SR, Austin TR, Jensen PN, Floyd JS, Psaty BM, Soliman EZ, et al. Yield and consistency of arrhythmia detection with patch electrocardiographic monitoring: The Multi-Ethnic Study of Atherosclerosis. Journal of Electrocardiology. 2018;51(6):997-1002.

Kaura A, Sztriha L, Chan FK, Aeron-Thomas J, Gall N, Piechowski-Jozwiak B, et al. Early prolonged ambulatory cardiac monitoring in stroke (EPACS): an open-label randomised controlled trial. Eur J Med Res. 2019;24(1):25-.

Keibel A, Carlson S, Saxon L, Chang P, Doshi R, Shinbane J, et al. Diagnostic yield of a 14 day ambulatory ECG recorder in patients with suspected syncope. Journal of Cardiac Failure. 2015;1):S43.

M.A N, Faye L. Norby MR, Ph.D (c), MPH, Aaron Falsom, MD, MPH, Elsayed Z. Soliman, MD, Alvaro Alonso, MD, PhD, Lin Chen, MD and Lin Y. Chen, MD. . Prevalence of subclinical atrial fibrillation in the elderly population: the Atherosclerosis Risk In Communities (ARIC) study. Heart Rhythm. 2018;15(5, Supplement):S388-S487.

Malhotra A, Tahir A, Bulleros P, Fanton Z, Potterton A, Sharma S. The efficacy of the Ziopatch patch- novel leadless prolonged ECG monitoring in athletes. European Journal of Preventive Cardiology. 2018;25 (2 Supplement 1):S94.

Miller JD, Hoang D, Perino A, Azarbal F, Ullal A, Than C, et al. Comparative effectiveness of 14-day Zio patchbased versus 24-hour holter ambulatory ECG monitoring for atrial fibrillation: Insights from an interrupted time series analysis. Heart Rhythm. 2014;1):S230.

Mullis AH, Ayoub K, Shah J, Butt M, Suffredini J, Czarapata M, et al. Fluctuations in premature ventricular contraction burden can affect medical assessment and management. Heart Rhythm. 2019.

Reed MJ, Grubb NR, Lang CC, Gray AJ, Simpson K, MacRaild A, et al. Diagnostic yield of an ambulatory patch monitor in patients with unexplained syncope after initial evaluation in the emergency department: the PATCH-ED study. Emergency Medicine Journal. 2018;35(8):477.

Rho R, Vossler M, Blancher S, Poole JE. Comparison of 2 ambulatory patch ECG monitors: The benefit of the P-wave and signal clarity. American Heart Journal. 2018;203:109-17.

Rosenberg MA, Samuel M, Thosani A, Zimetbaum PJ. Use of a noninvasive continuous monitoring device in the management of atrial fibrillation: a pilot study. Pacing Clin Electrophysiol. 2013;36(3):328-33.

Salazar MA, Riva G, Shinbane JS, Cesario DA, Cao M, Saxon LA. Efficacy of leadless patch for ambulatory monitoring. Heart Rhythm. 2011;1):S436.

Sattar A, Drigalla D, Higgins S, Schreiber D. Prevalence of arrhythmias in ED patients discharged using a novel ambulatory cardiac monitor. Journal of the American College of Cardiology. 2012;1):E642.

Schreiber D, Sattar A, Drigalla D, Higgins S. Ambulatory cardiac monitoring for discharged emergency department patients with possible cardiac arrhythmias. West J Emerg Med. 2014;15(2):194-8.

Schultz KE, Lui GK, McElhinney DB, Long J, Balasubramanian V, Sakarovitch C, et al. Extended cardiac ambulatory rhythm monitoring in adults with congenital heart disease: Arrhythmia detection and impact of extended monitoring. Congenital Heart Disease. 2019;14(3):410-8.

Solomon MD, Yang J, Sung SH, Livingston ML, Sarlas G, Lenane JC, et al. Incidence and timing of potentially high-risk arrhythmias detected through long term continuous ambulatory electrocardiographic monitoring. BMC Cardiovascular Disorders. 2016;16(1):35.

Steinhubl SR, Waalen J, Edwards AM, Ariniello LM, Mehta RR, Ebner GS, et al. Effect of a Home-Based Wearable Continuous ECG Monitoring Patch on Detection of Undiagnosed Atrial Fibrillation: The mSToPS Randomized Clinical Trial. JAMA. 2018;320(2):146-55.

Su G. Impact of a novel ambulatory ecg monitoring technology in an urban safety net hospital. Heart Rhythm. 2014;1):S262.

Tung CE, Su D, Turakhia MP, Lansberg MG. Diagnostic Yield of Extended Cardiac Patch Monitoring in Patients with Stroke or TIA. Front Neurol. 2015;5:266-.

Turakhia M, Hoang D, Zimetbaum P, Yang F, Froelicher V, Heidenreich P. Clinical experience and diagnostic yield from a national registry of 14-day

ambulatory ECG patch monitoring. Journal of the American College of Cardiology. 2012;1):E646.

Turakhia MP, Hoang DD, Zimetbaum P, Miller JD, Froelicher VF, Kumar UN, et al. Diagnostic Utility of a Novel Leadless Arrhythmia Monitoring Device. American Journal of Cardiology. 2013;112(4):520-4.

Turakhia MP, Ullal AJ, Hoang DD, Than CT, Miller JD, Friday KJ, et al. Feasibility of extended ambulatory electrocardiogram monitoring to identify silent atrial fibrillation in high-risk patients: the Screening Study for Undiagnosed Atrial Fibrillation (STUDY-AF). Clinical Cardiology. 2015;38(5):285-92.

Ullal AJ, Hoang DD, Than C, Heidenreich PA, Miller JD, Friday K, et al. Feasibility of outpatient ambulatory ECG monitoring to screen for silent atrial fibrillation: Pilot findings from screening trial for undiagnosed atrial fibrillation (study-AF). Circulation: Cardiovascular Quality and Outcomes Conference: American Heart Association's Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke. 2013;6(3 SUPPL. 1).

Wineinger NE, Barrett PM, Zhang Y, Irfanullah I, Muse ED, Steinhubl SR, et al. Identification of paroxysmal atrial fibrillation subtypes in over 13,000 individuals. Heart Rhythm. 2019;16(1):26-30.

Yenikomshian M, Jarvis J, Patton C, Yee C, Mortimer R, Birnbaum H, et al. Cardiac arrhythmia detection outcomes among patients monitored with the Zio patch system: a systematic literature review. Current Medical Research & Opinion. 2019;35(10):1659-70.

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Anthony Shannon
Highly Specialist Cardiac Physiologist, Liverpool Heart and Chest Hospital

Gregory Lip
Price-Evans Chair of Cardiovascular Medicine, University of Liverpool,

Dr Matthew J Reed
Consultant and NRS Fellow in Emergency Medicine, NHS Lothian,

James Teo
Consultant Stroke Neurologist & Clinical Director of Data Science, Kings College Hospital NHS Foundation Trust,

Jacqueline Colwill
Cardiac Physiologist and Cardiology Service lead, South Tyneside and Sunderland NHS Foundation Trust

Joseph Mills
Consultant Cardiologist, Liverpool Heart & Chest NHS FT

Mark A Tanner
Consultant Cardiologist and Honorary Clinical Senior Lecturer, Western Sussex Hospitals NHS Trust and Imperial College London

Please see the clinical expert statements included in the committee pack for full details.

Appendix C: Comments from patient organisations

The following patient organisations were contacted:

- Arrhythmia Alliance
- Atrial Fibrillation Association
- British Cardiac Patients Association (BCPA)
- British Heart Foundation
- Cardiac Risk in the Young (CRY)
- Cardiovascular Care Partnership
- Children's Heart Federation
- Down's Heart Group
- Heart Rhythm Alliance
- Heart Valve voice
- Pumping Marvellous
- The Ashley Jolly SADS Trust (SADS UK)

Responses were received from Arrhythmia Alliance and Atrial Fibrillation Association, please see the responses in the pack for full details.

Appendix D: decision problem from scope

Population	Adults (18 years or older) with suspected cardiac arrhythmia referred for ambulatory ECG monitoring
Intervention	Zio ECG monitoring service (Zio Service)
Comparator(s)	• Current pathway for ambulatory cardiac arrhythmia detection, which includes Holter and/or event monitoring (external and implantable)
Outcomes	The outcome measures to consider include: Procedure-related outcomes: • Diagnostic yield and accuracy (sensitivity and specificity) • Number of symptomatic and asymptomatic arrythmia events detected over total wear time • Ability to quantify atrial fibrillation (AF) burden (amount of time spent in AF) • Time to first arrhythmia event and time to first symptomatic event • Time to return device, analysis and report production • Test failure rate • Signal quality Clinical management outcomes: • Time to diagnosis or rule out of cardiac arrythmia • Time to initiation of preventative treatment • Impact of test results on clinical decision making • Total number of hospital outpatient appointments for testing • Total number of hospital outpatient appointments or admissions for device-related complications • Number of outpatient visits and staff time for undertaking and analyzing diagnostic tests • Morbidity (including stroke, thromboembolism, heart failure, and complications associated with preventative treatment) • Mortality Patient outcomes: • Patient compliance (average wear time and analyzable wear time) • Ease of use (for patients and healthcare professionals), including training requirements • Device acceptability and patient satisfaction • Health-related quality of life • Device-related adverse events

Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	
Subgroups to be considered	Adults referred for ambulatory ECG monitoring, who experience asymptomatic arrhythmia events Adults referred for ambulatory ECG monitoring in primary care Adults referred for ambulatory ECG monitoring in secondary care	
Special considerations, including those related to equality	The area of skin in which the Zio patch is applied will need shaving if hair is present. Some religions forbid cutting or shaving bodily hair. Zio service is not approved for paediatric use. Religion and age are protected characteristics under the Equality Act. Contraindications are listed the instructions for use for Zio Service.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristics?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure MTAC will have relevant information to consider equality issues when developing guidance?	No
	Cardiac arrhythmias can develop in people of any age but are more common in people over 60 years. Women tend to be at higher risk of certain arrhythmias, including atrioventricular nodal tachycardia, whereas men are 3 times more likely to develop atrial fibrillation at any age. However, of those people who develop atrial fibrillation, women have a much higher incidence of morbidity and mortality. Age and sex are protected characteristics under the Equality Act. People whose first language is not English or who cannot write may not be able to give written information on their symptoms while using the Zio Service.	

DHT005 Zio XT Service for detecting cardiac arrhythmias – ADDENDUM

Contents

1. Review of Hannun et al. (2019)

The Hannun et al. (2019) study is a technical evaluation of the Zio XT Service deep neural network algorithm using retrospective data (from January 2013 to March 2017) from adults who were clinically indicated to use the Zio monitor. The study did not compare results with standard care and was not carried out in a clinical setting. The reference standard was clinical consensus and rather than 12 lead ECG (the latter is typically considered a more objective gold standard).

The authors developed an algorithm to classify 10 arrhythmias as well as sinus rhythm and noise for a total of 12 output rhythm classes from a training dataset consisting of 91,232 ECG records from 53,549 patients. A median of one 30s record per patient was extracted to construct the training dataset. The mean age of patients was 69 ± 16 years and 43% were women. The 12 classes included atrial fibrillation, atrioventricular block, bigeminy, ectopic atrial rhythm, idioventricular rhythm, junctional rhythm, noise, sinus rhythm, supraventricular tachycardia, ventricular tachycardia, and Wenckebach.

The algorithm was validated using a test dataset that consisted of 328 ECG records collected from 328 unique patients. Mean age of patients in the test dataset was 70 ± 17 years and 38% were women. This was annotated by a consensus committee of eight cardiac electrophysiologists and one cardiologist (all referred to as cardiologists by the authors) who were divided into three groups of three. The mean inter-annotator agreement on the test dataset was 72.8%. To obtain estimates of how the algorithm compared to an average cardiologist, the characteristics of cardiologist performance were averaged across the six cardiologists who individually annotated each record. Every record in the test dataset received one committee consensus annotation from a group of three cardiologists and six individual cardiologist annotations.

Compared with committee consensus, the algorithm achieved an average area under the receiver operating characteristic curve of 0.978 against the test dataset (range: 0.913 for ectopic atrial rhythm to 0.998 for trigeminy). The algorithm's F1[1] score was compared to the average individual cardiologist F1 score. The average F1 score for the algorithm (0.837) exceeded that of cardiologists' average score (0.780). Diagnostic performance was highest in both the algorithm and average cardiologist for trigeminy, sinus rhythm and bigeminy and lowest for supraventricular tachycardia, ectopic atrial rhythm, and ventricular tachycardia. With specificity fixed at the average specificity achieved by cardiologists, the sensitivity of the algorithm exceeded the average cardiologist sensitivity for all rhythm classes. These results need to be confirmed in a clinical setting.

2. Additional cost modelling - exploring the impact of outpatient appointments

In their base case analysis, the EAC assumed that all monitoring tests would be followed up with an outpatient visit regardless of findings. Clinical experts indicated heterogeneity of practice regarding follow-up appointments around England with many centres informing patients and their GPs of negative findings by letter. The EAC undertook additional sensitivity analysis to test different assumptions on the use of outpatient visits following monitoring. The EAC reran analysis on all three of the company's models (stroke, cardiology and downstream stroke model) and the EAC revised versions of each model. The EAC examined the following assumptions

- SA1 - No outpatient appointment after any monitoring regardless of result

[1] F1 is the harmonic mean of the positive predictive value and sensitivity (the harmonic mean is the number of observations by the reciprocal of each number in the series)

- SA2 - Outpatient visit after all monitoring with Holter or CER, no outpatient visit after any monitoring with Zio Service
- SA3 – No outpatient appointment after a negative result (which is not repeated) following monitoring with any device
- SA4 – Outpatient visit after all monitoring with Holter or CER, no outpatient visit after a negative result following monitoring with Zio Service
- SA5 – No outpatient appointment after any negative result (whether or not it is repeated) following monitoring with any device

The results of the sensitivity analysis are reported in Tables 2-5. Table 1 provides the base case analysis for comparison. The findings of the company's downstream stroke model are included for completeness. However, the results are invariant to assumptions on outpatient visits as these costs were not included in the model. The costs were included in the EAC's revised version of the model.

SA1 - No outpatient appointment after any monitoring regardless of result

Costs fall for both Zio Service and current care when it is assumed that there are no follow-up appointments. The impact is larger for current care because in all models patients undergo more monitoring under current care than they do with Zio Service (due to repeat tests). If no outpatient assessment is undertaken after monitoring Zio Service remains cost saving in the company's cardiology model but not in its stroke model.

SA2 - Outpatient visit after all monitoring with Holter or CER, no outpatient visit after any monitoring with Zio Service

Unsurprisingly, an assumption of no outpatient visit after Zio Service but an outpatient visit after current care has a substantial impact on incremental costs in favour of Zio Service. In this scenario Zio Service is cost saving in all models (both the company's and the EAC's revised models).

SA3 – No outpatient appointment after a negative result following monitoring with any device

An assumption of no outpatient visit after a negative test potentially reduces costs for both Zio Service and current care. The impact is different across different models and reflects assumptions on decisions to repeat the test following an inconclusive or negative test. The impact is also modified by changes in the structure of the in the EAC's revised cardiology model in which inconclusive and negative results were combined. The assumption has no impact on the company's cardiology model. In the company's cardiology model a negative finding with any monitoring device is associated only with the cost of monitoring. Hence no changes to the model were made. In the EAC's revised cardiology model the reduction in savings in the current care pathway is larger than that for Zio Service. In both the company's and the EAC's revised stroke model the impact of assuming no outpatient appointment after negative monitoring results is larger for current care than for Zio Service. Both the company's stroke model and the EAC's stroke model find Zio Service is cost incurring in this scenario. In the EAC's revised downstream stroke model which included the costs of monitoring, an assumption of no outpatient visit after a negative finding has a larger impact on Service than on monitoring with either Holter or CER. The EAC assumed that all negative tests which were subsequently repeated would incur an outpatient visit. Consequently, the removal of outpatient visit costs after a negative result (which is not repeated) has a larger impact on the costs of Zio Service than it does on monitoring with Holter or CER, and Zio Service becomes cost saving in this scenario

SA4 – Outpatient visit after all monitoring with Holter or CER, no outpatient visit after a negative result following monitoring with Zio Service

Again, not surprisingly, an assumption of no outpatient visit following a negative assessment with Zio service leads to changes in inference on relative costs. In this scenario all six models find that Zio service is cost saving. Note that there is no change to the results for any of the company's models as none of the company's models included an outpatient visit after a negative finding with Zio Service.

SA5 – No outpatient appointment after any negative result (whether or not it is repeated) following monitoring with any device

This scenario represents a slight alteration to SA3. Here the EAC assumed that all negative results would be communicated to patient's and GPs by letter with the exception of negative results which proceeded to fitting of an ILR. The assumption resulted in no changes to the company's cardiology model, but led to significant reductions in the cost of current care in the company's stroke model with the result that Zio Service was no longer cost saving. In each of the EAC's models Zio Service remained cost incurring but the assumption increased the magnitude of the difference in costs between current care and Zio Service.

Assumptions in which monitoring results are followed up with an outpatient appointment after current care but not after Zio Service generated analysis in which Zio Service was cost saving compared to current care across the company's and the EAC's revised models. When assumptions were applied regardless of the type of monitoring used Zio Service was frequently, but not always more expensive than current care.

Base case – outpatient appointment after all test results

	Company's results			EAC's results		
	Intervention arm	**Comparator arm**	**Cost saving per patient**	**Technology**	**Comparator**	**Cost saving per patient**
Cardiology model	£431.33	£516.59	£84.76	£466.78	£465.96	-£0.82
Stroke model	£382.69	£437.97	£55.28	£493.94	£423.13	-£70.81
Downstream stroke model	£1,256.15	£1,332.65*	£76.50	£1237.45	£1216.62*	-£20.83

*Results for CER comparator, Holter comparator is more expensive

SA1 – no outpatient appointment after any test

	Company's results			EAC's results		
	Intervention arm	**Comparator arm**	**Cost saving per patient**	**Technology**	**Comparator**	**Cost saving per patient**
Cardiology model	£317.62	£333.37	£15.75	£315.01	£283.50	-£31.51
Stroke model	£347.83	£262.07	-£85.76	£345.83	£243.45	-£102.38
Downstream stroke model	£1,256.15	£1,332.65*	£76.50	£1095.45	£1026.74*	-£68.71

*Results for CER comparator, Holter comparator is more expensive

SA2 – no outpatient visit following Zio

	Company's results			EAC's results		
	Intervention arm	**Comparator arm**	**Cost saving per patient**	**Technology**	**Comparator**	**Cost saving per patient**
Cardiology model	£349.21	£516.59	£167.48	£346.16	£465.96	£119.80
Stroke model	£368.84	£437.97	£69.13	£369.28	£423.13	£53.85
Downstream stroke model	£1,256.15	£1,332.65*	£76.50	£1095.45	£1216.62*	£121.17

*Results for CER comparator, Holter comparator is more expensive

SA3 – no outpatient appointment after any negative test provided it is not repeated

	Company's results			EAC's results		
	Intervention arm	**Comparator arm**	**Cost saving per patient**	**Technology**	**Comparator**	**Cost saving per patient**
Cardiology model	£431.33	£516.59	£84.76	£420.11	£398.53	-£21.58
Stroke model	£382.69	£340.08	-£42.61	£381.14	£326.71	-£54.43
Downstream stroke model	£1,256.15	£1,332.65*	£76.50	£1,118.31	£1,145.86*	£27.55

*Results for CER comparator, Holter comparator is more expensive

SA4 – no outpatient appointment after negative Zio service test

	Company's results			EAC's results		
	Intervention arm	**Comparator arm**	**Cost saving per patient**	**Technology**	**Comparator**	**Cost saving per patient**
Cardiology model	£431.33	£516.59	£84.76	£431.54	£465.96	£34.42
Stroke model	£382.69	£437.97	£55.28	£391.44	£423.13	£31.69
Downstream stroke model	£1,256.15	£1,332.65	£76.50*	£1118.31	£1216.62*	£98.31

*Results for CER comparator, Holter comparator is more expensive

SA5 – no outpatient appointment after any negative test regardless of whether it is repeated

	Company's results			EAC's results		
	Intervention arm	**Comparator arm**	**Cost saving per patient**	**Technology**	**Comparator**	**Cost saving per patient**
Cardiology model	£431.33	£516.59	£84.76	£354.52	£319.77	-£34.75
Stroke model	£365.02	£268.40	-£96.62	£371.07	£252.10	-£118.97
Downstream stroke model	£1,256.15	£1,332.65	£76.50*	£1118.31	£1039.52*	-£78.79

*Results for CER comparator, Holter comparator is more expensive

3. Additional cost modelling with modified model structure

The economic models submitted by the company, and amended by the EAC, did not explicitly estimate the sensitivity and specificity of either Zio Service or conventional monitors. Instead estimates were taken from the literature of the diagnostic yield. This raises concerns of bias where underlying rates of AF differ due to different populations used to inform the estimates of diagnostic yield. This was a concern for the cardiology, stroke and downstream stroke models before and after modification by the EAC. In the cardiology model the same observational source (American hospital administrative data) is used to inform estimates of the diagnostic yield for 24-h Holter and 7-day CER (Tsang 2014). We cannot be certain that the underlying event rate was the same in patients selected for each type of monitor, but the authors matched populations on age, diagnosis and other patient characteristics. Data on the diagnostic yield for Zio Service is taken from a different source. In both stroke models the diagnostic yield of Zio Service and 24h Holter are taken from the same source – the EPACS study which randomised the patients to either Zio Service or Holter (Kaura 2019). For these data we can be confident that the underlying rate of AF is the same, at least in expectation. The diagnostic yield of 7day CER in the stoke models is taken from a different source.

The EAC searched the literature to try to find evidence on the sensitivity and specificity of Zio Service, 24-hour Holter and 7-day CER. Data on symptomatic patients relevant to the cardiology model was limited and no data allowed a direct comparison between Zio Service and either 24-hour Holter or 7-day CER. Therefore, the EAC did not undertake any further amendments to the cardiology model. The literature on cryptogenic stroke was more abundant. The recent HTA assessment by Edwards at al. provides a summary of the evidence comparing ILR with both Holter and event recorders. Sensitivities for Holter and event recorders are calculated from the CRYSTAL-AF trial and an observational study (Zeigler et al.) on the assumption that the sensitivity of the ILR is 100%. The data from Zeigler indicates a sensitivity for 24-hour Holter and 21-day CER of 2.9% and 22.0%. The data from CRYSTAL-AF trial indicates a sensitivity for 24-hour Holter and 21-day CER of 1.3% and 14.0% (Choe 2015).

The EAC undertook further modification of the stroke model and the downstream stroke model. The EAC retained the underlying assumption that incidence of AF in the cryptogenic stroke population is 30%. The EAC further assumed a specificity of 100% for all tests. The EAC then calculated a sensitivity of 7% for 24-hour Holter and 53.7% for Zio Service based on diagnostic yields of 2.1% for 24-hour Holter and 16.1% for Zio Service from the EPACS study. Applying a sensitivity of 7% for 24-hour Holter to the data from Zeigler generates an underlying incidence of AF of 41.4%. The comparable figure from CRYSTAL-AF is 18.6%. In turn, these incidences of AF provide an estimate of sensitivity for 21-day event recorders of 53.1% from Zeigler and 75.3% from CRYSTAL-AF.

A further calculation is required to estimate sensitivity for 7-day CER from the data for 21-day CER. Edwards reports diagnostic yields for 7-day Holter and 30-day Holter from both Zeigler and CRYSTAL-AF trial. The yields from Zeigler are 11.0% and 25.0%. The yields from CRYSTAL-AF trial were 8.0% and 22.8%. The EAC applied the ratio of the 7-day and 30-day yields for Holter from Zeigler to the diagnostic yield over 21 days for CER of 22.0% to estimate a 7-day CER diagnostic yield of 6.2%. The same calculation was undertaken on the data from CRYSTAL-AF trial to generate a 7-day CER diagnostic yield of 4.9%. Applying the estimated incidence of AF in the two studies generates a sensitivity of 15.0% from data in Zeigler and a sensitivity of 26.3% from CRYSTAL-AF trial.

The EAC modified both the stroke and the downstream stroke model to include the sensitivity of the three tests assuming a specificity of 100% for all tests. The EAC applied sensitivity estimates for 7-day CER based on data from Zeigler and form CRYSTAL-AF trial.

3.1. Results

The table below shows the results before and after modification of the model. The impact of parameterising sensitivity of CER at either 15.0% or 26.3% is very modest. The results are mostly unchanged from the original analysis. The relatively large change in the sensitivity of CER has little difference on the overall costs. Whilst the cost of stroke is high at £13,452 the incidence over one year is only around 2% if the entire cohort is untreated, reducing to around 1% if all patients with AF (30%) are identified and treated. Hence moving from a sensitivity of 0% to 100% reduces stoke costs by around £135. It also increases the cost of anticoagulation therapy for the cohort from £0 to about £135 - the net effect on costs is zero. The higher sensitivity does reduce overall costs. This is because it reduces the proportion of patients with a negative result who are retested.

	Previous model results			Sensitivity of CER 15.0%			Sensitivity of CER 26.3%		
	Zio Service	Comparator	Cost saving	Zio Service	Comparator	Cost saving	Zio Service	Comparator	Cost saving
Stroke model	£493.94	£423.13	-£70.81	£494.13	£424.43	-£69.70	£493.91	£422.91	-£71.00
Downstream stroke model vs CER	£1237.45	£1216.62	-£20.83	£1237.43	£1227.35	-£10.08	£1237.43	£1214.85	-£22.58
Downstream stroke model vs Holter	£1237.45	£1236.18	-£1.27	£1237.43	£1236.18	-£1.25	£1237.43	£1236.18	-£1.25

References

Choe WC, Passman RS, Brachmann J, et al. A Comparison of Atrial Fibrillation Monitoring Strategies After Cryptogenic Stroke (from the Cryptogenic Stroke and Underlying AF Trial). The American Journal of Cardiology. 2015 Sep 15;116(6):889-93.

Edwards SJ, Wakefield V, Jhita T, et al. Implantable cardiac monitors to detect atrial fibrillation after cryptogenic stroke: a systematic review and economic evaluation. Health Technology Assessment, Southampton (UK): NIHR Journals Library; 2020 Jan.

Hannun, A. Y. Pranav, R., Masoumeh, H. et al. Cardiologist-level arrhythmia detection and classification in ambulatory electrocardiograms using a deep neural network. 2019: Nature Medicine 25(1): 65-69.

Kaura A, Sztriha L, Chan FK, Aeron-Thomas J, Gall N, Piechowski-Jozwiak B, et al. Early prolonged ambulatory cardiac monitoring in stroke (EPACS): an open-label randomised controlled trial. European Journal of Medical Research. 2019: 24(1):25.

Tsang JP, Mohan S. Benefits of monitoring patients with mobile cardiac telemetry (McT) compared with the Event or holter monitors. Medical Devices: Evidence and Research. 2014: 7.

Ziegler PD, Rogers JD, Ferreira SW, Nichols AJ, Richards M, Koehler JL, Sarkar S. Long-term detection of atrial fibrillation with insertable cardiac monitors in a real-world cryptogenic stroke population. International Journal of Cardiology. 2017: 244:175–9.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

SCOPE

Zio Service for detecting cardiac arrhythmias

1 Technology

1.1 Description of the technology

Zio ECG monitoring service (Zio Service, iRhythm Technologies) is a remote cardiac monitoring system used to detect cardiac arrhythmias. It is comprised of 3 components:

- Zio biosensor: a wearable single lead ambulatory electrocardiogram (ECG)
- ZEUS: a proprietary, regulated software platform and online portal that stores, analyses and sorts the ECG data to generate a report of the findings
- Zio technical report: a clinically actionable summary of the recorded ECG data

The Zio Service is intended to replace or enhance the current assessment pathway for cardiac arrhythmia detection in people with palpitations, fainting (syncope) and suspected cardiac arrhythmia. The adhesive Zio biosensor is placed on the person's left upper chest and records a continuous beat-to-beat ECG for up to 14 days. The device is designed to facilitate patient compliance and thereby improve data collection. Without external leads or wires, noise artefacts are reduced in the data and the wearer may go about normal daily activities, including light exercise or showering, without required monitor maintenance. Each Zio biosensor is intended for single-patient use. After the monitoring period is completed, the wearer removes the biosensor and sends it to the company by freepost. The ECG recordings are analysed using the artificial intelligence led algorithm within ZEUS and overseen by accredited

cardiac physiologists. A technical report is produced, containing information regarding arrhythmia episodes, wear and analysis time and patient-captured events, and is sent to the prescribing clinician for final analysis and interpretation. There are no patient identifiers in or on the Zio Patch and data cannot be accessed if the Zio Patch were to be physically intercepted.

For the Evidence Standards Framework for digital health technologies, Zio Service is classified as an active monitoring technology and so has a tier 3b evidence level.

1.2 Regulatory status

Zio Service received a CE mark in December 2014 as a Class IIa device.

1.3 Relevant diseases and conditions

Cardiac arrythmias are experienced by more than 2 million people a year in the UK. The term covers a number of conditions in which the heartbeat is irregular, too fast or too slow. Types of arrythmias are categorised by where they originate in the heart (atria or ventricles) and whether they increase (tachycardia) or decrease the heart rate (bradycardia). Important examples of cardiac arrythmia include atrial fibrillation, supraventricular tachycardia, bradycardia, heart block and ventricular fibrillation (NHS, 2018).

Zio Service is intended for use in people suspected of having cardiac arrhythmia, specifically those with symptoms or suspected arrhythmic episodes more than 24 hours apart. Common symptoms include palpitations, dizziness or light-headedness (presyncope) and fainting (syncope) and are known to account for a large number of emergency presentations each year in the UK. Cardiovascular events including arrhythmia are among the most serious causes of syncope.

Atrial fibrillation is the most common sustained cardiac arrhythmia. It causes an irregular and often abnormally fast heart rate which can lead to symptoms such as breathlessness, heart palpitations and dizziness or temporary loss of consciousness. Atrial fibrillation can also be asymptomatic. It has been estimated that 1.4 million people in England have atrial fibrillation, equating to

2.5% of the population (Public Health England, 2017). The likelihood of atrial fibrillation increases with age, with 80.5% of the total estimated atrial fibrillation in the population occurring in people over 65 years. The prevalence of atrial fibrillation is higher in men than women (2.9% compared with 2.0%), with 825,000 men expected to be living with it compared with 580,000 women. Public Health England also estimate that around 425,000 people in England have undiagnosed and untreated atrial fibrillation. Atrial fibrillation is associated with an increased risk of stroke, hospitalisation, and mortality. According to the European Society of Cardiology guidelines for the management of atrial fibrillation, untreated atrial fibrillation is associated with a 5-fold increased risk of stroke and a 3-fold increased risk of heart failure (European Society of Cardiology, 2012).

1.4 Current management

NICE's guidelines on transient loss of consciousness ('blackouts') in over 16s and guidelines on managing atrial fibrillation provide recommendations on current methods of arrhythmia detection.

The NICE guideline on transient loss of consciousness ('blackouts') in over 16s, recommends recording a 12-lead ECG using automated interpretation as the initial assessment. All people with transient loss of consciousness (TLoC) should be referred for specialist cardiovascular assessment, except those with a firm diagnosis after initial assessment of uncomplicated faint, situational syncope or orthostatic hypotension, or people whose presentation is strongly suggestive of epileptic seizure. For people with a suspected cardiac arrhythmic cause of syncope, the guideline recommends offering an ambulatory ECG. The type of device should be chosen on the basis of the patient's history and frequency of TLoC. Holter monitoring (up to 48 hours if necessary) is recommended in people who have TLoC at least several times a week. In those with TLoC every 1 to 2 weeks an external event recorder should be offered. An implantable event recorder should be offered to people with infrequent TLoC (less than once every 2 weeks).

The NICE guideline on managing atrial fibrillation recommends performing manual pulse palpation to assess for the presence of an irregular pulse in people presenting with any of the following:

- breathlessness/dyspnoea
- palpitations
- syncope/dizziness
- chest discomfort
- stroke/transient ischaemic attack

It is recommended that an ECG be performed in all people, whether symptomatic or not, in whom atrial fibrillation is suspected because an irregular pulse has been detected. Arrhythmias may be missed by a 12-lead ECG in people with paroxysmal AF (that is, intermittent atrial fibrillation) because of the occasional nature of the arrhythmic episodes. If arrhythmia is not detected on the initial 12-lead ECG and further assessment of suspected paroxysmal atrial fibrillation is needed, ambulatory ECG monitoring is recommended. The choice of monitor used depends on symptoms and symptom frequency. The guideline recommends the following:

- use a 24-hour ambulatory ECG monitor (such as a Holter monitor) in people with suspected asymptomatic episodes or symptomatic episodes less than 24 hours apart
- use an event recorder ECG (which can be external or implantable) in people with symptomatic episodes more than 24 hours apart.

Zio Service would be used for monitoring up to a 14-day period in place of current methods of cardiac event detection, such as Holter monitoring or event recording (external or implantable) in people suspected of having cardiac arrhythmia. The use of the Zio Service would be prescribed by a clinician, most often a cardiologist or GP, in primary, secondary or tertiary care. It may also be prescribed by a stroke clinician or neurologist.

1.5 Claimed benefits

The benefits to patients claimed by the company are:

- Improved diagnostic yield, minimising the number of repeat tests needed to confirm or rule out arrhythmia
- Greater diagnostic accuracy and efficiency in detecting clinically relevant arrhythmias, including symptomatic and silent atrial fibrillation
- Earlier diagnosis and initiation of preventative treatment (such as anticoagulants), potentially leading to a reduction in the occurrence of clinical sequelae of arrhythmia such as syncope, stroke and heart failure
- Minimal disruption to patients' daily activities leading to improved patient compliance and data collection (wear time, analysable time and signal quality)
- Streamlined patient pathways reduced number of outpatient visits (aligned to NHS Long Term Plan objectives), thereby increasing patient access and reducing health inequalities

The benefits to the health and social care system claimed by the company are:

- Reduction in costs and resources that could be avoided through earlier diagnosis and treatment, such as repeat hospital admissions related to the clinical sequelae of arrhythmia, such as syncope, stroke or heart failure
- Reduction in staff, estate and capital equipment resource use in the ambulatory ECG monitoring pathway, due to reduced repeat testing, reduced in-clinic analysis of ECG recordings and reduced outpatient appointments
- Standardisation and efficiency gains in cardiac diagnostic services within and across NHS trusts through simplified processes, supported by Artificial Intelligence and service evaluation tools
- Ease of implementation; minimal changes in facilities or infrastructure needed when Zio Service adopted in standard practice, including in rural areas

2 Statement of the decision problem

Population	Adults (18 years or older) with suspected cardiac arrhythmia referred for ambulatory ECG monitoring
Intervention	Zio ECG monitoring service (Zio Service)
Comparator(s)	• Current pathway for ambulatory cardiac arrhythmia detection, which includes Holter and/or event monitoring (external and implantable)
Outcomes	The outcome measures to consider include: Procedure-related outcomes: • Diagnostic yield and accuracy (sensitivity and specificity) • Number of symptomatic and asymptomatic arrythmia events detected over total wear time • Ability to quantify atrial fibrillation (AF) burden (amount of time spent in AF) • Time to first arrhythmia event and time to first symptomatic event • Time to return device, analysis and report production • Test failure rate • Signal quality Clinical management outcomes: • Time to diagnosis or rule out of cardiac arrythmia • Time to initiation of preventative treatment • Impact of test results on clinical decision making • Total number of hospital outpatient appointments for testing • Total number of hospital outpatient appointments or admissions for device-related complications • Number of outpatient visits and staff time for undertaking and analyzing diagnostic tests • Morbidity (including stroke, thromboembolism, heart failure, and complications associated with preventative treatment) • Mortality Patient outcomes: • Patient compliance (average wear time and analyzable wear time) • Ease of use (for patients and healthcare professionals), including training requirements • Device acceptability and patient satisfaction • Health-related quality of life • Device-related adverse events

Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	
Subgroups to be considered	• Adults referred for ambulatory ECG monitoring, who experience asymptomatic arrhythmia events • Adults referred for ambulatory ECG monitoring in primary care • Adults referred for ambulatory ECG monitoring in secondary care	
Special considerations, including those related to equality	The area of skin in which the Zio patch is applied will need shaving if hair is present. Some religions forbid cutting or shaving bodily hair. Zio service is not approved for paediatric use. Religion and age are protected characteristics under the Equality Act. Contraindications are listed the instructions for use for Zio Service.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristics?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure MTAC will have relevant information to consider equality issues when developing guidance?	No
	Cardiac arrhythmias can develop in people of any age but are more common in people over 60 years. Women tend to be at higher risk of certain arrhythmias, including atrioventricular nodal tachycardia, whereas men are 3 times more likely to develop atrial fibrillation at any age. However, of those people who develop atrial fibrillation, women have a much higher incidence of morbidity and mortality. Age and sex are protected characteristics under the Equality Act. People whose first language is not English or who cannot write may not be able to give written information on their symptoms while using the Zio Service.	

3 Related NICE guidance

Published

- Lead-I ECG devices for detecting symptomatic atrial fibrillation using single time point testing in primary care. NICE diagnostics assessment guidance DG35 (2019).

- Leadless cardiac pacemaker implantation for bradyarrhythmias. NICE Interventional procedures guidance IPG626 (2018).
- Subcutaneous implantable cardioverter defibrillator insertion for preventing sudden cardiac death. NICE Interventional procedures guidance IPG603 (2017).
- Atrial fibrillation and heart valve disease: self-monitoring coagulation status using point-of-care coagulometers (the CoaguChek XS system). NICE Diagnostics guidance DG14 (2017).
- ENDURALIFE powered CRT-D devices for treating heart failure. NICE Medical technologies guidance MTG33 (2017).
- Percutaneous endoscopic laser balloon pulmonary vein isolation for atrial fibrillation. NICE Interventional procedures guidance IPG563 (2016).
- Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation. NICE Technology appraisal guidance TA355 (2015).
- Dual-chamber pacemakers for symptomatic bradycardia due to sick sinus syndrome and/or atrioventricular block. NICE Technology appraisal guidance TA88 (2014).
- Atrial fibrillation: management. NICE Clinical guideline CG180 (2014).
- Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure. NICE Technology appraisal guidance TA314 (2014).
- Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation. NICE Technology appraisal guidance TA275 (2013).
- WatchBP Home A for opportunistically detecting atrial fibrillation during diagnosis and monitoring of hypertension. NICE Medical technologies guidance MTG13 (2013).
- Dronedarone for the treatment of non-permanent atrial fibrillation. NICE Technology appraisal guidance TA197 (2012).
- Percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation. NICE Interventional procedures guidance IPG427 (2012).

- Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. NICE Technology appraisal guidance TA256 (2012).
- Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. NICE Technology appraisal guidance TA249 (2012).
- Thoracoscopic exclusion of the left atrial appendage (with or without surgical ablation) for non-valvular atrial fibrillation for the prevention of thromboembolism. NICE Interventional procedures guidance IPG400 (2011).
- Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism. NICE Interventional procedures guidance [IPG349 (2010).
- Percutaneous (non-thoracoscopic) epicardial catheter radiofrequency ablation for atrial fibrillation. NICE Interventional procedures guidance IPG294 (2009).
- Percutaneous (non-thoracoscopic) epicardial catheter radiofrequency ablation for ventricular tachycardia. NICE Interventional procedures guidance IPG295 (2009).
- Thoracoscopic epicardial radiofrequency ablation for atrial fibrillation. NICE Interventional procedures guidance IPG286 (2009).
- High-intensity focused ultrasound for atrial fibrillation in association with other cardiac surgery. NICE Interventional procedures guidance IPG184 (2006).
- Percutaneous radiofrequency ablation for atrial fibrillation. NICE Interventional procedures guidance IPG168 (2006).
- Cryoablation for atrial fibrillation in association with other cardiac surgery. NICE Interventional procedures guidance IPG123 (2005).
- Microwave ablation for atrial fibrillation in association with other cardiac surgery. NICE Interventional procedures guidance IPG122 (2005).
- Radiofrequency ablation for atrial fibrillation in association with other cardiac surgery. NICE Interventional procedures guidance IPG121 (2005).
- Laser sheath removal of pacing leads. NICE Interventional procedures guidance IPG63 (2004).

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Implantable cardiac monitors to detect atrial fibrillation after cryptogenic stroke. NICE diagnostics assessment guidance. Publication expected December 2019.
- TYRX Absorbable Antibacterial Envelope for preventing infection from cardiac implantable electronic devices [ID1440]. NICE technology appraisal guidance. Publication expected February 2020.
- Atrial fibrillation: management. NICE guideline. Publication expected September 2020.
- Atrial fibrillation - idraparinux sodium [ID375]. NICE technology appraisal guidance. Publication expected TBC.
- Atrial fibrillation - vernakalant [ID454]. NICE technology appraisal guidance. Publication expected TBC.

4 External organisations

4.1 Professional organisations

The following societies have been alerted to the availability of the draft scope for comment:

- British Association for Nursing Cardiovascular Care
- British Cardiovascular Society
- British Heart Rhythm Society
- Royal College of Emergency Medicine
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Physicians
- Society for Cardiological Science and Technology

4.2 Patient organisations

NICE's Public Involvement Programme contacted the following organisations for patient commentary and alerted them to the availability of the draft scope for comment:

- Arrhythmia Alliance
- Atrial Fibrillation Association
- British Cardiac Patients Association (BCPA)
- British Heart Foundation
- Cardiac Risk in the Young (CRY)
- Cardiovascular Care Partnership
- Children's Heart Federation
- Down's Heart Group
- Heart Rhythm Alliance
- Heart Valve voice
- Pumping Marvellous
- The Ashley Jolly SADS Trust (SADS UK)

NICE National Institute for Health and Care Excellence

Adoption report: DHT Zio XT Service for detecting cardiac arrhythmias

Summary – for first meeting

Adoption levers

- Longer recording time has the potential for a greater diagnostic yield compared with the commonly used external ambulatory monitors.
- May improve the speed of diagnosis allowing initiation of appropriate treatment and reduce unnecessary investigations, treatment and follow up
- Good patient acceptance. It is discreet, practical, and is self-removed (no appointment required).

Adoption barriers

- Cost. Reimbursement tariffs do not account for increased technology cost compared with external ambulatory monitors
- Duplication of effort. NHS Trusts already employ cardiac technicians to interpret ambulatory monitoring
- Staff with skills and experience in cardiology are needed for suitable patient selection and to interpret results alongside other clinical factors.
- Limited long-term adoption from those who have piloted.

1 Introduction

The adoption team has collated information from healthcare professionals working within NHS organisations, 6 of whom have experience of using the Zio XT service.

This adoption report includes some of the adoption considerations for the routine NHS use of the technology.

2 Current practice in clinical area

Across all the clinical pathways in which ambulatory cardiac monitoring is used contributors reported:

- Variation in whether external ambulatory monitoring is initiated in primary or secondary care. Some GPs organise an ECG and 24 hour Holter prior to referral whereas others refer without testing.
- Variation in monitoring options available. Some only have access to 24 hour monitors whilst others offer 5 day monitoring as standard (post stroke).
- Repeat testing being common because ambulatory monitoring for a short period of time may not identify an arrhythmia
- Delays in reporting results because of capacity in cardiology departments.
- Shortage of devices at some sites which meant delays in patients accessing the test (by which time symptoms may be less marked or frequent).
- Patients unable to wear ambulatory monitoring for the prescribed length of time due to the impact on activities of daily living.

3 Contributors and the use of the Zio XT Service in practice

Table 1 below provides more detail about the contributors and how the Zio XT Service had been adopted at their trust. All 6 sites who had adopted the Zio XT Service did so as part of a pilot or trial and only 1 had secured ongoing funding.

Job title	Adoption type	Care pathway	Site reported findings	Current use of Zio XT Service at site
Consultant Cardiologist & Physician	Pilot January 2017	Assessment of patients with palpitations or suspected cardiac arrhythmias.	82.1% (108/132 patients) had a documented arrhythmia 1 patch lost	Ongoing trust funded during the pilot
Clinical Cardiac Physiologist	Pilot	Adults presenting to primary care with symptoms of arrhythmia	93% (13/14) had symptoms and a positive report 0 patches lost	No. Currently redefining pathway
Neurologist, Clinical Director of Data Science	Research study (RCT)	Feb 2016 – Feb 2017 Monitoring immediately following TIA/stroke for detection of AF (applied in hospital prior to discharge)	16.3% (7/43) detection of paroxysmal AF at 90 days 0 patches lost	Funding secured from research and innovation funds only. Continued NHS funding not available due to lack of economical HRG tariff
Consultant in Emergency Medicine	Research study (Prospecti ve pilot)	November 2015 – June 2017 Adults presenting to ED within 6 hours of unexplained syncope	27.9 (24/86) had a significant arrhythmia 10 patches lost	No. Request for funding rejects from emergency department finance and management teams.
Associate Professor a nd Consultant Cardiologist	Not adopted	Cardiology offers 24 hour monitoring, 7 day monitoring or implantable cardiac monitors.	N/A	N/A
Consultant Cardiologist / Electrophysi ologist	Pilot	January 2018 Patient referred to cardiology with signs and symptoms of arrhythmia including Transient Loss of Consciousness (TLoC).	50% (5/10) of reports identified a clinically significant finding 0 patches lost	No. Business case has been submitted to the trust finance and management teams awaiting approval.

Consultant Neurologist.	Pilot	Monitoring for AF immediately following stroke or TIA (applied prior to discharge)	10% (1/10) had AF 0 patches lost	No, however the site continue to seek funding.

The adhesive Zio biosensor is placed on the person's left upper chest, generally by a nurse, as soon as the decision is made to use it. After 2-weeks use, the patient removes it and posts it back to the company. Patients are provided with a box and preaddressed envelope. The company say that the envelope is pre-paid for first-class Royal Mail (no tracking or recording).

When the result is available the clinician responsible for requesting the test is notified by email.

Only a very small number of devices are reported to be 'lost' in transit (i.e. not received at the Zio XT Service analysis centre) and the greatest number lost were from a pilot in patients presenting to the emergency department where 10 of 86 were not returned. Where a sensor was 'lost' patients reported they had returned them. At 1 site, a patient removed the patch before the 2-week monitoring period had finished because they got their dates confused. At another site 2 patients (in a trial of 43 people) preferred to bring the patch back to hospital rather than post it.

4 Reported benefits

The potential benefits of adopting the Zio XT Service, as reported to the adoption team by the healthcare professionals using the technology are that:

- It offers longer, continuous monitoring time compared with the commonly used external ambulatory monitors. This may offer a greater diagnostic yield which can:
  - improve the speed of diagnosis allowing initiation of appropriate treatment and re-assurance for patients
  - reduce unnecessary investigations, treatment and follow up
- It is a single use item meaning there are no delays waiting for monitoring equipment to be returned.

- There are no ongoing maintenance costs.
- It releases cardiac physiologists time for other tasks within cardiology.
  - There is increased patient satisfaction because it should not get in the way of normal daily activities, and
  - It is discreet with no need to return to a healthcare professional for removal and it can be returned by post.

5 Insights from the NHS

Care pathway

The care pathway within which the Zio XT Service fits is important for ensuring it is being used in the most cost-effective way. Contributors said adoption should happen as part of a review and update of the existing cardiac monitoring care pathway. The overall pathway should be integrated between primary and secondary care. However, most contributors thought the Zio XT Service should be used by those with the skills and experience to select the most suitable patients and make a clinical diagnosis from the results.

Contributors report having a small number of Zio patches in stock. When required the person responsible logs on to the Zio IT system, activates a test for the patient, inputs the relevant information and assigns the Zio patch serial number to that test. The company then replace the patch in the trust's stock.

Due to the nature of the pilots only a small number of patients used the Zio XT Service with 1 or 2 clinicians registered to receive results. If the Service was to be adopted on a larger scale, contributors said processes at their trusts would need to be established to cope with an increased workload and ensure all results were reviewed, including identification of red flags, and actioned in a timely manner.

Patient selection

Contributors agreed that appropriate patient selection is important for using this technology cost-effectively. Contributors identified the following groups of patients as potentially suitable for the Zio XT Service:

- Those who have had a TIA or stroke where cardiac causes are being investigated (AF or other arrhythmia). However, one contributor thought that when monitoring for AF following stroke, 2 weeks was not long enough.
- People presenting with symptoms of palpitations or suspected cardiac arrhythmias.
- People who experience transient loss of consciousness (including syncope, blackouts). However, one contributor said TLoC is not commonly a weekly event and therefore unlikely to be picked up by the Zio XT Service.
- Children and young people being investigated for cardiac arrhythmias (children under age 3 may too small for the patch because of the relative sizes).

Across all groups the following factors were important for decision making about whether to use Zio XT Service:

- Whether the result would change the patient's clinical management plan. If not it may not be worth doing it. For example, identifying AF in a patient following stroke who cannot take anticoagulants.
- Frequency and duration of symptoms.
- The patients' social situation; whether they can travel easily between home and hospital (required for Holter monitor appointments) and the degree to which they would tolerate a Holter monitor.

Patient experience

All contributors reported that patients who used the Zio XT Service had a positive experience. The positioning site for the patch must be shaved and cleaned before application (both men and women). No patients' experienced skin irritation. Compliance with wearing the monitor was greater than for Holter monitors.

Cost

Cost is cited as the main barrier to adoption as most trusts employ cardiac technicians to interpret ambulatory monitoring results and already own Holter equipment. However, contributors thought these could be off-set by a reduction in multiple appointments and the re-monitoring and maintenance associated with the Holter monitors.

Of the 6 sites where Zio XT Service has been used as part of a trial or pilot, only one had secured funding from the trust to continue to offer the service. Reasons included uncertainty about whether use of the technology would reduce mortality, facilitate faster discharge or prevent admissions.

Contributors said that whilst the Zio XT Service costs more than using a Holter monitor the reimbursement for both is the same. The NICE resource impact assessment (RIA) team identified that 24 hr electrocardiography (U192), 48hr electrocardiography (U1930) and Holter extended electrocardiography (U195) all map to the same HRG code EY51 which achieves a reimbursement of £122.The RIA team said the Zio XT Service would be coded as a Holter extended electrocardiography. The NICE MIB says the manufacturer has given an example list price of £800 per unit for the Zio XT Service, this compares with the documented price of a Holter monitor including monitoring and interpretation of £118.60 (with overheads).

Clinician confidence/acceptance

Contributors were aware that IT software was supporting cardiac technicians to analyse the recordings. This process did not pose any concerns to contributors. All contributors are positive about the technology. They said it worked well with a quick turnaround time from the patch being received at the company to them being alerted that the report was available (2 days). Reports were of a high quality.

Two contributors highlighted that it does not offer ‘live feedback’ which means there would be a delay in action and treatment if an arrhythmia had occurred during the monitoring period. Implantable cardiac monitors can send an alert on the same day as an arrhythmia has occurred.

Contributors said that potentially cardiac technicians could feel apprehensive about adopting the Zio XT Service because interpretation of results is part of their role.

Training in patient selection and diagnosis

The free training in how to apply the Zio patch and how to use the Zio XT Service database was said to be quick and easy.

Zio users should have, or have access to, the cardiac skills and experience to:

- undertake a clinical cardiac assessment to decide if the Zio XT Service is most suitable. Two contributors said that healthcare professionals in primary care could initiate the Zio XT Service but this would need to be as part of a strict protocol,
- interpret from the report (which will detail all arrhythmias) what is clinically significant within the context of the patient.

Those with these skills are most likely cardiac physicians, cardiac nurse specialists and cardiologists, or a member of the stroke medical team.

IT and information governance

As part of their adoption planning contributors' trusts considered if there were any data protection and governance risks. All were satisfied by the assurance from the company and allowed adoption to proceed. One contributor said their trust-level firewalls needed to be adapted to allow access to the Zio website, but this was easily done.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

DHT005 Zio XT Service for detecting cardiac arrhythmia

Company evidence submission

Part 1: Decision problem, clinical evidence and outline of economic evidence

Company name	iRhythm Technologies
Submission date	25/09/2019
Regulatory documents attached	CE Certificate Clinical Reference Manual Declaration of Conformity
Contains confidential information	Yes

August 2019 v1.0

Contents

Abbreviations used in this submission

Abbreviation	Full Text
24HM	24-Hour Holter Monitor
ACHD	Adults with Congenital Heart Disease
AF	Atrial Fibrillation
AFP	Pause During Atrial Fibrillation
AHM	AliveCor Heart Monitor
ARVD/C	Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy
ASD	Atrial Septal Defect
AUD	Australian Dollars
AV	Av Block
AVT	Atrial Ventricular Tachycardia
CAM	Carnation Ambulatory Monitor
CI	Confidence Interval
CS	Cryptogenic Shock
CVD	Cardiovascular Disease
DDDRP	Atrial Preventive Pacing And Atrial Antitachycardia Pacing
DNN	Deep Neural Network
ECAM	Extended Continuous Ambulatory Rhythm Monitors
ECG	Electrocardiogram
ECR	Episodic Card Recorder
ED	Emergency Department
EKG	Electrocardiogram
ELCR	External Cardiac Loop Recorder
ELR	External Loop Recorder
EP	Electrophysiology
ER	Emergency Room
GP	General Practitioner
GRS	Genetic Risk Score
HGHB	High-Grade Heart Block
HR	Hazard Ratio
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ICM	Insertable Cardiac Monitor
ILR	Implantable Loop Recorder
IM	Intermittent Monitoring
IMD	Intermittent Monitoring Device
IQR	Interquartile Range
LTCM	Long Term Cardiac Monitoring
MCOT	Mobile Cardiac Outpatient Telemetry
MESA	Multi-Ethnic Study Of Atherosclerosis
MRI	Magnetic Resonance Imaging

NA	Not applicable
NIAM	Non-Invasive Ambulatory ECG Monitor
NPV	Negative Predictive Value
NR	Not reported
MVP	Managed Ventricular Pacing
NSVT	Non-Sustained Ventricular Tachycardia
OPD	Out Patient Department
OR	Odds Ratio
PAF	Paroxysmal AF
PAPVR	Partial Anomalous Pulmonary Venous Return
PDS	Pds Heart Event Monitor
POIP	Policardiógrafo IP
PPV	Positive Predictive Value
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
RFC	Radiofrequency Current
RR	Relative Risk
RT	Real Time
SD	Standard Deviation
SOC	Standard Of Care
SP	Sinus Pause
SVT	Sustained Ventricular Tachycardia
TELE-ECG	Telephone Electrocardiogram
TIA	Transient Ischemic Attack
TT	Trans-Telephonic
TTECG	Trans-Telephonic Electrocardiogram
TTM	Trans-Telephonic Monitor
VT	Ventricular Tachycardia

1 Decision problem

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
Population	Adults (18 years or older) with suspected cardiac arrhythmia referred for ambulatory ECG monitoring		
Intervention	Zio XT ECG monitoring service (Zio XT Service)		
Comparator(s)	Current pathway for ambulatory cardiac arrhythmia detection, which includes Holter and/or event monitoring (external and implantable)	Current pathway for ambulatory cardiac arrhythmia detection, which includes Holter and/or event monitoring	Although implantable cardiac monitors are recommended for ambulatory ECG monitoring in specific clinical scenarios (in particular in patients presenting with infrequent TLoC), in reality implantable cardiac monitors are rarely used first line. Verified patient pathways suggest implantable event recorders are not standard of care and are only used second or third line, when other methods of ECG ambulatory monitoring have failed to diagnose or rule out arrhythmia
Outcomes	Procedure-related outcomes: • Diagnostic yield and accuracy (sensitivity and specificity)	Remove the following: • Health-related quality of life	No evidence to demonstrate this outcome.

	• Number of symptomatic and asymptomatic arrhythmia events detected over total wear time • Ability to quantify atrial fibrillation (AF) burden (amount of time spent in AF) • Time to first arrhythmia event and time to first symptomatic event • Time to return device, analysis and report production • Test failure rate • Signal quality Clinical management outcomes: • Time to diagnosis or rule out of cardiac arrhythmia • Time to initiation of preventative treatment • Impact of test results on clinical decision making • Total number of hospital outpatient appointments for testing • Total number of hospital outpatient appointments or admissions for device-related complications • Number of outpatient visits and staff time for undertaking and analysing diagnostic tests • Morbidity (including stroke,		

	thromboembolism, heart failure, and complications associated with preventative treatment) • Mortality Patient outcomes: • Patient compliance (average wear time and analysable wear time) • Ease of use (for patients and healthcare professionals), including training requirements • Device acceptability and patient satisfaction • Health-related quality of life • Device-related adverse events		
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.		

Subgroups to be considered	Adults referred for ambulatory ECG monitoring, who experience asymptomatic arrhythmia events Adults referred for ambulatory ECG monitoring in primary care Adults referred for ambulatory ECG monitoring in secondary care	Adults referred for ambulatory ECG monitoring, with symptoms of arrhythmia Adults referred for ambulatory ECG monitoring, without symptoms of arrhythmia (e.g., patients with cryptogenic stroke or TIA) Adults referred for ambulatory ECG monitoring in secondary care	The primary care referral pathway is included within the general medicine pathway as a route to diagnostic services but will not be considered separately within the economic modelling.
Functional classification and risk category	Zio XT Service is classified as an active monitoring technology and so has a tier 3b evidence level. Risk category is low		
Special considerations, including issues related to equality	The area of skin in which the Zio XT patch is applied will need shaving if hair is present. Some religions forbid cutting or shaving bodily hair. Zio XT Service is not approved for paediatric use. Religion and age are protected characteristics under the Equality Act. Contraindications are listed the instructions for use for Zio XT Service.	Note: Traditional approaches to ECG monitoring also require shaving of bodily hair for electrode placement on the body	

2 The technology

2.1 Overview of the technology

Give the brand name, approved name and details of any different versions of the same technology (including future versions in development and due to launch within

12 months). Please also provide links to (or send copies of) the instructions for use for each version of the technology.

Brand name	Zio XT Service
Approved name	Zio XT ECG Monitoring System
CE mark class and date of authorisation	CE Mark Class IIa Original approval: 2 December 2014 Last amended: 25 June 2019
Main function	Electrocardiographic ambulatory recorder
Development stage	Post-launch
Current availability in the UK	Commercially available

Version(s)	Launched	Features
Zio XT Service	2016	The Zio XT Service is intended to record, store, and report continuous electrocardiogram (ECG) rhythms for long-term monitoring. The Zio XT Service is comprised of the Zio XT biosensor, ZEUS software platform and the Zio XT technical report.

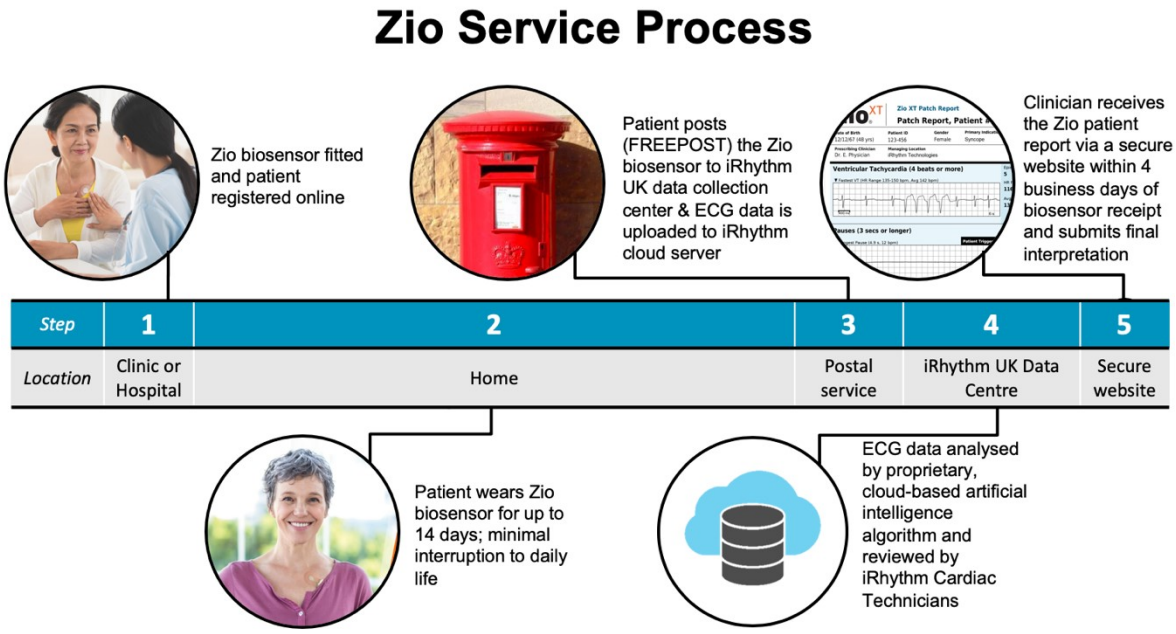
Briefly describe the technology (no more than 1,000 words). Include details on how the technology works, functionality, integration with other systems, any innovative features, and if the technology must be used alongside another treatment or technology. Include diagrams if appropriate.

Zio XT ECG monitoring service (Zio XT Service, iRhythm Technologies) is a remote cardiac monitoring system used to detect cardiac arrhythmias. It is comprised of 3 components:

- Zio XT biosensor: a wearable single lead ambulatory electrocardiogram (ECG)
- ZEUS: a proprietary, regulated software platform and online portal that stores, analyses and sorts the ECG data to generate a report of the findings
- Zio XT technical report: a clinically actionable summary of the recorded ECG data

The Zio XT Service is intended to replace or enhance the current assessment pathway for cardiac arrhythmia detection in people with palpitations, fainting (syncope) and suspected cardiac arrhythmia. The adhesive Zio XT biosensor is placed on the person's left upper chest and records a continuous beat-to-beat ECG for up to 14 days. The device is

designed to facilitate patient compliance and thereby improve data collection. Without external leads or wires, noise artifacts are reduced in the data and the wearer may go about normal daily activities, including light exercise or showering, without required monitor maintenance. Each Zio XT biosensor is intended for single-patient use. After the monitoring period is completed, the wearer removes the biosensor and sends it to the company by freepost. The ECG recordings are analysed using the artificial intelligence led algorithm within ZEUS and overseen by accredited cardiac physiologists. A technical report is produced, containing information regarding arrhythmia episodes, wear and analysis time and patient-captured events, and is sent to the prescribing clinician for final analysis and interpretation. There are no patient identifiers in or on the Zio XT Patch and data cannot be accessed if the Zio XT Patch were to be physically intercepted.



2.2 Claimed benefits of the technology

What are the claimed benefits for patients and the NHS of using the technology for the decision problem described in Section 1?

Claimed benefit	Supporting evidence	Rationale
Patient benefits		
Improved diagnostic yield, minimising the number of repeat tests needed to	• Rosenberg 2013 • Barrett 2014 • Kaura 2019	Compared with the 24-hour Holter monitor, studies have shown the Zio XT Service significantly increased the detection of cardiac arrhythmias

confirm or rule out arrhythmia	• Zio XT Service Evaluation Tool • Zio XT Service in Primary Care Pilot Project • Clinical pathways (with vs. without Zio XT) • Hospital Episode Statistics (HES)	(please refer to section 8.2 for more detail) In the current pathway patients are often required to have repeat tests due to suboptimal diagnostic yield of current monitoring modalities. As shown across clinical studies and in real world findings, improved diagnostic yield of the Zio XT Service reduces the number of repeat tests required to diagnose or rule out.
Greater diagnostic accuracy and efficiency in detecting clinically relevant arrhythmias, including symptomatic and silent atrial fibrillation	• Eysenck 2019 • Barrett 2014 • Eisenberg 2014 • Turakhia 2015 • Steinhubl 2018	Zio XT clinical studies show greater diagnostic accuracy, sensitivity and specificity in detecting arrhythmias, than the comparator (please refer to Section 8.2 for more detail). Zio XT Service Evaluation Tools echo these findings, with high rates of symptomatic and asymptomatic arrhythmia detection.
Earlier and increased diagnosis helps to close the detection gap, enabling more patients to receive appropriate preventative strategies. This reduces the occurrence of the clinical sequelae of arrhythmia such as syncope, stroke and heart failure	• Rosenberg 2013 • Kaura 2019 • AF High Impact Intervention Tool	In the current pathway, patients must frequently undergo repeat ambulatory monitoring tests before a diagnosis of arrhythmia is reached and they can commence treatment. The Ealing pilot has shown in some areas, patients typically wait up to 11 weeks between initial referral and result becoming available to their GP. Greater detection of AF leads to stroke reduction, as shown by the ICHP High Impact Tool. National programmes by Rightcare are focusing on strategies to increase detection of AF in order to reduce the burden of stroke. The Zio XT Service leads to earlier diagnosis and initiation of preventative treatment. In Kaura et al, a significantly higher proportion of patients randomised to the Zio XT Service were taking anticoagulants at 90 days, 16.3% compared with 2.1% of patients who only had 24-hour

		Holter monitoring (Kaura et al., 2019). In Rosenberg et al, 28.4% of patients had a change in classification of their AF and had their management changed as a result of using the Zio XT Service., with 17.3% having a change in their antiarrhythmic medication and 5.3% changing oral anticoagulant use (Rosenberg et al., 2013).
Minimal disruption to patients' daily activities leading to improved patient compliance and data collection (wear time, analysable time and signal quality)	• Rosenberg 2013 • Eysenck 2014 • Barrett 2014 • Kaura 2019	Several studies comparing Zio XT with other monitors reference ease of use of the Zio XT biosensor by a wide range of patients. High patient compliance yields consistently high wear time compared to prescribed time as well as high analysable time. Median wear time for the Zio XT Service was 10.8 days (Rosenberg et al., 2013), 11.1 days (Barrett et al., 2014), 11.8 days (Kaura et al., 2019) and 12.8 days (Eysenck et al., 2019) out of the scheduled 14 days. This was longer than the mean 22.5 to 25 hours' wear time for the 24-hour Holter monitor in these three studies. Please refer to Section 8.2 for more detail.
Streamlined patient pathways reduced number of outpatient visits (aligned to NHS Long Term Plan objectives), thereby increasing patient access and reducing health inequalities	• Rosenberg 2013 • Barrett 2014 • Kaura 2019 • Zio XT Service Evaluation Tool • Clinical pathways (with vs. without Zio XT)	The Zio XT Service enables the Zio XT biosensor to be placed at the first appointment so patients do not have to return to have a separate monitor fitting. Also, patients return the Zio XT biosensor by post, so do not have to return the monitor to the hospital when the monitoring period is over. The extended length of wear time (up to 14 days) and the improved diagnostic yield achieved with the Zio XT Service also minimises the number of appointments for repeat tests needed to confirm or rule out

		arrhythmia. Therefore, overall the Zio XT Service can be expected to streamline the patient pathway and improve access to ambulatory ECG monitoring among hard-to-reach populations, both those populations living in rural areas and those who have difficulties in attending frequent hospital appointments.
System benefits		
Reduction in costs and resources that could be avoided through earlier diagnosis and greater rate of detection of AF, such as repeat hospital admissions related to the clinical sequelae of arrhythmia, such as syncope, stroke or heart failure	• Kaura 2019 • Clinical pathways (with vs. without Zio XT) • AF High Impact Intervention Tool • Economic analysis (Part 2) • Hospital Episode Statistics (HES)	Economic modelling is expected to show the Zio XT Service to be cost neutral relative to existing current pathways using current technologies, when considered at a system level. This reflects savings in the cost of hardware, maintenance and consumables, out-patient appointments for fitting and removal of the standard device (single attendance assumed for the Zio XT pathway), cardiac physiologist time to analyse and report on the result (bundled into Zio XT Service charge), repeat testing (the diagnostic yield of existing technologies is substantially lower than for the Zio XT Service, necessitating repeat testing for many patients). Improved diagnostic yield with the Zio XT Service is likely to result in earlier diagnosis and greater detection of arrhythmias. This is particularly important for patients with undiagnosed atrial fibrillation, in whom prompt treatment with anticoagulation can be expected to yield a reduction in stroke risk. Economic modelling is expected to demonstrate long-term savings from reduced risk of stroke. In Kaura et at, an economic evaluation concluded that there would be an estimated 10.8 fewer strokes per year for the NHS Trust

		with use of Zio XT Service, which could save healthcare costs of up to £162,491 over 5 years and societal costs of £410,449 over 5 years.
Reduction in staff, estate and capital equipment resource use in the ambulatory ECG monitoring pathway, due to reduced repeat testing, reduced in-clinic analysis of ECG recordings and reduced outpatient appointments	• Kaura 2019 • Zio XT Service Evaluation Tool • Clinical pathways (with vs. without Zio XT) • Zio XT Service in Primary Care Pilot Project • Economic analysis (Part 2) • Hospital Episode Statistics (HES)	The Zio XT Service results in system savings that come about as a result of: The Zio XT biosensor can be fitted at the first appointment, reducing the need for additional outpatient appointments for monitor fitting. Outsourced cardiac physiologist time is included in the Zio XT Service, reducing the time required for in-house staff to analyse and report on the test result The diagnostic yield of existing technologies is substantially lower than for the Zio XT Service, necessitating repeat testing for many patients. With the Zio XT Service, a diagnosis (or rule out) is mostly reached in a single test.
Standardisation and efficiency gains in cardiac diagnostic services within and across NHS trusts through simplified processes, supported by Artificial Intelligence and service evaluation tools	• Zio XT Service Evaluation Tool • Clinical pathways (with vs. without Zio XT)	Current cardiac diagnostic services workforce supports the fitting, removal and analysis of the ambulatory recording. There is a current national shortage of qualified cardiac physiologists across all grades and services are supplementing with locum and agency staff. A cardiac diagnostic service using the Zio XT Service would free qualified staff from sessions they would normally analyse ambulatory monitoring to support other areas of the service in need of qualified staff. Zio XT's AI led algorithm reduces the involvement of hospital medical staff in the creation and review of the Zio XT patient reports. As shown in Hannun's paper, the Zio XT algorithm met or exceeded the ECG

		interpretation of expert cardiologists. In the current pathway today, medical staff must carefully review and correct each patient report. The Zio XT Service lifts that burden as it requires no staff input or oversight and eliminates the potential for inadvertent human error in the creation of the report. Additionally, iRhythm provides the Zio XT Service Evaluation Tool to each customer on a quarterly basis. This comprehensive summary of Zio XT utility and clinical results assists the hospital in monitoring arrhythmia findings, determining which patients with which indications are best suited for Zio XT and in evaluating the service overall.
Ease of implementation; minimal changes in facilities or infrastructure needed when Zio XT Service adopted in standard practice, including in rural areas	• Rosenberg 2013 • Eysenck 2019 • Barrett 2014 • Kaura 2019 • Clinical pathways (with vs. without Zio XT)	The Zio XT Service is easily implemented and does not require changes in facilities or infrastructure. The number of visits to hospital that the patient is required to make to undergo ambulatory ECG monitoring are also reduced because the monitor is readily available and easily fitted at the first appointment, and then can be returned by post. Improved diagnostic yield also minimises the number of repeat tests needed to confirm or rule out arrhythmia. Therefore, the Zio XT Service can be expected to improve access to ambulatory ECG monitoring among hard-to-reach populations, both those populations living in rural areas and those who have difficulties in attending frequent hospital appointments. NHS Western Isles (Scotland) has seen a reduction in patient visits and extended transport time by adopting the Zio XT Service.

Cost benefits		
Reduction in cardiac arrhythmia detection pathway costs compared to current pathway	• Kaura 2019 • Zio XT Service in Primary Care Pilot Project • Economic analysis (Part 2) • Hospital Episode Statistics (HES)	Current care pathways based on the use of standard Holter monitors are associated with a substantially lower diagnostic yield than is seen with Zio XT, as evidenced by Kaura et al. This results in a higher proportion of Holter patients returning for re-monitoring on multiple occasions (HES data). This multiple cycling through the pathway results in similar or higher overall costs for Holter tested patients, compared with Zio XT patients. Even with multiple Holter monitoring, the net diagnostic yield for Zio XT remains higher, with consequent potential for clinical gain (see below)
Reduction in costs associated with stroke	• Kaura 2019 • Hart 2007 • Xu 2018 • Economic analysis (Part 2)	The higher diagnostic yield achieved by Zio XT compared with Holter monitoring is likely to result in a) earlier diagnosis of paroxysmal AF and b) fewer missed diagnoses of paroxysmal AF. The impact of effective management of AF has been well documented in the literature (Hart 2007). By ensuring rapid diagnosis with a reduction in false negatives, Zio XT may be expected to minimise the number of avoidable strokes attributable to untreated AF. After offsetting the cost consequences of these avoided strokes (Xu 2018), the use of Zio XT can be shown to be cost saving.
Sustainability benefits		
Reduction in transportation-related pollution due to decreased hospital visits	• Hospital Episode Statistics (HES), NHS Digital	By minimising patient visits to hospital and/or clinic, transportation-related environmental pollution is reduced. See Section 2.3 for additional information.
Reduction in waste due to fewer cardiac tests and iRhythm's recycling practices	• iRhythm recycling policies and practices	The Zio XT biosensor is designed to maximize re-usage and recycling of its component parts. Additionally, the Zio XT Service reduces waste by decreasing the number of ambulatory

		monitors required and thereby single-use disposable equipment such as electrodes. See Section 2.3 for additional information.

2.3 Other considerations

Describe any training (for healthcare professionals and patients or their carers) that would be needed if the NHS were to adopt the technology (no more than 500 words).

For healthcare professionals (Cardiac Physiologists and Assistant Cardiac Physiologists) no additional training would be required as the training for the clinical tasks and duties associated with the Zio XT Service is already delivered through in-house training for bands 1 – 4, and through the practical modules of the BSc (Hons) Healthcare Science degree for all bands 5 and above required to practice. Any technical instructions, specifically for the registration of the patients' identification details are delivered by iRhythm market sales representatives to any healthcare service staff involved with the fitting of the Zio XT biosensor, as well as being fully explained in the product packaging, which every Zio XT biosensor comes enclosed.

For patients and carers all instructions for wear and removal of the Zio XT biosensor are delivered during the fitting procedure by the healthcare professional. Instructions for wear, removal and symptom recognition are also clearly outlined in the Patient Instructions & Button Press Log (please see Appendix D) given to the patient or carer to take home.

Briefly describe the environmental impact of adopting the technology across the NHS, including for example the impact of the manufacturing process and waste disposal process, and any sustainability considerations (no more than 500 words).

The existing ambulatory cardiac monitoring industry uses tens of thousands of disposable AA or AAA batteries each year to power their devices. Lead wires, electrode patches and antiquated or broken devices also end up in landfills. Conversely, iRhythm designed the Zio XT biosensor with the environment in mind. iRhythm recycles 100% of each device returned following patient wear; no part of the device ends up in a landfill. Below are a few examples of what the recycled Zio XT biosensors may be used for:

- Plastic Case: The plastic case will be recycled into park benches, trash containers, non-critical plastic uses, drums and parking blocks, to name a few.
- PCB Board: The metals from the board and components are recovered. The list of metals includes gold, copper, silver and iron. The plastic and fiber of the PCB Board can be used for coasters, drums, golf clubs, and packaging fillers among other commercial uses.
- Cables: The metals from the cable are recovered, while the plastic and PVC are recycled for reuse in the plastic industry.
- Batteries: The metals and elements from the batteries are recovered and sold back to their respective industries. The metals and elements in batteries include lead, polypropylene, gypsum, nickel, steel, cadmium, zinc and manganese.

Additionally, the Zio XT Service may reduce the number of visits to hospital that the patient is required to make to undergo ambulatory ECG monitoring because the monitor is readily available and easily fitted at the first appointment, and then can be returned by post. As a result, patients travel fewer miles and the environmental impact of transport is decreased. To calculate approximate miles saved due to a reduction in required appointments, a cohort of 765,469 patients from across England who had a cardiac monitoring appointment between April 2017 to March 2018 was examined using Hospital Episode Statistics. To estimate miles traveled per appointment, analysis was performed on the distance between the patients' GP office and hospital in which the cardiac monitoring appointment was held. An average distance of 8.95 miles was traveled per appointment, a total of 6.8 million miles per year.

Source: Hospital Episode Statistics (HES), NHS Digital, analysed by Imperial College Health Partners.

If the technology provides any health information, such as advice to users, briefly describe how this is aligned with best available sources such as NICE guidance or guidance from other relevant professional organisations or bodies. Describe how this is kept up to date and accurate (no more than 500 words).

The Zio XT technical report is provided to the prescribing clinician for final review and clinical interpretation following ECG analysis by the AI based algorithm and Cardiac Technician review. The arrhythmias are classified in the report according to guidelines from the British Society of Cardiology (BSC), the European Society of Cardiology (ESC), the American College of Cardiology (ACC), the Heart Rhythm Society (HRS) and the American Heart Association (AHA). Additionally, input into the report is sought on an ongoing basis from global clinical experts through iRhythm's Scientific Advisory Board and Medical Directors composed of cardiologists and electrophysiologists.

iRhythm also contacts the prescribing clinician when an urgent arrhythmia is detected in a patient's ECG data, for example ventricular tachycardia or a pause over 6 seconds in duration. iRhythm Cardiac Technicians place an immediate phone call when these arrhythmias appear in a Zio XT technical report to alert the clinician prior to publishing the report. The criteria for urgent notification was also determined based on guidelines from the professional societies.

Please see the sample Zio XT technical report and Urgent Notification form in Appendix D.

iRhythm does not provide health information to patients.

If peer-support or other similar communication functions are available within the technology please describe what safeguarding measures are in place to ensure the safety of users, for example user agreements or moderation. Describe who has access to the platform and their roles and why these people are suitable and qualified to have access (no more than 500 words).

Not applicable.

Does the technology use recognised behaviour change techniques or frameworks? If yes, please provide details of these and provide academic references supporting the use of these techniques or frameworks. Please state how the principles of these techniques or frameworks have been incorporated into the technology and how the technology will be updated/aligned with best practice going forward (no more than 1,000 words).

Not applicable

Does the effectiveness of the technology rely on the use of artificial intelligence (AI)? If yes, please describe how AI is embedded into the technology, the type(s) of

AI used and how the technology will be updated/aligned with best practice going forward (no more than 1,000 words). Provide any relevant references.

The Zio XT Service is powered by ZEUS, the Zio XT ECG Utilisation System, a regulated data analysis and reporting software platform. ZEUS consists of a collection of software modules responsible for the download, storage, analysis and reporting of electrocardiogram data captured by the Zio XT biosensor, including AI-based algorithms for rhythm and beat classification.

Zio XT biosensors applied at the clinic are registered into the Zio XT Service by clinical staff using the secure website provided by ZEUS. Upon receipt at the data collection center, the ECG data recorded by the Zio XT biosensor across the wear period is extracted by a technician using ZTrans, the intake software module provided by ZEUS.

Extracted ECG data is provided to the ZEUS ECG Analysis software module to identify beats, beat types (Normal, PVCs, PACs), and rhythms present in the recording. Analysis is performed across a pool of machines, managed by a scaling service that expands the number of processing servers based on the count of ECG recordings to be analyzed.

In total fourteen rhythm categories, plus artifact/noise, are classified by the ZEUS ECG Analysis software:

1. Atrial fibrillation
2. Complete heart block
3. Second degree AV block –Type I
4. Second degree AV block –Type II
5. Pause >3 seconds
6. Supraventricular tachycardia
7. Ventricular fibrillation
8. Ventricular bigeminy
9. Ventricular trigeminy
10. Ventricular tachycardia
11. Ectopic atrial rhythm
12. Junctional rhythm
13. Idioventricular rhythm
14. Sinus rhythm
15. Artifact/Noise

At the core of the ECG Analysis software module is a deep-learned AI algorithm designed to provide expert-level rhythm annotations. Developed in conjunction with the Stanford University Open AI laboratory, the algorithm leverages data from iRhythm's massive curated database of over 400 million hours of ECG data and arrhythmia labels from over 1.5 million patient records, as well as advances in artificial intelligence, specifically Deep neural networks (DNNs).

DNNs are computational models comprised of several processing layers, each of which can learn increasingly abstract representations of the input data. DNNs have been utilized in the fields of speech and image recognition as well as medical applications. DNNs recognize patterns and learn from raw input data; the more training data consumed, the better the performance, making them well suited for ECG interpretation.

The rhythm classification DNN utilised within ZEUS is a 34-layer neural network based on techniques used in speech recognition and trained against a targeted curated set of over 90,000 labels from 50,000 de-identified Zio XT patient records. In a head-to-head study described in Nature Medicine, the deep-learned algorithm met or exceeded individual expert cardiologist rhythm classification performance (Hannun, 2019; see Table 2 in Section 5.1 for more detail). In 2018, iRhythm deployed the FDA cleared deep-learned algorithm for clinical use.

Through sophisticated pattern recognition, ZEUS's AI-based algorithms enable more accurate, efficient and consistent identification of arrhythmias than rules-based rhythm classification approaches commonly used in Holter and event monitor data analysis. These attributes make the algorithm essential to the Zio XT Service by providing accurate findings consistently for extended ECG recordings (up to 14 days) across population variations observed when processing several thousands of patient records yearly. With AI-based algorithms, in particular deep neural networks, the company has overcome the major challenge with rules based approaches, in particular incomplete sets of detection rules resulting in poorer classification performance (Shah, 2007). In the new paradigm, iRhythm is able to continually improve the algorithm through training on additional data extracted from its expansive and growing curated database. The company ensures that updates to the algorithm improve the quality of the results produced, by managing changes through the company design control process, including performing formal verification testing prior to release into production.

Following algorithmic analysis, iRhythm's certified cardiac physiologists use the Quality Assurance Tool, a ZEUS software module, to conduct a quality review before posting a report for physician review. The Zio XT technical report is made available using the same secure website used to enroll patients in the Zio XT Service.

Clinicians receive this report from the secure website through which they may raise queries if needed and can enter their interpretation, if desired, to finalise the report. Once the pending interpretation is complete, ZEUS posts a final report of the analysis findings that can be retrieved and filed to patient records.

3 Clinical context

3.1 Clinical care pathways

Describe the existing clinical care pathway(s) and the new clinical care pathway(s) that includes the proposed use of the technology, ideally using a diagram or flowchart. If there are multiple options for new care pathways all should be detailed below.

Outlined below are six clinical pathways.

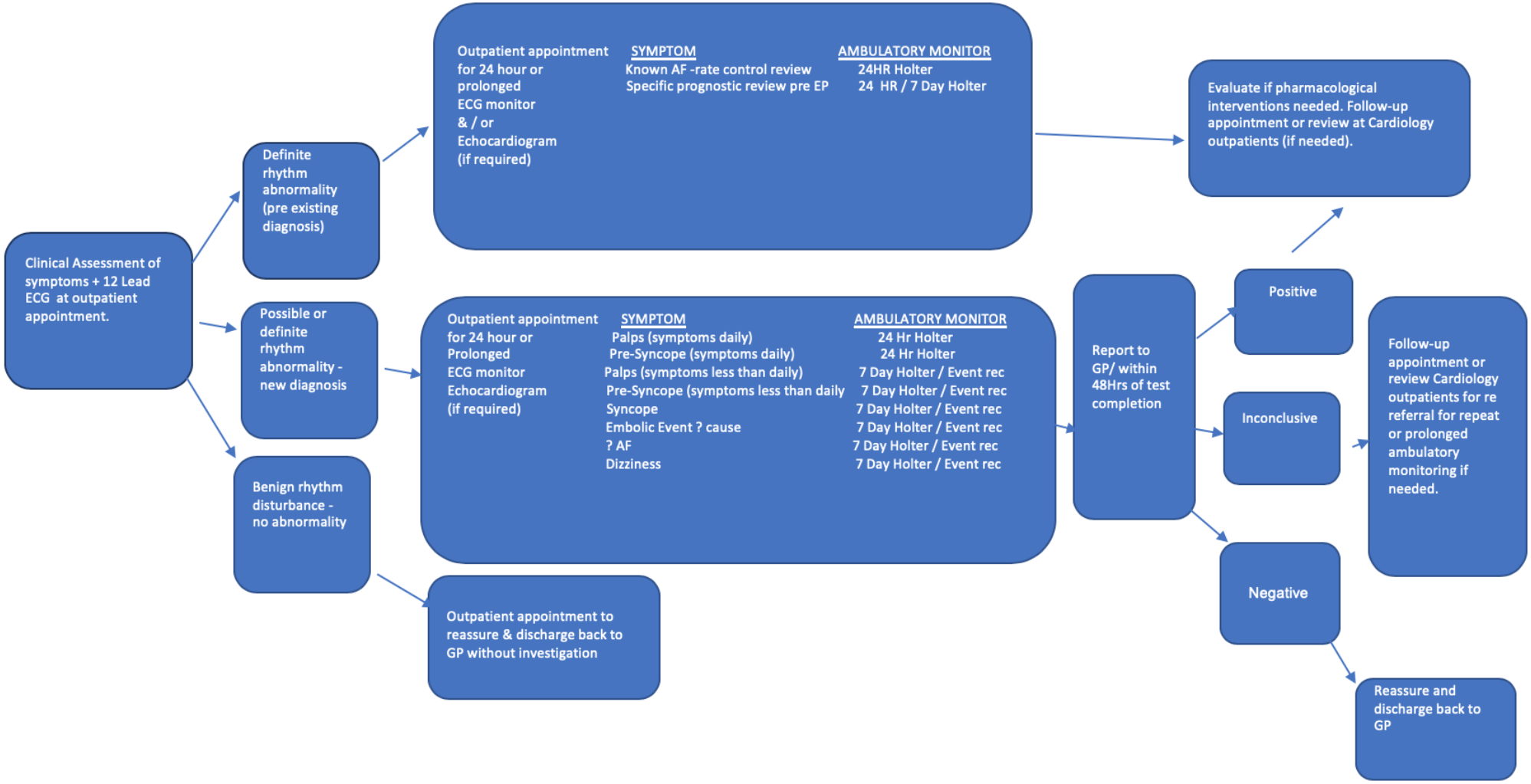
Three current clinical pathways for the referral and clinical management for patients undergoing cardiac diagnostic ambulatory monitoring:

1. Current Cardiology clinical services referral for cardiac diagnostic ambulatory monitoring pathway
2. Current Stroke / Trans Ischaemic Attack clinical services referral for cardiac diagnostic ambulatory monitoring pathway
3. Current General Medicine clinical services, and all other clinical service referral routes, for cardiac diagnostic ambulatory monitoring pathway

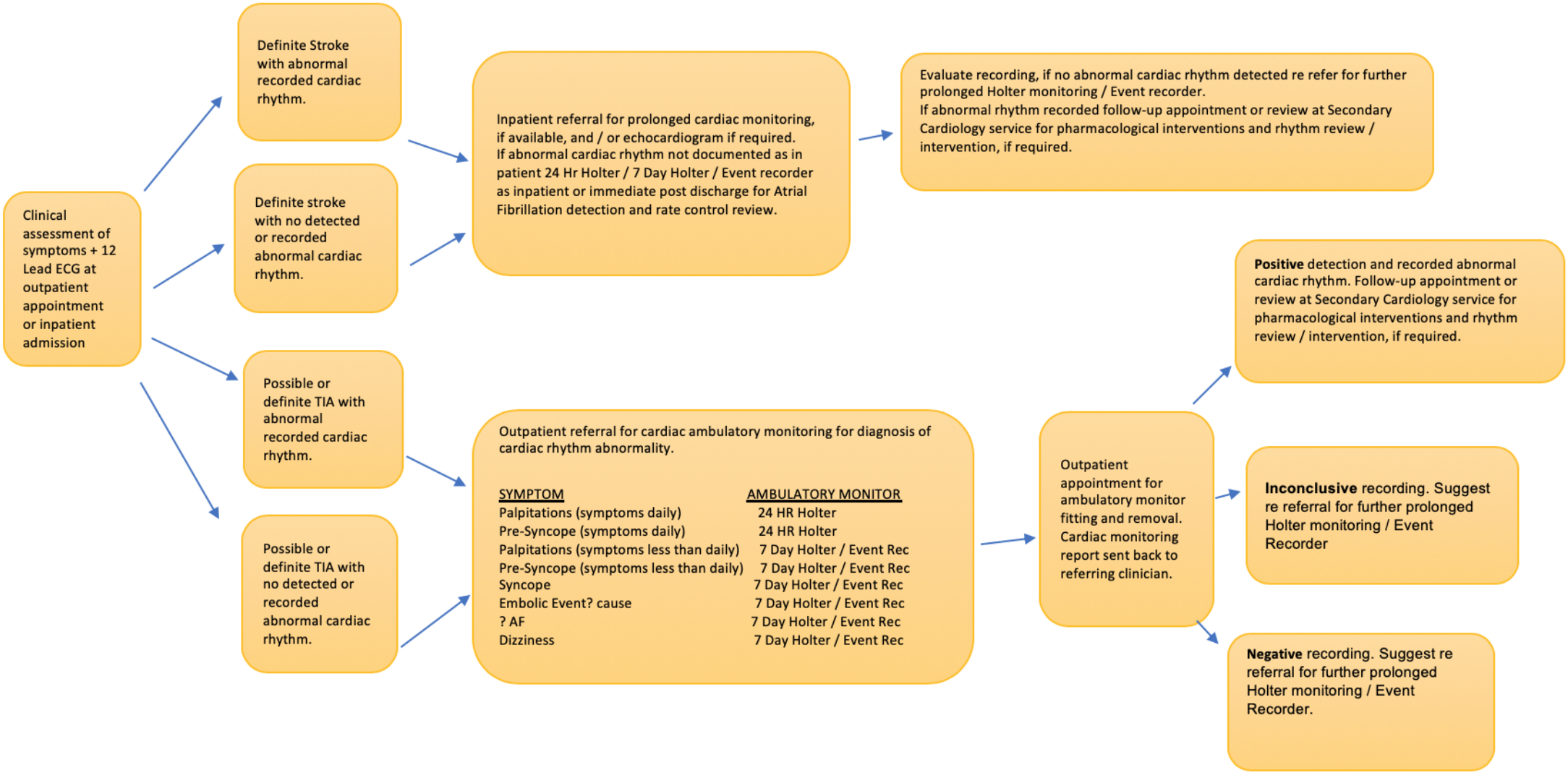
Three proposed clinical pathways for the referral and clinical management for patients undergoing cardiac diagnostic ambulatory monitoring including Zio XT Service:

4. Cardiology clinical services referral for cardiac diagnostic ambulatory monitoring, including Zio XT Service, pathway
5. Stroke / Trans Ischaemic Attack clinical services referral for cardiac diagnostic ambulatory monitoring, including Zio XT Service, pathway
6. General Medicine clinical services, and all other clinical service referral routes, for cardiac diagnostic ambulatory monitoring, including Zio XT Service, pathway

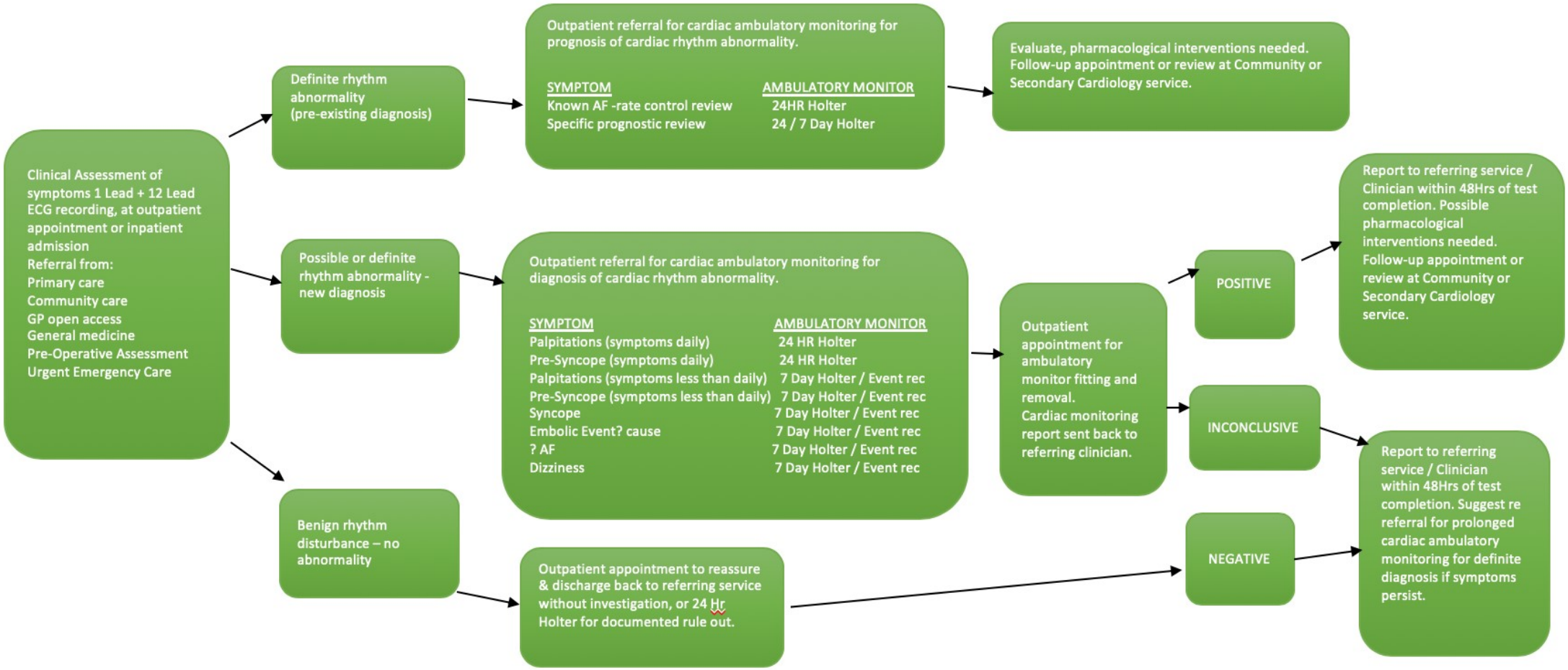
1. Current Cardiology clinical services referral for cardiac diagnostic ambulatory monitoring pathway



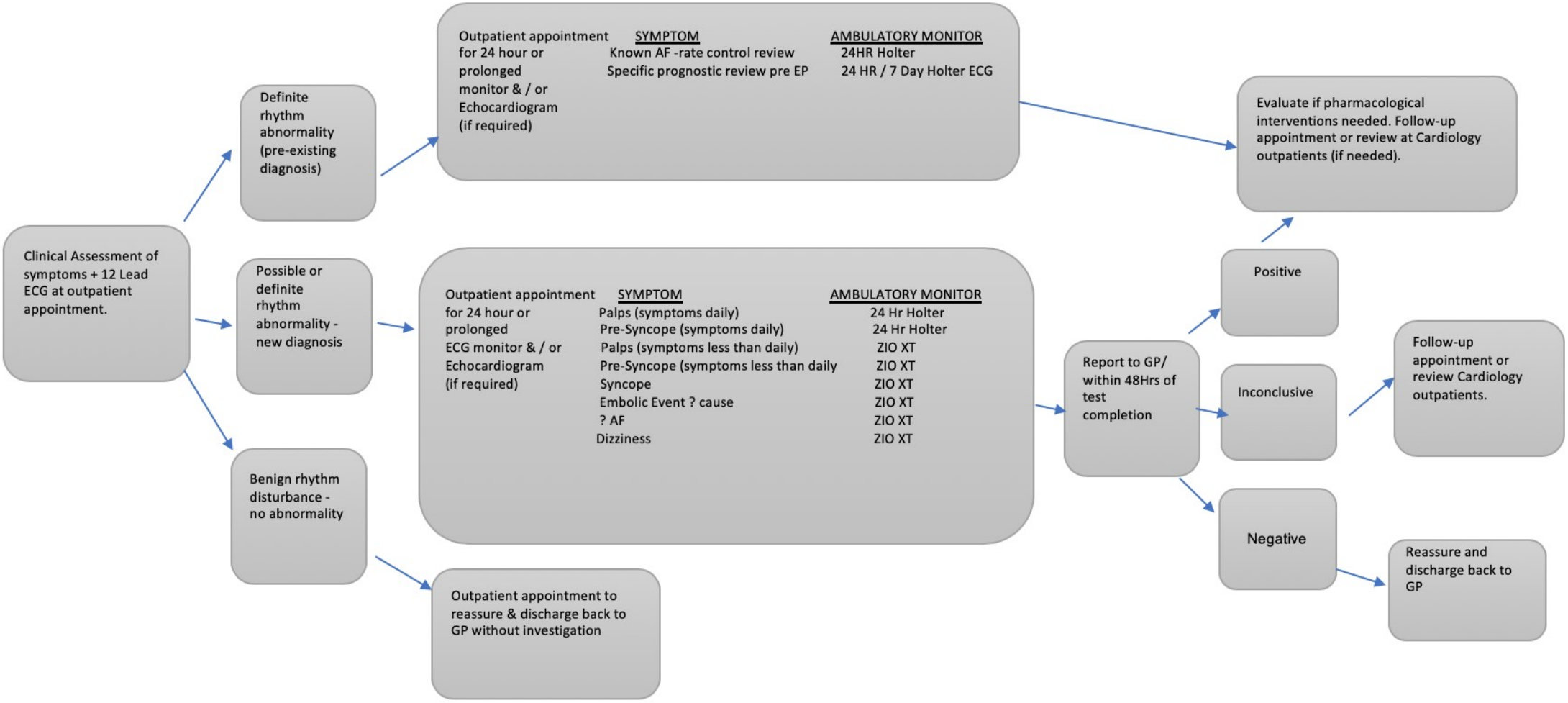
2. Current Stroke / Trans Ischaemic Attack clinical services referral for cardiac diagnostic ambulatory monitoring pathway



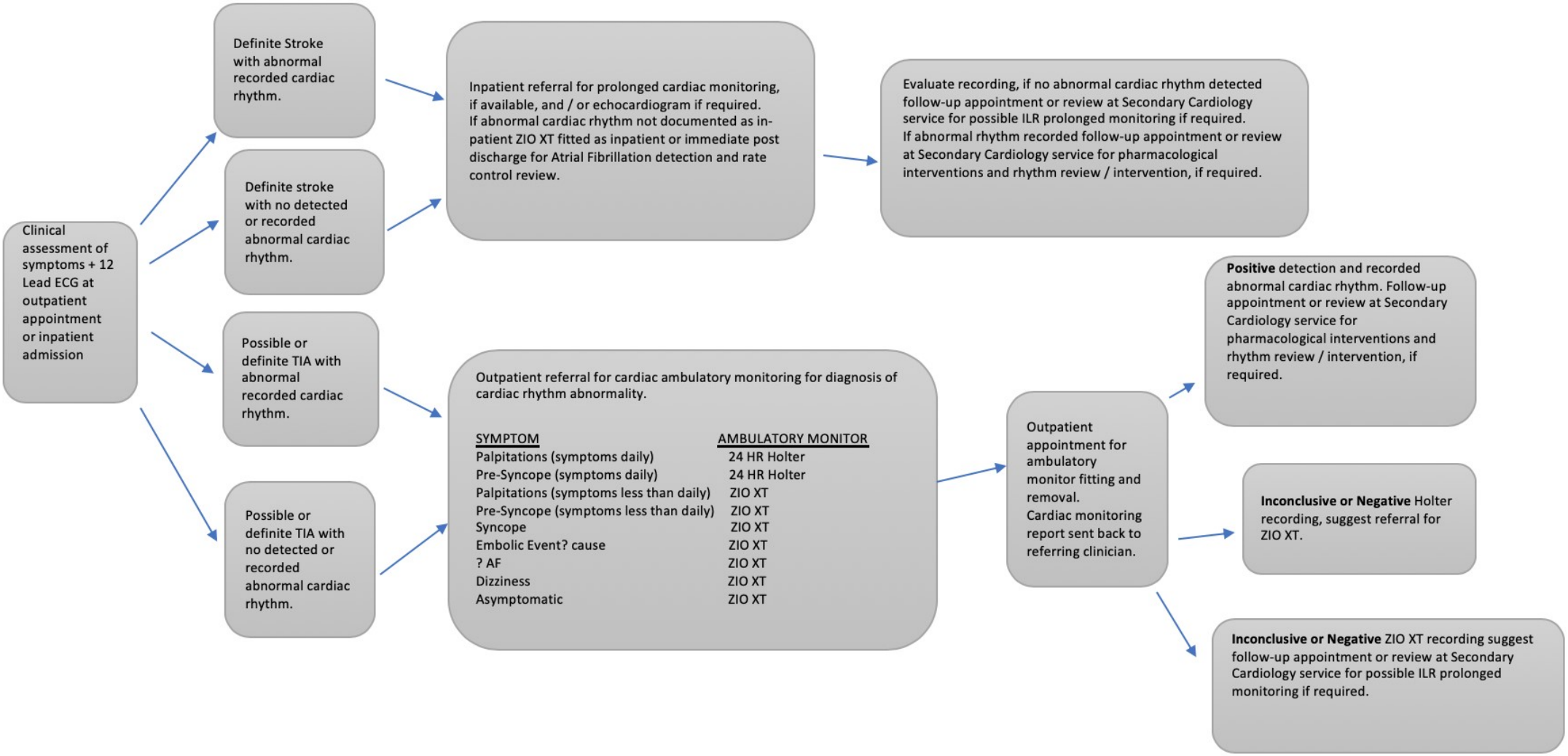
3. Current General Medicine clinical services, and all other clinical service referral routes, for cardiac diagnostic ambulatory monitoring pathway



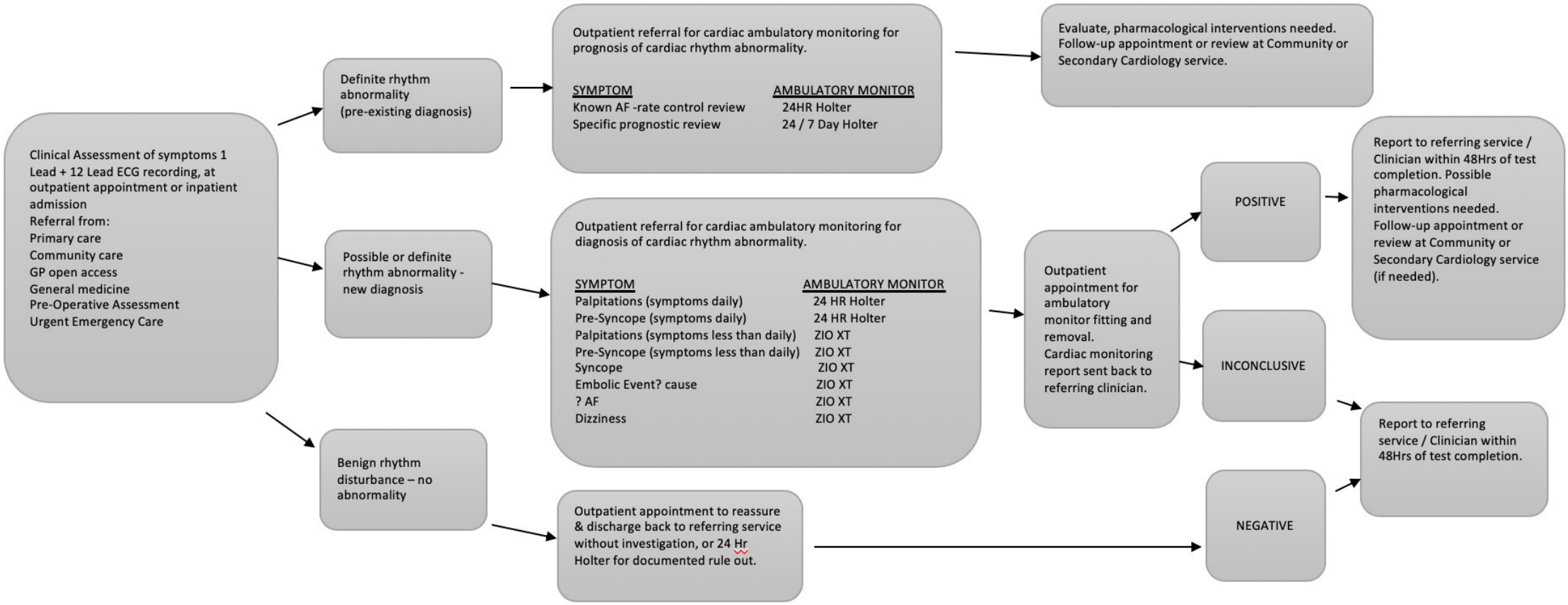
4. Cardiology clinical services referral for cardiac diagnostic ambulatory monitoring, including Zio XT Service, pathway



5. Stroke / Trans Ischaemic Attack clinical services referral for cardiac diagnostic ambulatory monitoring, including Zio XT Service, pathway



6. General Medicine clinical services, and all other clinical service referral routes, for cardiac diagnostic ambulatory monitoring, including Zio XT Service, pathway



Validation of pathways

Provide information for new pathways to demonstrate that UK health/social care professionals have been involved in the design/development/testing and/or sign-off of the technology, and that the technology has been successfully piloted or implemented within the NHS (no more than 500 words).

Sources for the three new pathways have been validated by the professionals listed below:

- Cardiology clinical services referral for cardiac diagnostic ambulatory monitoring, including Zio XT Service, pathway:
  - Clare Appleby – Consultant Cardiologist, Liverpool Heart and Chest Hospital. [redacted]
- Stroke / Trans Ischaemic Attack clinical services referral for cardiac diagnostic ambulatory monitoring, including Zio XT Service, pathway - validation has been authorised by:
  - Dr Andrew Hill – Clinical Director for Stroke service, Stroke Physician, St Helens & Knowsley Hospital Trust, Knowsley, Merseyside. [redacted]
- General Medicine clinical services, and all other clinical service referral routes, for cardiac diagnostic ambulatory monitoring, including Zio XT Service, pathway – validation has been authorised by:
  - Mrs Nicola Williams – Cardiac Clinical Service Manager, St Catherine's Hospital Foundation Trust, Birkenhead, Cheshire. [redacted]

Sources for successful sites within the NHS have been validated by the professionals listed below:

- Gloucestershire Hospitals NHS Trust
  - Dr. Mrinal Saha, Consultant Cardiology. [redacted]
- Liverpool Heart and Chest Hospital NHS Foundation Trust
  - Dr. Derick Todd, Consultant Cardiologist. [redacted]
- NHS Western Isles (Scotland)
  - Lynne Whitaker, Healthcare Scientist in Cardiology. [redacted]
- South Tyneside and Sunderland NHS Foundation Trust
  - Dr Mickey Jachuck, Clinical Director, Cardio Thoracic Medicine. [redacted]
- St. George's University Hospitals NHS Foundation Trust
  - Dr. Anthony Pereira, Consultant Neurologist. [redacted]

3.2 System changes

Describe any system changes (for example staff changes, IT infrastructure and changes to clinical protocols) that would be needed if the NHS were to adopt the technology (no more than 500 words).

No clinical application or IT implementation changes needed to incorporate the Zio XT Service into NHS services as Zio XT Service has no additional needs that the NHS services don't already support within the current clinical services and IT infrastructure.

Clinical referral protocols and pathways would need to be redesigned to incorporate the system referral pathway for any specific NHS service who will adopt the Zio XT Service into their cardiac diagnostic ambulatory monitoring service. Clinical teams within NHS services will decided on the symptom referral criteria and incorporate into their cardiac diagnostic ambulatory monitoring pathway in line with clinical guidelines.

3.3 Reducing health inequalities and improving access

Describe any contribution the technology makes to improving health inequalities in the UK health and social care system, or improving access to care among hard-to-reach populations (no more than 500 words).

Variations in the extent to which atrial fibrillation (AF) is detected and managed is one of the leading causes of health inequalities associated with CVD. In some parts of England, as many as 40% of people with AF remain undiagnosed [Source: AF High Impact Intervention Tool http://afhiit.imperialcollegehealthpartners.com/afimpact]. Without a diagnosis, these people do not have access to optimal management and are at increased risk of stroke. The Zio XT Service is associated with a greater diagnostic yield than the current pathway. It therefore reduces health inequality by increasing the number of people with AF being diagnosed and being appropriately detected as needing treatment to reduce the risk of stroke.

The Zio XT Service is easily implemented and does not require changes in facilities or infrastructure. The number of visits to hospital that the patient is required to make to undergo ambulatory ECG monitoring are also reduced because the monitor is readily available and can be easily fitted at the first appointment (compared with the current

pathway where the patient is often required to return for a separate appointment to have the monitor fitted see Section 3.1), and then can be returned by post. Improved diagnostic yield also minimises the number of repeat tests needed to confirm or rule out arrhythmia. Therefore, the Zio XT Service can be expected to improve access to ambulatory ECG monitoring among hard-to-reach populations, both those populations living in rural areas and those who have difficulties in attending frequent hospital appointments.

4 Evidence search

Undertake a systematic literature search to identify clinical and economic evidence on the technology. Also present any unpublished evidence.

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search and study identification strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		8071
Number of **clinical** studies identified as being relevant to the decision problem.		85
Number of **economic** studies identified as being relevant to the decision problem[1].		16
Of the relevant **clinical** studies identified:	Number of published **clinical** studies (included in table 1).	47
	Number of **clinical** abstracts, unpublished clinical studies or other clinical data sources (included in table 2).	32
	Number of **clinical** ongoing studies (included in table 3).	6
Of the relevant **economic** studies identified:	Number of published **economic** studies (to be included in company submission part 2).	13
	Number of **economic** abstracts, unpublished **economic** reports (to be included in company submission part 2).	3
	Number of economic ongoing studies (to be included in company submission part 2).	0

[1] Further detail about economic studies is required in Section 10

5 Clinical evidence

5.1 List of relevant clinical studies

In the following tables, give brief details of all studies identified as being relevant to the decision problem.

- Summarise details of published clinical studies in table 1.
- Summarise details of clinical abstracts, unpublished clinical studies and other clinical data sources in table 2.
- Summarise details of ongoing clinical studies in table 3.
- List the results of all clinical studies and data sources (from tables 1, 2 and 3) in table 4

Economic studies will be presented in part 2 of the submission. An overview of economic evidence is required in Section 10.

For any unpublished clinical studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

The search identified 47 publications of 45 comparative studies on the efficacy and safety of the Zio XT Service or a relevant comparator to detect cardiac arrhythmias. Of these:

- 4 publications of 4 studies involving 366 patients assessed the Zio XT Service.
- 22 publications of 22 studies involving 4,403 patients assessed external cardiac event recorders.
- 5 publications of 5 studies involving 393 patients assessed external continuous ambulatory cardiac monitors.
- 15 publications of 13 studies involving 1,639 patients assessed implantable cardiac monitors or loop recorders.

The relevant technologies are summarised below and the details of the relevant studies are then described in the following section.

Technology name	Category	Description of technology	Relevant citations
Zio XT Service	Patch/ Cutaneous continuous monitor	Described in section 2	Barrett 2014 Eysenck 2019 Kaura 2019 Rosenberg 2013
AliveCor Kardia	Handheld event recorder	AliveCor Kardia Mobile Heart Monitor consists of a pair of electrodes incorporated into a smartphone case capable of recording a standard lead 1 of a 12 lead ECG. One finger from each hand is placed on the electrodes and the tracing is downloaded wirelessly for immediate interpretation.	Halcox 2017 Narashima 2018 Reed 2019 Tarakji 2015
BioMonitor, BioMonitor 2	Implantable loop recorder	A leadless ILR that is implanted subcutaneously and uses three electrodes to continuously monitor the ECG. The BioMonitor can store a maximum of 35.8 minutes of recordings. BioMonitor2 can store up to 55 episodes each lasting 40 to 60 seconds.	Ciconte 2017 Lauschke 2016 Piorkowski 2019

CardioBip	Handheld event recorder	CardioBip monitor is a hand-held wireless device with 5 electrodes producing a 3-lead ECG acquisition suitable for 12 lead ECG reconstruction.	Gussak 2012
Cardiomemo	Handheld event recorder	Cardiomemo is applied to the precordium. ECG recordings are stored in a 32-second digital memory that can be transmitted via telephone.	Kamvaland 1997
CardioNet Mobile Cardiac Outpatient Telemetry System	Patch/ Cutaneous event recorder	The CardioNet system includes a 2-lead ECG monitor and pocket-sized wireless recorder/transmitter in a personal data assistant (PDA). It operates via a home internet base unit to transmit ECG rhythm strips continuously, which are screened continuously by technicians and physicians alerted when arrhythmias are detected.	Rothman 2007
Carnation ambulatory monitor	Patch/Cutaneous event monitor	A P-wave centric ECG patch that is placed on the sternum for 7 days of continuous recording. Patients can also press the button to record clinical events. All data are recorded and analysed for the entire duration of wear.	Eysenck 2019
CONFIRM	Implantable cardiac monitor	Implantable cardiac monitor that detects arrhythmias based on R-R interval analysis. The device stores up to 147 episodes each lasting 10 to 60 seconds for up to 18 months.	Nolker 2016
Event recorder (unspecified)	Handheld event recorder	Patients push a button when they begin to experience symptoms and the recorder will begin recording. Results are transmitted to a smartphone or computer for analysis.	Ad 2009 Gladstone 2014 Kinlay 1996 Scalvini 2005 Scherr 2008
External Loop Recorder	Patch/Cutaneous continuous monitor	An external loop recorder can record data for up to seven days. It consists of a patch and a transmitter. The patch is placed on the chest, and the transmitter is worn or carried by the patient for the duration of monitoring. The patch records and sends data to the transmitter, which relays it via a cellular network to an ECG monitoring centre.	Narashima 2018 Sejr 2017 Rothman 2007
HeartScan (Omron)	Handheld event recorder	A portable ECG recording device with an LCD display that collects data on a storage card for offline analysis. To start	De Asmundis 2014

		recording a 30-second ECG trace the patient places the lower surface of the device on the chest and the right index finger on the other end and presses the button.	
Heartwave 500	Handheld event recorder	A PDA-sized, battery powered, 5-lead recording device that can record up to 3 events at any one time. Recordings are downloaded onto a computer. If it detects an abnormal rhythm, a text message is sent to the technician or physician.	Tan 2010
Hertcard ECG	Handheld event recorder	Hertcard recorder can store up to 12 ECG recordings, each lasting 32 seconds. 125 samples are taken per second is used and the system bandwidth is 0.05 to 40 Hz. The patient applies a reusable electrode to each wrist, connects the two electrodes with the recorder using the patient cable, and then presses the activation button.	Makowska 2000
Kardia Heartwatch	Wearable event recorder	The Heartwatch takes 30-second ECG recordings when the patient applies the palm of the right hand to the recording electrode of the device. Recordings can be transmitted over the telephone.	Kamvaland 1997 Wasserlauf 2019
King of Hearts	Handheld event recorder	The King of Hearts records a single lead ECG rhythm strip continuously in a 5-minute loop and for an additional minute after the patient freezes the recording due to symptoms. Recordings are sent via telephone for analysis.	Zimetbaum 1998
Novacor R-Test monitor	Patch/ Cutaneous continuous monitor	The Novacor R-Test is a reusable monitor that can store data for up to 31 days but battery life is only 7-14 days. Continuous analysis of every heartbeat enables arrythmia detection. The patient activation button allows the capture of corresponding symptoms. Patients are required to change their chest electrodes daily.	Eysenck 2019 Higgins 2013 Sejr 2017
NUUBO vest	Wearable event recorder	A 5-electrode system consisting of an electronic device (nECG minder) attached to the garment that transmits the ECG signal via Bluetooth to a computer with a shirt that captures the ECG signal via textile electrodes. The nECG minder must be charged for 30 minutes a day. Patient triggered clinical events can be recorded	Eysenck 2019

		by pressing the device. The device can be used for up to 90 days.	
Reveal LINQ	Implantable cardiac monitor	Enhanced version of the Reveal XT with an improved AF detection algorithm and smaller size, which is inserted using a standardised technique into a tight subcutaneous pocket to improve the signal quality.	Sanders 2016 Wasserlauf 2019
Reveal PLUS	Implantable loop recorder	Implantable loop recorder that can record for at least 12 months.	Giada 2007
Reveal XT	Implantable loop recorder	Small leadless device that is implanted subcutaneously in the left pectoral area and is programmed to automatically store ECG data on the detection of arrythmia through analysis of R-R intervals.	Brachmann 2016 Damiano 2016 Davtyan 2018 Hanke 2009 Hindricks 2009 Sanna 2014 Phillippsen 2017 Ritter 2013 Eitel 2011
Spyder NIAM	Patch/ Cutaneous continuous monitor	A waterproof, external monitor that analyses three leads of the ECG and selects the one of the highest amplitude with the least noise for recording. Data is continuously transmitted during recording via Bluetooth to a smartphone.	Mamchur 2019
Vitaphone	Handheld event recorder	An episodic card recorder that is attached to the chest and has embedded electrodes and buttons for manual activation by the patient. The Vitaphone can store three 30-second recordings at a time.	Chovancik 2019
Zenicor thumb ECG	Handheld event recorder	Patients register their ECG data by placing their thumbs on two electrodes for 30 seconds. Readings are transferred via a mobile network to a central ECG database.	Doliwa Sobocinski 2012 Hendrickx 2014 Poulson 2017

Table 1 Summary of all relevant published clinical studies

Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention (and version(s))	Comparator(s)	Main outcomes	Risk of bias
Studies evaluating the Zio XT Service						
Barrett 2014, United States	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 150 Population: adults aged ≥18 years under evaluation for cardiac arrhythmia Median age: 64 years Male: 42% Setting: patients recruited from hospital cardiac investigations laboratory Withdrawals = 3%	Zio XT Service for up to 14 days	24-hour Holter monitor	Detection rate Accuracy of detection Rate of missed arrhythmia Wear time Patient satisfaction	Low risk
Eysenck 2019, United Kingdom	Prospective, randomised, within-person comparative study	Enrolled = 21 Population: Patients with a history of AF who already had a dual chamber permanent pacemaker and implantable cardioverter-defibrillator Mean age: 75 years	Zio XT Service for up to 14 days	Novacor 'R' Test 4 (RT) external monitor for 14 days; NUUBO Vest for 14 days; Carnation Ambulatory Monitor (CAM) for 14 days	AF detection rate Wear time Patient satisfaction	Low risk

		Male: 76% Setting: patients recruited from hospital clinic Withdrawals: 0				
Kaura 2019, United Kingdom	Randomised controlled trial	Enrolled = 120 Population: patients with ischaemic non-lacunar stroke or TIA within the past 72 hours Mean age: 70 to 71 years Male: 61% Setting: patients recruited from hospital Withdrawals: 22%	Zio XT Service for 14 days	24-hour Holter monitor	Detection rate AF burden Wear time Compliance Mortality Stroke/ TIA rate OAC use Safety Cost-effectiveness	Some concerns
Rosenberg 2013, United States	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 75 Population: patients with paroxysmal AF Mean age: 64 years Male: 55% Setting: patients recruited from hospital clinic Withdrawals: 1%	Zio XT Service for 14 days	24-hour Holter monitoring	Detection rate Wear time AF burden Time to detection OAC use Antiarrhythmic use Safety	Low risk
Studies evaluating external event recorders						
Kinlay 1996, Australia	Crossover randomised controlled trial	Enrolled = 45 Population: patients with previously un-	Aerotel event monitor used for 3 months or until 2	48 hr Holter monitoring with symptoms recorded	Detection rate Wear time Compliance	Low risk

		investigated palpitations who were referred for Holter monitoring. Mean age: 45 years Male: 12% Setting: patients recruited from a hospital diagnostic service Withdrawals: 4%	recordings were obtained during symptoms	in a diary during the recording period	Economic evaluation	
Narasimha 2018, United States	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 38 Population: adults with palpitations with prior nondiagnostic ECGs or Holter monitoring Mean age: 48years Male: 47% Setting: patients recruited from outpatient cardiology clinics Withdrawals: 13%	AliveCor Kardia Mobile smartphone case and app, used twice a day for 30 to 60 seconds at a time plus whenever symptoms occurred, plus symptom diary or to record the symptoms on the smartphone app	LifeWatch external loop recorder used continuously for 14 to 30 days and activated during the presence of symptoms, plus symptom diary	Detection rate Compliance Patient satisfaction Safety	Some Concern
Halcox 2017, UK	Randomised controlled trial	Enrolled = 1004 Population = adults aged >65 years with CHADS-VASc score	AliveCor Kardia smartphone ECG monitor used twice weekly plus	Standard of care	Detection rate Stroke/ TIA rate Patient preference	Low risk

		≥2, with no prior AF diagnosis Mean age = 73 years Male = 46% Setting: patients recruited via GP records or attendance at study clinic Withdrawals: 1%	when symptomatic for 12 months		Safety	
Reed 2019, United Kingdom	Randomised controlled trial	Enrolled = 243 Population: patients presenting to an emergency department with palpitations or presyncope with a nondiagnostic underlying ECG rhythm Mean age: 40 years Male: 43% Setting: patients recruited from emergency departments and acute medical units of 10 tertiary and district general hospitals Withdrawals: 1%	AliveCor smartphone case and app, patients asked to email recordings taken during episodes of palpitations or presyncope, plus symptom diary	Standard of care	Detection rate Resource use/ costs Patient satisfaction Safety	Low risk

Tarakji 2015, United States	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 60 Population: patients with a history of paroxysmal or persistent AF and scheduled for AF ablation Mean age: 60 years Male: 78% Setting: patients recruited at a single tertiary hospital centre Withdrawals: 8%	AliveCor smartphone heart monitor (AHM). ECGs were recorded at least once a week plus during symptoms	Traditional trans telephonic monitor (TTM) with recordings sent to Holter laboratories. Patients recorded data whenever they had symptoms or at least once a week	Accuracy of detection Patient satisfaction	Low risk
Gussak 2012, Serbia	Prospective single-arm study evaluating 2 interventions simultaneously in each participant.	Enrolled = 25 Population: patients with recurrent paroxysmal or persistent AF Mean age: 51years Male: 84% Setting: patients recruited from a single clinical centre Withdrawals: 8%	CardioBip wireless hand-held monitor used for 2 months after ablation then for 1 month at 6 months after ablation	12 lead ECG or 24-hour Holter monitor	Detection rate Time to diagnosis Wear rate	Low risk
Ad 2009, United States	Prospective single-arm study evaluating 2 interventions simultaneously	Enrolled = 76 Population: patients who had a Cox-Maze procedure for atrial arrhythmias at least 6 months before	CardioNet or Medicomp cardiac event monitors used for 5 days	24-hour Holter monitor or standard ECG	Detection rate	Low risk

	in each participant	Mean age: not reported Male: not reported Setting: patients recruited from hospital clinic Withdrawals: 0				
Rothman 2007, United States	Randomised controlled trial	Enrolled = 305 Population: patients with a high clinical suspicion of a significant arrhythmia, or symptoms of syncope, presyncope, or severe palpitations occurring less than every 24 hours and nondiagnostic 24-hour Holter Mean age: 55 to 57 years Male: 31% to 37% Setting: unclear; patients recruited from 17 centres Withdrawals: 13%	CardioNet Mobile cardiac outpatient telemetry system (MCOT) for up to 30 days	External loop monitors (unspecified)	Detection rates Time to diagnosis Compliance	High risk
Kimura 2017, Japan	Prospective single-arm study evaluating 2 interventions	Enrolled = 30 Population: patients undergoing catheter ablation for AF	Cardiophone telemonitoring ECG device, with 30-second	24-hour Holter monitoring every month for 6 months; standard	Detection rate, Accuracy of detection OAC use	Low risk

	simultaneously in each participant	Mean age: 59 years Male: 87% Setting: patients recruited from hospital cardiology department Withdrawals: 7%	recordings twice daily plus at the time of any symptoms for 6 months	ECG taken at every clinic follow-up visit	Antiarrhythmic use	
Gladstone 2014, Canada	Randomised controlled trial	Enrolled = 572 Population: patients with cryptogenic ischemic stroke or TIA of unknown cause within the previous 6 months without known AF Mean age: 72 to 73 years Male: 45% Setting: patients recruited from stroke centres within Canadian Stroke Consortium Withdrawals: 4%	ER910AF 30-day event recorder worn for 30 days or until a diagnosis was made, with telephone transmission of recorded ECG data	24-hour Holter monitor	Detection rate Time to diagnosis Accuracy of detection OAC use Compliance Safety	Low risk
Scalvini 2005, Italy	Randomised controlled trial	Enrolled = 310 Population: patients with palpitations Mean age: 52 to 53 years Male: 24%	Event recorder for 7-days or until 2 recordings were obtained during symptoms	24-hour Holter monitor	Detection rate	Some concern

		Setting: unclear; probably patients attending hospital department of cardiology Withdrawals: not reported				
Kamalvand 1997, United Kingdom	Crossover randomised controlled trial	Enrolled = 24 Population: patients who had undergone cardioversion for chronic AF Mean age: reported as 5 years (seems unlikely) Setting: patients recruited from hospital cardiology department Withdrawals: none reported	HeartWatch event monitor that records for 30 seconds when triggered, ECG data transmitted wirelessly to telephone receiving centre	Cardiomemo ECG recorder, which records for 32 seconds when triggered and ECG data transmitted via telephone	Detection rate Patient satisfaction Safety	Low risk
Wasserlauf 2019, United States	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 26 (validation cohort) Population: patients with history of paroxysmal AF who had been previously implanted with Reveal LINQ ICM Mean age: 72 years Male: 65%	HeartWatch with Kardia band worn during waking hours; data analysed by SmartRhythm 2.0, a convolutional neural network	Reveal LINQ ICM	Detection rate Accuracy of detection AF burden	Low risk

		Setting: patients recruited from a single hospital Withdrawals: 8%				
Tan 2010, Singapore	Randomised controlled trial	Enrolled = 120 Population: patients having palpitations or episodes of presyncope, (light-headedness or dizziness) or syncope Mean age: 44 to 50 years Male: 38% Setting: patients recruited from National Heart Centre Withdrawals: 0	HeartWave500 (HW) web-based ambulatory ECG monitoring device, and symptom diary for 2 weeks	Standard Rhythm Card trans-telephonic event recorder, and symptom diary for 2 weeks	Detection rate Time to detection	Low risk
Makowska 2000, Poland	Crossover randomised controlled trial	Enrolled = 33 Population: patients with undiagnosed palpitations occurring at least once a month Mean age: 50 years Male: 27% Setting: patients recruited from a hospital arrhythmia centre	Hertcard ECG event recording system for 4 weeks	48-hour Holter monitor with symptoms recorded in a diary during the monitoring period	Detection rate Time to detection	Some concern

		Withdrawals: none reported				
Sivakumaran 2003, Canada	Randomised controlled trial	Enrolled = 100 Population: patients who had episodes of syncope, presyncope, or both and were referred for ambulatory ECG monitoring Mean age: 56 years Male: 56% Setting: patients recruited from a Health Sciences Centre Withdrawals: 0	King of Hearts Express loop recorder used for 1 month or until 2 episodes of symptoms had been recorded	48-hour Holter, with date stamping when patients experienced symptoms and a symptom diary	Detection rate Rule out rate Time to detection Patient preference	Low risk
De Asmundis 2014, Belgium	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 625 Population: patients with paroxysmal symptoms suggestive of cardiac arrhythmias Mean age: 37 years Male: 48% Setting: patients recruited from a Heart Rhythm Management Centre Withdrawals: not reported	OMRON HeartScan patient-activated event recording system for up to 15 days	24-hour Holter monitor	Detection rate Time to detection	Some concern

Senatore 2005, Italy	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 72 Population: patients undergoing radiofrequency catheter ablation for symptomatic, refractory, paroxysmal or persistent AF who had already undergone ≥3 electrical cardioversions Mean age: 62 years Male: 60% Setting: patients recruited from hospital cardiology department Withdrawals: none reported	Trans-telephonic electrocardiogram (TTECG) worn by the patients for 90 days; recordings were taken for 30 seconds once daily and during symptomatic palpitations.	24-hour Holter monitor at 30 and 120 days after ablation	Detection rate	Low risk
Liu 2010, China	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 92 Population: patients with paroxysmal or persistent AF undergoing primary catheter ablation Mean age: 54 years Male: 78% Setting: patients recruited from hospital	Trans-telephonic external loop recorder (TTECG) worn by the patients for 12 months; recordings were taken for 30 seconds once daily for 90 days and during	Standard 12-lead ECG and 24-hour Holter monitor	Detection rate	Low risk

		Withdrawals: none reported	symptomatic palpitations			
Chovancik 2019, Czech Republic	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 105 Population: patients undergoing their first catheter ablation for paroxysmal AF Mean age: 58 years Male: 61% Setting: patients recruited from hospital Withdrawals: 3%	Vitaphone episodic card recorder, with 30-second recordings transmitted twice daily plus during arrhythmia episodes for 12 months	Vitaphone Tele-ECG Loop recorder applied for at least 7 days at months 6 and 12	Detection rate Accuracy of detection Time to diagnosis Wear time Compliance Antiarrhythmic use	Low risk
Hendrikx 2014, Sweden	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 108 Population: patients with ambiguous palpitations or dizziness/presyncope but no known arrhythmia Mean age: 54 years Male: 39% Setting: patients recruited from hospital physiology department Withdrawals: 12%	Zenicor EKG thumb intermittent hand-held ECG monitor, used twice daily plus during cardiac symptoms for 28 days	24-hour Holter monitor	Detection rate Time to diagnosis Accuracy of detection Compliance	Low risk
Poulsen 2017, Denmark	Prospective single-arm study evaluating 2	Enrolled = 100 Population: patients admitted to hospital	Zenicor thumb-ECG monitor used twice daily	Lifecard 5-day Holter monitor	Detection rate Accuracy of detection	Low risk

	interventions simultaneously in each participant	after an ischaemic stroke or TIA Mean age: 78 to 79 years Male: 45% Setting: patients recruited from hospital neurology ward Withdrawals: 17%	plus during any palpitations for 30 days		Time to diagnosis Patient preference	
Doliwa Sobocinski 2012, Sweden	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 290 Population: patients with ischaemic stroke or TIA in the previous 14 days with no prior diagnosis of AF Mean age: 72 years Male: 57% Setting: patients recruited from stroke units at 3 hospitals Withdrawals: 14%	Zenicor-EKG hand-held ECG recorder with thumb sensors used twice a day plus any time they experienced symptoms for 30 days	24-hour Holter monitor	Detection rate Time to diagnosis Accuracy of detection Wear time	Low risk
Studies evaluating continuous ambulatory cardiac monitors						
Sampaio 2018, Brazil	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 52 Population: adults with a cryptogenic stroke or TIA in the previous 14 days, controls with no stroke or TIA but with risk	Ambulatory ECG monitoring system with mobile data transmission (PoIP) used for 7 days	24-hour Holter monitor	Detection rate	Low risk

		factors for these events Mean age: 71 years Male: 52% Setting: patients recruited from hospital wards or outpatient clinics Withdrawals: 0				
Higgins 2013, United Kingdom	Randomised controlled trial	Enrolled = 100 Population: patients in sinus rhythm within 7 days of an ischaemic stroke or TIA with no history of AF or flutter Mean age: 66 years Male: 56% Setting: patients recruited from 2 acute stroke services Withdrawals: 0	Novacor R-test Evolution loop recorder, used at 24, 72 and 168 hours after randomisation, plus 12-lead ECGs at 24 and 72 hours	Standard of care: 12-lead ECGs, 24-hour Holter monitor and echocardiography	Detection rate Compliance OAC use Stroke/ TIA rate Safety	Low risk
Sejr 2017, Denmark	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 191 Population: patients aged 60 years and older with stroke or TIA within the previous week, no history of AF and no AF on baseline ECG Mean age: 71 years	R-Test Evolution external loop recorder that triggers a recording when an arrhythmia is detected, used for 7 days	48-hour Holter monitor	Detection rate Wear time Compliance	Low risk

		Male: 57% Setting: patients recruited from hospital neurology department Withdrawals: 0				
Scherr 2008, United States	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 18 Population: patients referred for evaluation of palpitations that had remained undiagnosed after at least one standard 24-h ECG Holter monitor Mean age: 56 years Male: 61% Setting: patients recruited from a hospital arrhythmia clinic Withdrawals: 0	Omron leadless monitor used for 30 days	PDS Heart event monitor used simultaneously for 30 days	Detection rate Accuracy of detection Patient satisfaction	Low risk
Mamchur 2019,Russia	Randomised controlled trial	Enrolled = 32 Population: patients with paroxysmal AF who were scheduled for catheter ablation Mean age: 57 to 59 years Male: 62% Setting: unclear	Spyder non-invasive ambulatory ECG monitor (NIAM) used continuously for up to 14 days, with patient recording the time when symptoms	Reveal XT implantable loop recorder implanted subcutaneously and used for up to 3 months	Accuracy of detection AF burden	Low risk

		Withdrawals: 0	were experienced, transmitting data for analysis via a smartphone			
Studies evaluating implantable cardiac monitors versus Holter monitors or standard of care						
Piorkowski 2019, Germany	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 92 Population: patients with indication for ICM such as unexplained syncope, paroxysmal AF, or catheter ablation of persistent AF Mean age: 63 years Male: 64% Setting: patients recruited from a heart centre department of invasive electrophysiology Withdrawals: 11%	BioMonitor 2 implantable cardiac monitor for 3 months	48-hour Holter-monitor between 1-week and 3-month follow-ups.	Detection rate Accuracy of detection Compliance Safety	Low risk
Lauschke 2016, Austria, Czech republic, Denmark, Germany, Hungary and Slovakia	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 153 Population: patients with accepted indication for ICM, including suspected cardiac arrhythmia, AF diagnosis or stroke of unknown origin	BioMonitor Implantable cardiac monitor for 12 months	48-hour Holter monitor	Detection rate Accuracy of detection Safety	Some concern

		Mean age: 62 years Male: 51% Setting: patients recruited from 17 clinical sites Withdrawals: 24%				
Ciconte 2017, Germany	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 66 Population: patients who had an implanted ICM and who had documented or symptomatic AF Mean age: 60 years Male: 86% Setting: patients recruited from hospital arrhythmia department Withdrawals: 4%	BioMonitor subcutaneous implantable cardiac monitor	48-hour Holter monitor	Detection rate Accuracy of detection AF burden	Low risk
Nolker 2016, Germany, Netherlands, United States	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 90 Population: patients with diagnosed or suspected paroxysmal AF who had previously been fitted with the CONFIRM ICM Mean age: 66 years Male: 61%	CONFIRM Implantable cardiac monitor (ICM) fitted with an electronic symptom marker	Holter monitoring for 4 days, fitted with an electronic symptom marker	Detection rate Wear time Accuracy of detection AF burden Safety	Low risk

		Setting: 12 clinical centres Withdrawals: 0				
Sanders 2016, Australia, Austria, Russia, Netherlands	Prospective single-arm study evaluating 2 interventions simultaneously in each participant.	Enrolled = 151 Population: phase 1: patients with any indication for an internal cardiac monitor; phase 2: patients with a documented history of AF and candidate for ablation Mean age: 57 years Male: 67% Setting: patients recruited from participating clinical centres Withdrawals: 1%	Reveal LINQ ICM with 1-month follow-up	24-hour Holter monitoring at 1-month post insertion	Detection rate Accuracy of detection	Low risk
Giada 2007, Italy	Multicentre crossover randomised controlled trial	Enrolled = 50 patients Population: patients with clinically significant sustained palpitations and non-diagnostic investigation Mean age: 43 to 51 years Male: 34%	Reveal Plus implantable loop recorder for at least 12 months	24-h Holter monitor plus 4-week ambulatory ECG event recorder if Holter was negative	Detection rate Time to diagnosis Safety	Some concerns

		Setting: patients recruited from hospitals Withdrawals: 0				
Philippsen 2017, Denmark	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 82 Population: patients with no known or suspected AF, but with hypertension or diabetes mellitus Mean age: 71years Male: 63% Setting: patients recruited from a hospital diabetic outpatient clinic Withdrawals: 18%	Reveal XT ICM implanted subcutaneously, and data transmitted once every month for median 588 days	72 Holter monitor used 1 month after ICM implantation	Detection rate Time to diagnosis OAC use Antiarrhythmics use	Low risk
Ritter 2013, Germany	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 61 Population: patients admitted with cryptogenic stroke and embolic stroke patterns on cerebral imaging Mean age: 63 years Male: 57% Setting: patients recruited from a hospital inpatient stroke unit	Reveal XT implantable cardiac monitor for a median of 382 days	7-day Holter monitor	Detection rate Time to diagnosis Stroke/ TIA rate	Low risk

		Withdrawals: 2%				
Davtyan 2018, Russia	RCT comparing 2 methods of ablation; also evaluated 2 devices simultaneously in each participant	Enrolled = 108 Population: patients with non-valvular symptomatic paroxysmal AF undergoing ablation Mean age: 56 to 58 years Male: 46% Setting: patients recruited from a single clinical centre Withdrawals: 18%	Reveal XT implantable loop recorder	ECG and 24-hour Holter monitor	Detection rate Compliance	Some concerns
Hindricks 2010, Europe and Canada (linked publication to Eitel 2011)	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 247 Population: patients with frequent or symptomatic AF and an implanted loop recorder who were scheduled for surgical ablation Mean age: 57 years Male: 67% Setting: patients recruited from 24 medical centres Withdrawals: 5%	Reveal XT implantable loop recorder	46-hr Holter plus expert evaluation of surface ECG recordings from the Holter to give true positive rate	Detection rate Accuracy of detection AF burden Safety	Low risk
Damiano 2016, United States	Prospective single-arm study	Enrolled = 47	Reveal XT Implantable loop	ECG and 24-hour Holter monitor at 0,	Detection rate, Serious	High risk

	evaluating 2 interventions simultaneously in each participant	Population: patients receiving surgical ablation for cardiac arrhythmia Mean age: 65 years Male: 57% Setting: patients recruited from hospital cardiology department Withdrawals: 28%	recorder for 12 months	3, 6, and 12 months	adverse events, Rate of missed arrhythmia episodes, compliance and symptoms of trigger	
Eitel 2011, Germany (Linked publication to Hindricks 2010)	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 64 Population: patients with paroxysmal AF Mean age: 60years Male: 69% Setting: patients who had been recruited to the XPECT study Withdrawals: 20%	Reveal XT implantable loop recorder inserted subcutaneously, with upgraded software for arrhythmia detection to reduce noise in the signal.	7-day Holter monitor, used at 3, 6 and 12 months after ablation	Detection rate Accuracy of detection	Some concern
Hanke 2009, Germany	Prospective single-arm study evaluating 2 interventions simultaneously in each participant	Enrolled = 45 Population: patients undergoing ablation for AF with or without additional cardiac surgery Mean age: 70 years Male: 82%	Reveal XT implantable monitoring device implanted subcutaneously promptly after chest surgery for 3 years	24-hour Holter monitor every 3 months	Detection rate Accuracy of detection AF burden Safety	Low risk

		Setting: patients recruited from a department of cardiac and thoracic vascular surgery Withdrawals: 9%				
Brachmann 2016, Europe, Canada and United States (and Sanna 2014)	Randomised controlled trial	Enrolled = 441 Population: patients who had cryptogenic stroke or TIA within the previous 90 days Median age: 61 years Male: 63% Setting: patients recruited from 55 clinical centres Withdrawals: 8% at 6 months, 89% by 36 months	Reveal XT implantable cardiac monitor	Standard of care	Detection rate Time to detection AF burden OAC use Stroke/ TIA rate Safety	Some concerns

Table 2 Summary of all relevant clinical abstracts, unpublished clinical studies or other clinical data sources

Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention (and version(s))	Comparator(s)	Main outcomes
Comparative clinical trials only available as abstracts					
Coutinho Cruz 2017 Unknown location	Prospective clinical trial comparing monitoring devices concurrently	34 patients (mean age 65 years, 49% male) referred for ECG monitoring, of whom 31 were analysed	72-hour ePatch® (wearable continuous recording device)	24-hour Holter monitor	Significantly more quality recordings were available for analysis with ePatch® versus Holter (99.6% and 97.7%, p=0.017). ePatch® identified 87% of patients with supraventricular premature beats and 92% of patients with ventricular premature beats.
Francisco-Pascual 2017 Unknown location	Cost-benefit analysis	96 patients with non-documented palpitations referred to an outpatient arrhythmia clinic, mean age 47 years, 26% male, plus a historical cohort of 58 patients, mean age 45 years, 26% male	External loop recorder (ELR)	Clinical practice	Diagnostic yield was significantly higher in the ELR group compared to the control group (86.5% vs. 20.7%, p<0.01)
Garcia Quintana 2011 Unknown location	Prospective clinical trial	96 patients with unexplained palpitations or syncope, mean age 48 years, 40% male	1-week HOLTIN (ambulatory monitor)	24-hour Holter monitor	The HOLTIN yields more clinically relevant diagnoses, had a higher sensitivity for bradycardia detection, and was deemed more comfortable

Hendrikx 2012 Unknown location	Prospective clinical trial comparing monitoring devices	108 patients referred for Holter ECG were invited to the study, 92 patients were included in the analysis (45% male, mean age 54 years)	Twice-daily handheld ECG	Holter ECG	Handheld ECG identified 9 patients with AF, 6 patients with supraventricular tachycardia and 1 patient with AV-block II (17.4% relevant arrhythmias [95% CI 11 to 26.4]), compared to 2 patients with AF, 1 patient with a broad tachycardia and 1 patient with AV-block II identified using Holter (4.3% relevant arrhythmias [95% CI 1.8 to 10.6]).
Howlett 2014 United Kingdom	Prospective clinical trial comparing consecutive monitoring devices	69 patients were enrolled, mean age of 68 years, 32% male. 90% completed the study.	12-week OMRON handheld monitor	1-week Novacor R	Significantly more arrhythmias were detected over a 12-week monitoring period compared to a 1-week monitoring period (23 vs. 13, p=0.04). 35% of cases were identified using the standard device, 48% using the handheld ECG monitor and 17% with both devices.
Interian 2011 United States	Observational study of monitoring devices and cost comparisons	98 patients with recurrent syncope or pre-syncope referred to an ER or outpatient centre, mean age 75 years, 38% male	Implantable Loop Recorder	Targeted approach	Of 21 patients with implantable loop recorder data, the average cost of medical testing and workup was $12,577 (SD = $4,268).

Locati 2016 Unknown location	Prospective clinical trial comparing monitoring devices	104 patients with unexplained palpitations or syncope, median age 57 years, 64% male	Wearable continuous recording device; 7-days 3-channel vest recorder performing ECG morphologic analysis	Wearable continuous recording device; 21-day 1-channel belt recorder performing RR analysis	For patients with unexplained palpitations and syncope, the diagnostic yield was significantly more with 21-day vs 7-day recordings ($p < 0.01$), while in patients with history of paroxysmal atrial fibrillation or unsustained ventricular tachycardia the increase was not significant.
Locati 2017 Unknown location	Prospective clinical trial comparing monitoring devices	300 patients with unexplained palpitations or syncope, 60% male (median age 65 years), 40% female (median age 59 years)	Wearable continuous recording device; 7-day 3-channel vest recorder performing ECG morphologic analysis	Wearable continuous recording device; 21-day 1-channel belt recorder performing R-R analysis	For patients with unexplained palpitations and syncope, the diagnostic yield was significantly more with 21-day vs 7-day recordings ($p < 0.01$), while in patients with history of paroxysmal atrial fibrillation or unsustained ventricular tachycardia the increase was not significant.
Proesmans 2019 Location unknown	Cost-effectiveness Markov model	Hypothetical cohort of 1000 post-cryptogenic stroke patients, aged ≥65 years	3-month monitoring PPG (photoplethys-mography) based smartphone application	Opportunistic screening and usual care	3-month intermittent PPG monitoring resulted in 26 quality-adjusted life-years and an ICER of €-1,189 per QALY gained, compared to conventional follow-up.

Reed 2019 United Kingdom	Open label, randomised controlled trial	243 patients presenting to UK emergency departments with palpitations and pre-syncope but with no obvious cause at initial consultation	AliveCor (smartphone-based event recorder) with standard of care	Standard of care alone	Secondary publication of Reed 2019, included in the full review.
Reiffel 2018 Location unknown	Model simulation	385 patients, mean age 71 years, 52% male	Insertable cardiac monitor	Various intermittent monitoring strategies (IM)	AF incidence rate via ICM at 12 months was 27.1% which exceeded the estimated rates from all forms of IM (0.8 to 10.5%).
Weerathunga 2014 Location unknown	Prospective clinical trial comparing two monitoring techniques	131 patients recruited over 2 years	7-day ambulatory ECG	24-hour Holter monitor	Of 16 patients with AF, 24-hour Holter detected 2 and 7-day ECG detected 5. Routine ECG plus 24-hour tape found 11 cases of AF and 7-day ambulatory monitoring found the additional 5. 60% of AF cases were detected on day 4.
Yinman 2011	Clinical trial comparing two monitoring techniques	72 patients (39 persistent AF and 33 paroxysmal AF) received ablation during 2009 to 2010	Trans-telephonic ECG (TTECG)	24-hour Holter monitor	After 3 months significantly more patients with AF recurrence were detected using TTECG (31 versus 17, p = 0.004) as well as after an average of 11 months (18 versus 9, p = 0.033).

Yong 2015	Cost-effectiveness analysis using a decision analytic model	Hypothetical cohort of patients after cryptogenic stroke or TIA based on the EMBRACE RCT	30-day non-invasive ECG monitors	Not reported	30-day monitoring was estimated to detect an additional 128 cases of AF per 1000 patients and to prevent 14 more recurrent ischemic strokes. 18 life-years and 13 QALYs would be gained. 30-day ECG monitoring is predicted to save $8 per patient.
Non-comparative studies of the Zio XT Service					
Turakhia et al. 2013, U.S.	A cross-sectional study of 26,751 consecutive patients fitted with a Zio XT Patch. Data from patients receiving their first-time patches were analysed. Data for repeated or subsequent patch monitoring was excluded. Interval to arrhythmia detection and diagnostic yield were among the outcomes assessed.	Patients receiving a single-use, long-term, continuous, cardiac monitoring patch for clinical indications (categorised into palpitations, AF, syncope or presyncope, bradycardia, SVT, unspecified tachycardia, VT, pause, second degree Mobitz II or third degree AVT block, polymorphic VT, and other). Mean age was 60 years and 46% were male.	Zio XT Patch monitor	None	Mean time to first arrhythmia and first symptom-triggered arrhythmias was 1.7±2.2 days and 3.0±.29 days respectively; 29.9% of first arrhythmias and 51.1% of first symptom-triggered arrhythmias occurred >48 hours after monitoring started. Single and multiple arrhythmias were detected in 16,142 (60.3%) of patients.

Schreiber et al.2014., U.S.	An observational study to determine the diagnostic yield of the Zio XT Patch and to determine the value of prolonged monitoring of low-risk discharged ED patients with possible cardiac arrhythmias. Eligible patients were given a Zio XT Patch on being discharged from ED, asked to wear it for up to 14 days and return it by post.	174 discharged adult ED patients >18 years with symptoms suggestive of possible cardiac arrhythmia who were deemed candidates for outpatient ambulatory cardiac monitoring were enrolled. Average age was 52 years and 45% were male. Palpitations (78, 44.8%), syncope (42, 24.1%) and dizziness (11, 6.3%) were the most common indications for ambulatory device placement.	Zio XT Patch monitor	None	Diagnostic yield of triggered events without arrhythmias (n=93) and significant symptomatic arrhythmias (n=17) was 63.2%. Eighty-three patients (47.7%) had ≥1 arrhythmias and 17 (9.8%) were symptomatic at the time of their arrhythmia. Median time to first arrhythmia was 1.0 days (IQR 0.2 to 2.8) and median time to first symptomatic arrhythmia was 1.5 days (IQR 0.4 to 6.7). The median time to the first triggered arrhythmia for potentially serious arrhythmias (ventricular tachycardia and pauses >3 seconds) was 3.1 and 4.2 days. Seven (4.0%) patients required immediate physician notification for serious arrhythmias. 53% of patients with symptoms, as noted by depressing the event button on the Zio XT monitor, did not have an arrhythmia present at the time.

Tung et al. 2015, U.S.	This study analysed ECG data from patients whose indication for monitoring was TIA or stroke. The duration of monitoring, analysable signal time, the number and type of arrhythmias, and the time to first arrhythmia were documented.	1171 reports from patients who underwent monitoring with the ZIO Service in the U.S. and whose indication for monitoring was stroke or TIA were included and analysed. Average age was 68 years and 55% were male.	Zio XT Patch monitor	None	The frequency of AF at 14 days was 5.0% (4.4% PAF and 0.6% chronic AF). The mean duration before the first episode of PAF was 1.5 days and the median duration before the first episode was 0.4 days. 14.3% of first PAF episodes occurred after 48 hours. Median wear time was 13.0 days and analysable time was 98.7%.
Eisenberg et al. 2014, U.S.	In this retrospective study, data from patients referred to an academic electrophysiology practice were reviewed. Arrhythmias were classified into 2 groups, brief ectopy and significant arrhythmias.	524 patients who had been referred to an academic electrophysiology practice and subsequently fitted with a patch monitor were included. Mean age was 57 years, 44% were male and the most common indications for monitoring were surveillance for unknown arrythmia/palpitations (47%), AF (30%), and syncope (8%).	Zio XT Patch monitor	None	An arrhythmia was detected in 99.5% of patients with the most common being ventricular premature beat (93%). 57% had significant arrhythmias with the most common being supraventricular tachycardia in 231 patients (44%), followed by atrial fibrillation/flutter in 105 patients (20%), and non-sustained ventricular tachycardia in 79 patients (15%). Over one-third of initial arrhythmias were recorded after 48 hours. The majority of AF episodes (62%) were asymptomatic. Patient-reported symptoms did not correlate with arrhythmias, including AF, in half of all symptom recordings.

Turakhia et al. 2014, U.S.	A single-centre prospective screening study to assess whether continuous ambulatory ECG monitoring can detect silent AF in asymptomatic patients with known risk factors. Patients wore the Zio XT patch for up to 2 weeks.	79 patients were enrolled from an outpatient setting. Inclusion criteria were age ≥55 years and ≥2 of coronary disease, heart failure, hypertension, diabetes, sleep apnoea. Patients with prior AF, stroke, TIA, implantable pacemaker or defibrillator, or with palpitations or syncope in the previous year were excluded. 75 patients completed the monitoring. Mean age was 69 years and all patients were male.	Zio XT Patch monitor	None	Overall, any arrhythmia of ≥8 consecutive beats was detected in 36 subjects (48%); 18 subjects (24%) had no arrhythmias. Atrial fibrillation was detected in 4 subjects (5.3%; all with CHADS2≥1 and CHA2DS2-VASc score ≥2). All 4 patients who were detected with AF had ≥1 episode in the first 48 hours, and 3 of 4 experienced the longest episode after the first 48 hours of monitoring. An additional 26 participants (35%) experienced an initial arrhythmia other than AF after the first 48 hours. No subjects reported symptoms during AF episodes.

Solomon et al. 2016, U.S.	In this retrospective study data from 122,815 Zio XT Patch monitors were examined and potentially high-risk arrhythmias were categorised into 2 types (1) ventricular arrhythmias including non-sustained and sustained ventricular tachycardia and (2) bradyarrhythmias including sinus pauses >3 s, atrial fibrillation pauses >5 s, and high-grade heart block (Mobitz Type II or third-degree heart block).	122,454 Zio XT Patch records were identified as suitable for inclusion. 47% of the devices were worn by men.	Zio XT Patch monitor	None	Incidence: 22,443 (18.3 %) records had at least one episode of non-sustained ventricular tachycardia (NSVT), 238 (0.2 %) had sustained VT, 1766 (1.4 %) had a sinus pause >3 s (SP), 520 (0.4 %) with a pause during atrial fibrillation >5 s (AFP), and 1486 (1.2 %) with high-grade heart block (HGHB). The differences in diagnostic yield between 2 and 7 days for both ventricular arrhythmias and bradyarrhythmias were statistically significant. Median time to first arrhythmia was 74 h (IQR 26 to 149 h) for NSVT, 22 h (IQR 5 to 73 h) for sustained VT, 22 h (IQR 7 to 64 h) for SP, 31 h (IQR 11 to 82 h) for AFP, and 40 h (SD 10 to 118 h) for HGHB.

Chen et al. 2015,	Patients from the ARIC (Atherosclerosis Risk in Communities) study presenting for MRI scans wore a Zio XT Patch monitor for up to 2 weeks. Data from the monitor were analysed for burden of AF and patients also underwent a series of neuropsychological tests.	325 patients were included with mean age of 77 years and 47% were male. 8% had known AF and 4.6% had a history of stroke.	Zio XT Patch monitor	None	Distribution of AF was bimodal: 14% of patients with AF had an AF burden ranging from 1% to 6%, and 12 had an AF burden of 100% (i.e., persistent). Patients with 100% AF burden, but not those with 1% to 6% burden, had lower executive and verbal cognitive test scores then those without AF.

Muse et al. 2018, U.S. and Canada	A patch-based or long-term Holter cardiac rhythm monitor was fitted to eligible individuals without AF on ECG, and they were monitored for up to 2 weeks. DNA was isolated from a blood sample, and an AF genetic risk score (GRS) was calculated for each participant. An AF event was the first diagnosis of AF by ECG, patch monitor, or long-term Holter monitor. The AF GRS was determined for each participant based on the weighted contribution of 12 genetic risk loci.	934 patients were recruited from an outpatient clinic setting between set dates. Eligible patients were ≥40 years, able to provide a blood sample, have ≥ 1 clinical risk factor for AF and either present with symptoms of AF or with the first diagnosis of AF on ECG. 30 patients were excluded from the final analysis. The mean age for participants with AF (68.5 years [SD 11.2]) was greater than for participants without AF (65.9 years [SD 11.8], p=0.046). Men made up most of the participants with AF (52%) and the minority of participants without AF (36%).	Zio XT Patch monitor or long-term Holter cardiac rhythm monitor	None	Of 904 participants with samples for genotyping, 85 manifested AF. Participants in the highest quintile of AF GRS were more likely (odds ratio 3.11; 95% CI 1.27–7.58; p = 0.01) to have had an AF event than participants in the lowest quintile after adjusting for age, sex, smoking status, BMI, hypertension, diabetes mellitus, heart failure, and prior myocardial infarction.

Go et al. 2018, U.S.	A retrospective cohort study that used the Zio XT Patch to identify adults who were found to have paroxysmal atrial fibrillation on 14-day continuous ambulatory electrocardiographic monitoring. Ischemic stroke and other arterial thromboembolic events occurring while patients were not taking anticoagulation were identified through using electronic medical records and were validated by manual review.	1,965 eligible adult patients who had paroxysmal AF were identified at 2 large integrated health care delivery systems. Mean age was 69 years, 55% were male, mean ATRIA stroke risk score was 4.3 (SD 2.8, p = 0.61), mean CHA2DS2-VASc score was 2.6 (SD 1.6, p = 0.97)	Zio XT Patch monitor	None	The median burden of atrial fibrillation was 4.4% (IQR,1.1% to 17.23%). During follow-up, 29 valid thromboembolic events were identified while patients were not taking anticoagulation. During 1,915 person-years of follow-up while patients were not taking anticoagulation, the unadjusted thromboembolism incidence was 1.51 per 100 person-years (95% CI,1.05 to 2.18). AF burden greater than 11.4% led to a more than three-fold increase of stroke or TE events. This is while the PAF individuals were not on anticoagulants. Data showed no association between the duration of the longest AF episode and the risk of stroke. Other standard risk scores (CHA2DS2-VASc, ATRIA) were also not associated with the risk of stroke.

Reed et al. 2018, U.K.	A prospective pilot study conducted in a single tertiary ED. Eligible patients were fitted in the ED with an ambulatory patch ECG recorder (Zio XT monitor) which continuously records a single-lead ECG for up to 14 days. Primary endpoint was symptomatic significant arrhythmia at 90-day follow-up.	Patients aged ≥16 years who presented to an ED within 6 hours of an episode of syncope and whose syncope remained unexplained after ED assessment were enrolled (n=86). Patients with an obvious underlying cause of syncope after ED assessment were excluded. An unmatched historical group of 603 syncope patients with no obvious diagnosis in ED, recruited to a prior cohort study, were used as a comparator.	Zio XT Patch monitor	None	Nine of 86 patients had a symptomatic significant (including serious) arrhythmia endpoint. Diagnostic yield of the patch monitor for symptomatic significant/serious arrhythmia was 10.5% (95% CI 4.0 to 16.9; 9 of 86) compared with 2.0% (95% CI 0.9 to 3.1; 12 of 603) in the comparator group.

Steinhubl et al. 2018, U.S.	A direct-to-participant randomised clinical trial and prospective matched observational cohort study were conducted among members of a large national health plan. For the clinical trial, individuals were randomised to active home-based monitoring to start immediately or delayed by 4 months. For the observational study, 2 deidentified age-, sex-and CHA2DS2-VASc–matched controls were selected for each actively monitored individual.	Patients were enrolled from the Aetna Fully Insured Commercial and Medicare Advantage populations. Eligibility for the study included age of ≥75 years, or a male age ≥55 years or female ≥65 years with ≥1 comorbidities (e.g., hypertension, diabetes, sleep apnoea). Exclusion criteria included any current or prior diagnosis of AF, atrial flutter, or atrial tachycardia. For the routine care, observational cohort, 2 matched controls were selected for each of the actively monitored participants.	Zio XT patch monitor	None	In the randomised study, new AF was identified by 4 months in 3.9% (53/1366) of the immediate group vs 0.9% (12/1293) in the delayed group (absolute difference, 3.0% [95% CI,1.8%-4.1%]). At 1 year, AF was newly diagnosed in 109 monitored (6.7 per 100 person-years) and 81 unmonitored (2.6 per 100 person-years; difference, 4.1 [95% CI, 3.9 to 4.2]) individuals. Zio XT monitoring also detected other actionable arrhythmias, including ventricular tachycardia (VT), pause, AV block and symptomatic supraventricular tachycardia (SVT). Active monitoring was associated with the increased initiation of anticoagulants (5.7%), antiarrhythmic medication (0.8%) and new pacemakers (0.8%).

Lutsey et al. 2016, U.S.	This was a double-blind pilot randomised trial to assess adherence to oral magnesium supplementation (400mg of magnesium oxide daily) and a matching placebo, estimate the effect on circulating magnesium concentrations, and evaluate the feasibility of using an ambulatory heart rhythm monitoring device (Zio XT Patch) for assessing premature atrial contractions. The patients were asked to wear the Zio XT Patches for 2 weeks after each clinic visit.	Participants aged ≥55 years were recruited using fliers, the University of Minnesota StudyFinder website, invitations to individuals enrolled in the ResearchMatch research volunteer database, and invitations to University of Minnesota School of Public Health employees. Exclusion criteria included a prior history of heart disease (coronary heart disease, heart failure, AF), stroke, or known kidney disease. 59 patients were randomised; mean age was 62 years; 27% were male; 1 discontinued intervention due to side effects and dropped out of study.	Zio XT Patch monitor	None	Zio XT Patch wear time was approximately 13 of the requested 14 days at baseline and follow-up. More than 90% of patients wore the patch for ≥ 12 days. 2 patients did not have data for the Zio XT patch at the end of the study, one where the device malfunctioned and one who dropped out of the study.

Heckbert et al. 2018, U.S.	In this ancillary study to the Multi-Ethnic Study of Atherosclerosis study (MESA), patients completed one or two monitoring episodes using the Zio XT Patch XT. Recordings were then analysed for AF, atrial flutter, atrioventricular block, pauses and supraventricular and ventricular ectopy.	A subset of 1122 MESA patients were enrolled. Patients with and without a history of heart disease or clinically-recognised AF were included. Mean age was 75 years; 52% were men and 15% had a prior history of clinically-recognised AF/flutter	Zio XT Patch XT monitor	None	AF/flutter was detected in 32 out of 804 patients with no previous clinical history of AF/flutter and at least 12 days monitoring; AF/flutter was detected during days 3 through to 12 of monitoring in 38% of these 32 pts. For patients with data from 2 ECG patch monitors (n=439), the kappa statistic for AF/flutter was 0.85 (95% CI; 0.75 to 0.94), for AV block: 2nd degree Mobitz II and 3rd degree it was 0.36 (0.27 to 0.45) and for pauses>3s it was 0.46 (0.37 to 0.55). Median monitoring duration was 13.8 days.

Mullis et al. 2019, U.S.	This study evaluated the extent of variability in 24-hour premature ventricular contraction (PVC) burden during 14-day ambulatory cardiac monitoring in patients with significant PVC burden. Patients referred for PVS evaluation received a Zio XT Patch monitor. The recordings were then analysed for mean 14-day burden, min and max 24-hour PVC burden and absolute change in 24-hour PVC burden.	All patients presenting in a cardiology or electrophysiology clinic for the evaluation of PVCs were evaluated. 59 patients with an overall mean PVC burden of ≥5% were taken forward. Mean age was 69 years, 81% were male, the 3 most common comorbidities were hypertension (n=44), heart failure (n=27) and diabetes mellitus (n=24)	Zio XT Patch Monitor	None	43 of 59 patients could be classified as being in at least 2 of the 3 categories of PVC burden (low, <10%; intermediate, 10% to 20%; or high, >20%) depending on the 24-hour period considered during the 14-day monitoring period. 8 patients were in all 3 categories again depending on the 24-hour period considered.

Wineinger et al. 2018, U.S.	This study was a retrospective analysis of longitudinal rhythm data obtained from 12,293 individuals with paroxysmal AF (PAF). Data were analysed to identify rhythm patterns.	Patients who had worn a Zio XT Patch monitor for up to 2 weeks and were considered to have PAF based on the Zio XT Service proprietary algorithm with confirmation by certified cardiographic technicians were included (n=13,293). Average age was 69 years and 60% were male.	Zio XT Patch monitor	None	Median daily rate of PAF was 1.21 (IQR 0.31 to 4.95). 13% of patients averaged 1 PAF event every 2 hours, 6.5% averaged at least 1 PAF event each hour and 13.5% experienced only a single event. Average duration was 1.6 minutes (median 2 minutes IQR 54 s to 6.7 mins). After 24 hours of monitoring, 49.4% of patients with PAF had experienced an event with this increasing to 63.1% after 48 hours of monitoring.

Camm et al. 2014, U.S.	This study assessed the variability of premature ventricular contractions (PVC) in arrhythmogenic right ventricular dysplasia/ cardiomyopathy (ARVD/C). Eligible patients were given Zio XT Patch monitors to wear for up to 7 days. PVC counts were analysed to evaluate variability.	Patients from the John Hopkins arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) registry who had undertaken genotype analysis and met the 2010 Task Force criteria were included (n=42)	Zio XT Patch monitor	None	Median 24-hour PVC count was 1,090.5 (IQR=1,711). The difference between maximum and minimum PVC count was highly variable with statistically significant inter-day variance in mean hourly PVC counts in 76% of participants (28/37, 3 cases excluded from analysis due to insufficient data).

Schultz et al. 2019, U.S.	This was a single centre, retrospective cohort study. Patient data, data from the Zio XT Patch and follow-up were collected and analysed. The primary aim was to determine if arrhythmia monitoring for >48 hours would identify more clinically significant arrhythmias than typical 24 to 48 hours of monitoring in adults with congenital heart disease (ACHD).	Patient data was taken from ACHD patients followed at the Adult Congenital Heart program at Stanford who had extended cardiac ambulatory monitoring (ECAM, n=314). Patients with a different type of monitoring were excluded. Median age was 31 years, 39% were male. The most common indication for monitoring was patient-reported symptoms in 39% of patients. The most common diagnoses included tetralogy of Fallot, atrial septal defect (ASD) and/or partial anomalous pulmonary venous return (PAPVR).	Zio XT Patch monitor	None	156 patients (50% of ECAM) showed a significant arrhythmia, 72 of those (46%) were during the first 48 hours. For total arrhythmias, arrhythmia incidence continued to increase as time went on: 15% at 1 day, 23% at 2 days, 39% at 5 days, 47% at 7 days, 52% at 10 days, and 62% at 14 days. A clinical management change based on an arrhythmia was made in 49 patients (16%) following ECAM.

Hannun et al. 2019, U.S.	A deep neural network (DNN) was designed to classify 12 rhythm classes using ECG data from patients who had worn a Zio XT Patch monitor. This was validated against an independent test dataset annotated by cardiologists. The performance of the DNN against the gold standard cardiologist consensus committee was compared.	Training dataset for the DNN consisted of 91,232 ECG records from 53,549 patients. Mean age was 69 years, 57% were male. Test dataset used to validate the DNN consisted of 328 ECG records collected from 328 patients. Mean age was 70 years, 62% were male.	Zio XT Patch monitor	None	The average F1 score, which is the harmonic mean of the positive predictive value and sensitivity, for the DNN (0.837) exceeded that of a consensus committee of expert cardiologists (0.780). With specificity fixed at the average specificity achieved by cardiologists, the sensitivity of the DNN exceeded the average cardiologist sensitivity for all rhythm classes.

Table 3 Summary of all relevant ongoing clinical studies

Principal investigator, and location [ClinicalTrials Identifier where appropriate]	Year (expected completion date)	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention (and version(s))	Comparator(s)	Outcomes
Louise Bowman, Professor of Medicine and Clinical Trials, and Honorary Consultant Physician (Lipidology), University of Oxford [www.amalfitrial.org]	Primary outcome will be analysed 2.5 years after randomization (approx. mid-2022) and the secondary outcome will be analysed 5 years post-randomization (approx. end of 2024/early 2025).	Randomised controlled trial	High risk individuals with a CHA2DS2-VASc score ≥ 3 (men) or ≥ 4 (women), aged ≥ 65 years without known atrial fibrillation (AF) identified from primary care records. Enrolling 2500; including 1250 randomized to the Zio XT Patch and 1250 in the control arm.	The intervention group will receive 2 weeks of continuous non-invasive ECG monitoring using the Zio XT Patch compared to usual care on rates and time diagnosed with AF over a follow up period of 5 years.	Usual care	Proportion of participants diagnosed with AF compared to usual care at 2.5 years of follow up.
David J. Gladstone, MD PhD FRCPC, Sunnybrook Research Institute,	2019	SCREEN-AF is an investigator-initiated, multicentre,	The trial targets patients aged 75 years or older with a history of	Eligible participants will be randomly allocated (1:1) to	The control group will receive standard care for 6 months	New diagnosis of ECG-confirmed atrial fibrillation or flutter within 6

University of Toronto [NCT02392754]		open-label, two-group randomised controlled trial investigating non-invasive, home-based AF screening. Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Screening	hypertension and without known AF who would be potential anticoagulant candidates if AF were detected. Eligible participants will be recruited from primary care practices. 856 study participants enrolled.	one of two groups: control or intervention. The intervention group will undergo ambulatory screening for AF with a 2-week continuous ECG patch monitor (Zio XT Service) worn at baseline and again at 3 months, in addition to standard care for 6 months (including a pulse check and heart auscultation by a physician at baseline and 6 months). The intervention group will also receive a home BP monitor with automatic AF detection	(including a pulse check and heart auscultation by a physician at baseline and 6 months).	months post randomisation, defined as at least one episode of continuous AF >5 minutes (or AF documented on 2 separate 12-lead ECGs >5 minutes apart).

				capability to be used twice daily for 2 weeks during the ECG monitoring blocks.		
Mechulan A. CCRIC Clairval Hospital, France [NCT03966976]	2020	Open label RCT	Patients after ablation for paroxysmal AF	VITAPHONE mobile ECG recorder	Conventional follow-up	AF recurrence at 3 to 6 months
Fitzgibbons TP. UMass Memorial Medical Center, USA [NCT03761394]	2021	RCT	Patients aged ≥50 years with stroke or TIA or at risk of stroke (CHA2DS2-VASc score ≥3)	1. Cardea Solo cardiac monitor + Pulsewatch smartwatch testing system for 14 days 2. Kardia Mobile smartwatch + pulsewatch testing system for 30 days	1. Cardea Solo cardiac monitor for 14 days Kardia mobile 2. No device for 30 days	Usability of Pulsewatch system AF detection rate Change in anxiety symptoms (GAD-7) Change in general health (SF-12) Change in Patient Activation Score (CHAI) Change in disease management self-efficacy (GDM) Change in medication adherence (ARMS)

Park H-S. Keimyung University Dongsan Medical Center, Korea [NCT03256812]	2018 (no results available)	RCT	Patients aged 20 to 80 years undergoing ablation for non-valvular AF or sustained AF despite medical therapy or prior ablation	Smartphone ECG monitor for 12 months	24-hour Holter at 3, 6 and 12 months	Arrhythmia detection rate Hospital visits Recurrence rate of AF or atrial tachycardia
Trines S. Leiden University Medical Center, Netherlands [NCT02507986]	2020	Open label RCT	Adults after symptomatic TIA or ischaemic stroke	Single-lead ECG device via smartphone	7-day Holter monitor	AF detection rate Pro-BNP levels Atrial ectopy rate Left atrial diameter Recurrent stroke or TIA Major bleeds Left atrial volume
Buck BH. University of Alberta, Canada [NCT02428140]	2018 (no results available)	Open label RCT	Adults with ischaemic stroke or TIA in the previous 90 days with negative ECGs	Sorin Spiderflash-t external loop recorder	Medtronic Reveal-LINQ implantable loop recorder	Cost-effectiveness for AF detection AF/Flutter detection Compliance Costs Duration of AF/ flutter Adverse events Ischaemic stroke/ TIA recurrence,

						death, haemorrhagic stroke, major bleed

5.2 Details of relevant clinical studies

Please give details of all relevant clinical studies (all studies in tables 1, 2 and 3). Copy and paste a new table into the document for each study. Please use 1 table per study.

This section includes summaries of all the full-text publications included in the review. We have not included additional summaries of efficacy publications that are only available as conference abstracts. Due to the sparse data available for these, they have not been included in the model and it is difficult to address the questions in these tables.

Studies evaluating the Zio XT Service

Barrett 2014	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with the Zio XT Service for up to 14 days compared with 24-hour Holter monitor in 146 patients who were referred for investigation of cardiac arrhythmias in the USA. This is a key study on the efficacy of the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Improved diagnostic yield: The Zio XT Service detected arrhythmias in significantly more patients than the 24-hour Holter monitor over the total wear time. The 24-hour Holter monitor detected significantly more patients as having one or more of 6 arrhythmias than the Zio XT Service over just the initial 24-hour simultaneous monitoring period, but the difference was not statistically significant when the 5 most clinically important arrhythmias were assessed. All the clinically significant arrhythmias that were undetected by the Zio XT Patch were later detected during prolonged monitoring with the patch. **Greater diagnostic accuracy:** Zio XT Service sensitivity was 99%, specificity 100%, PPV 98% and NPV 98%, compared with 63% sensitivity, 100% specificity, 100% PPV and 58% NPV with the Holter monitor. **Minimal disruption to daily life and improved compliance and data collection:** Patients were more likely to find the patch comfortable to wear and fewer reported that it interfered with daily life than with the Holter monitor. When offered a choice, 81% of patients said they preferred the Zio XT Service to the 24-hour Holter monitor.
Is any information from this study likely	Yes (supportive)

Barrett 2014	
to be used in the economic model?	
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; large sample size; Weaknesses: included a heterogeneous population of all patients referred for ambulatory ECG monitoring. Risk of Bias: Low risk
How was the study funded?	The study was funded by both Clinical and Translational Science Award funding to the Scripps Translational Science Institute and the device manufacturer iRhythm Technologies Inc.

Eysenck 2019	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with the Zio XT Service, NUUBO Vest, Carnation Ambulatory Monitor and Novacor R Test 4 external cardiac monitor compared with a DDDRP pacemaker in 21 patients with a history of AF. The other external cardiac monitors are relevant comparators for the Zio XT Service as they all allow continuous monitoring for 7 to 90 days with patient-triggered symptomatic event recording.
Does this evidence support any of the claimed benefits for the technology? If so, which?	**Improved diagnostic yield:** compared with the Novacor R test 4, detection rates for AF were significantly 12-times higher with Zio XT Service, five times higher with the Carnation Ambulatory Monitor and not significantly different with the NUUBO Vest. However, the Zio XT Service detected significantly fewer episodes of AF over 6 minutes than the pacemaker. The Zio XT Service also had excellent performance in AF burden compared to the pacemaker, with excellent R-square and very low MSE. **Minimal disruption to daily life and improved compliance and data collection:** use of the Zio XT Service was associated with low rates of discomfort attaching the device that were comparable with the Novacor R Test and NUUVO Vest. Patients reported significantly less discomfort wearing the Zio XT Patch than the NUUVO Vest. The total patient time needed was significantly shorter with the Zio XT Service, CAM and NUUBO Vest than the Novacor R Test.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and	Strengths: prospective study with both devices used simultaneously in the same patients who were randomised to receive each of the external devices in turn;

Eysenck 2019	
limitations of this evidence?	Limitations: a small study with only 21 participants; patients used the external monitors in series rather than contemporaneously so differences in detection rates may reflect changes in arrhythmia rate over time rather than device accuracy; all patients also had permanent pacemakers in place so the results may not be generalisable to other populations; data on the primary outcome of AF burden is only reported graphically as a fit plot, so is difficult to compare across studies. Risk of Bias: Low risk
How was the study funded?	Funding was not specifically reported but one author had received unrestricted research grants from the manufacturers iRhythm, NUUBO Smart Solutions and Bardy Diagnostics Ltd.

Kaura 2019	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with the Zio XT Service for 14 days compared with 24-hour Holter monitor in 90 patients who had an ischaemic stroke or TIA in the previous 72 hours. This is consistent with the decision problem.
Does this evidence support any of the claimed benefits for the technology? If so, which?	**Improved diagnostic yield**: the study demonstrates significantly more patients diagnosed with paroxysmal AF with the Zio XT Service than 24-hour Holter monitor at 28 and 90 days. **Earlier diagnosis and initiation of preventative treatment**: more patients were started on anticoagulation therapy within 90 days with the Zio XT Service than 24-hour Holter monitor. There were no significant differences in recurrent ischaemic strokes, TIAs or mortality at 90 days. **Minimal disruption to patients' daily activities:** of the 26 withdrawals, 23 were due to patient refusal to use the Holter monitor. No patient refused to use the Zio XT Service. **Reduction in costs and resources**: an economic evaluation concluded that there would be an estimated 10.8 fewer strokes per year for the NHS Trust with use of Zio XT Service, which could save healthcare costs of up to £162,491 over 5 years and societal costs of £410,449 over 5 years.
Is any information from this study likely to be used in the economic model?	Yes (primary source)
What are the strengths and limitations of this evidence?	Strengths: adequately sized RCT. Limitations: Drop-out rate was high, mainly due to Holter ECG service provision, which may have biased the outcomes. Risk of Bias: Some concern as 88.5% of withdrawals were due to refusal to comply with comparator

Kaura 2019	
How was the study funded?	The study was funded by Bristol-Myers Squibb-Pfizer alliance.

Rosenberg 2013	
How are the findings relevant to the decision problem?	The study assessed detection rates of arrhythmias and assessment of the pattern of AF with the Zio XT Service compared with 24-hour Holter monitor in 74 patients who were being managed for paroxysmal AF. This reflects the decision problem.
Does this evidence support any of the claimed benefits for the technology? If so, which?	**Improved diagnostic yield**: significantly more patients had an arrhythmia diagnosed with the Zio XT Service than the 24-hour Holter monitor. **Greater diagnostic accuracy**: clinical classification of AF pattern changed in 28% of patients following Zio XT Service monitoring. **Earlier diagnosis and initiation of preventive treatment:** 28.4% of patients had a change in management: 17.3% changed antiarrhythmic medication, 5.3% changed anticoagulation.
Is any information from this study likely to be used in the economic model?	Yes (supportive)
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: moderate sized pilot study Risk of Bias: Low risk
How was the study funded?	The study was funded by the manufacturer iRhythm Technologies Inc.

Studies evaluating external event recorders

Kinlay 1996	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF or flutter with an Aerotel event monitor used for up to 3 months compared with 48-hour Holter monitor in 45 patients who were referred for Holter monitoring for unexplained palpitations. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators.

Kinlay 1996	
the technology? If so, which?	**Improved diagnostic yield:** more clinically-significant arrhythmias were detected with the Aerotel event monitor than the 48-hour Holter. An economic evaluation concluded that the Aerotel device would be cost-saving per additional clinically-significant arrhythmia detected compared with the Holter monitor.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: crossover RCT; Limitations: small study. Risk of bias: Low risk
How was the study funded?	Funding and conflicts of interest not reported.

Halcox 2017	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with the AliveCor Kardia smartphone ECG monitor for 12 months compared with usual care in 1004 patients who had a CHADS-VASc score of ≥2 and were aged ≥65 years but with no prior diagnosis of AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: significantly more patients were diagnosed with AF by the AliveCor monitor than by usual clinical care. **Earlier diagnosis and initiation of preventive treatment**: patients were diagnosed more rapidly with the AliveCor monitor than usual care. **Minimal disruption to patients' daily activities**: patients were more likely to want to switch from usual care to AliveCor than from AliveCor to usual care.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: large RCT; Limitations: patients with no access to the internet and those who could not use the device could not participate which may have added bias; most patients submitted recordings twice a week so

	may episodes of AF may have been undetected; only the device group were brought back for clinical review so outcomes in control group are less certain; study was unblinded and conducted at one centre so population may not be generalisable. Risk of Bias: Low risk
How was the study funded?	The study was funded by a joint grant from the Welsh Government Health Technology and Telehealth Fund and the manufacturer AliveCor Ltd.

Narasimha 2018	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with the AliveCor Kardia smartphone monitor used twice a day plus during symptoms for 30 days compared with the LifeWatch external loop recorder used for 14 to 30 days in 33 patients who had undiagnosed palpitations. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: the AliveCor detected more symptomatic arrhythmias than the LifeWatch, but the LifeWatch detected more asymptomatic arrhythmias, resulting in no significant difference overall. **Minimal disruption to patient's daily activities**: patients found the AliveCor easier to use and more accessible at the onset of symptoms than the LifeWatch.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: small study where patients needed to be able to use smartphone technology, so may not be generalisable to other populations; compliance with ELR was low; no real-time monitoring of arrhythmias was possible which may have been a safety issue. Risk of Bias: Some concern due to missing outcome data
How was the study funded?	Smartphones were paid for by University of Buffalo, AliveCor devices were provided free of charge by the manufacturer, one author is also an investigator on a project funded by the manufacturer AliveCor.

Reed 2019	
How are the findings relevant to the decision problem?	The study assessed detection rates of arrhythmias with the AliveCor smartphone monitor used during symptomatic episodes for 90 days compared with standard care in 243 patients who presented to an emergency department with palpitations or presyncope and a non-diagnostic ECG. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: significantly more patients had an arrhythmia detected with the AliveCor monitor than with standard care. **Earlier diagnosis and initiation of preventive treatment**: the mean time to diagnosis was significantly shorter with the AliveCor monitor than standard care. **Minimal disruption to patient's daily activities**: 87% of patients found the AliveCor monitor easy to use. **Reduction in costs and resource use:** there were no significant differences in healthcare resource use but healthcare plus intervention costs were significantly higher with AliveCor than standard care.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: large RCT; Limitations: most patients were recruited during office hours by research staff; central ECG reading service is not available in routine clinical practice. Risk of Bias: Low risk
How was the study funded?	The study was funded by Chest, Heart and Stroke Scotland and British Heart Foundation.

Tarakji 2015	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with the AliveCor cardiac monitor for 3 to 4 months compared with a traditional trans-telephonic monitor for 3 to 4 months in 55 patients who had received ablation for paroxysmal or persistent AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators.

Tarakji 2015	
for the technology? If so, which?	**Greater diagnostic accuracy**: The AliveCor had a 97% specificity and 100% sensitivity compared with the trans-telephonic cardiac monitor. **Minimal disruption to patients' daily activities**: patients had a more favourable response and were more likely to say that the AliveCor was easy to use than the trans-telephonic monitor.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: only recruited patients who had smartphones already and were familiar with their use, which may have added bias. Risk of Bias: Low risk
How was the study funded?	The study was funded by the Cleveland Clinic Electrophysiology Research Fund. The manufacturer AliveCor Inc. provided the devices but was not involved in any part of the study.

Gussak 2012	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with the CardioBip wireless hand-held monitor used daily or twice daily for 2 months plus ad-hoc recordings during arrhythmia episodes, then used again for 30 days at 6 months compared with a 24-hour Holter monitor at 1, 2 and 6 months in 25 patients who underwent ablation for AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: more patients were diagnosed with AF or flutter with the CardioBip wireless monitor than the 24-hour Holter monitor. **Earlier diagnosis and initiation of preventive treatment**: time to diagnosis of AF or flutter was a mean 24 days earlier with the CardioBip monitor than the 24-hour Holter monitor.
Is any information from this study likely to be used in the economic model?	No

Gussak 2012	
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: small study. Risk of Bias: low risk
How was the study funded?	The study was funded by the manufacturer NewCardio.

Rothman 2007	
How are the findings relevant to the decision problem?	The study assesses detection rates of arrhythmias with the Cardionet mobile cardiac outpatient telemetry system used for up to 30 days compared with an external loop monitor in 266 patients who had suspected arrhythmias, palpitations or presyncope and a non-diagnostic 24-hour Holter monitor or telemetry. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: more patients had a diagnosis after 30 days with the Cardionet MCOT than with the external loop monitor. **Earlier diagnosis**: similar median time to diagnosis with both devices.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: large RCT; Limitations: no blinding of subjects or investigators so bias could be present; patient compliance was an issue with both devices; devices were not used continuously so arrhythmia episodes could have been missed; loop recorders with an autotrigger algorithm could not be issued consistently. Risk of Bias: High risk of bias due to missing outcome data
How was the study funded?	The study was funded by the manufacturer Cardionet Inc.

Kimura 2017	
How are the findings relevant to the decision problem?	The study assessed detection rates of arrhythmias with a cardiophone telemonitoring ECG device used twice daily plus during symptoms for 6 months compared with 24-hour Holter monitor in 30 patients who were undergoing catheter ablation for AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield:** AF or tachycardia detection was higher with the cardiophone monitor than the 24-hour Holter monitor. **Greater diagnostic accuracy:** anticoagulants and antiarrhythmics could be gradually discontinued in patients shown to have no AF. **Improved compliance**: Compliance was higher with the 24-hour Holter monitor than the cardiophone monitor.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: small study with short follow-up; poor compliance with Holter monitoring and telemonitoring. Risk of Bias: Low risk
How was the study funded?	Funding not reported, authors report no conflict of interest.

Gladstone 2014	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with a 30-day cardiac event monitor compared with 24-hour Holter monitor in 572 patients who had a cryptogenic stroke or TIA in the previous 6 months and no known AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: more patients were diagnosed with AF using the 30-day event monitor than the 24-hour Holter monitor. **Earlier diagnosis and initiation of preventive treatment**: significantly more patients were switched from antiplatelets to

Gladstone 2014	
	anticoagulants after 30-day event monitor than 24-hour Holter monitor.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: very large RCT; Limitations: patients stopped recording once a diagnosis had been made which may affect accuracy data; AF burden could not be determined due to limited recording capacity of the device; recording started a mean 75 days after stroke or TIA, reducing the overall sensitivity to AF detection; detection of other causes of stroke was not rigorous so not all patients were truly cryptogenic. Risk of Bias: Low risk
How was the study funded?	The study was funded by operating grants from the Canadian Stroke Network. The authors did not report any financial support from a device manufacturer.

Ad 2009	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with a 5-day cardiac event monitor compared with 24-hour Holter monitor in 76 patients who had a Cox-Maze procedure for atrial arrhythmias but who were currently asymptomatic. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: 5-day cardiac monitors significantly increased the number of patients with an identified arrhythmia compared with 24-hour Holter monitors.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; automatic transmission of ECG recording when the device registered an arrhythmia Limitations: none reported. Risk of bias: Low risk
How was the study funded?	Not reported. Authors are employees of the Inova Heart and Vascular Institute, Falls Church, Virginia, USA

Scalvini 2005	
How are the findings relevant to the decision problem?	The study assessed detection rates of arrhythmias with a 7-day cardiac event monitor compared with 24-hour Holter monitor in 310 patients who had palpitations. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: no significant difference in proportion of patients with arrhythmia diagnosed with the 24-hour Holter monitor compared with the 7-day event monitor. Risk of Bias: Some concern as the method for measuring the outcome was inappropriate.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: large RCT; Limitations: few details reported in this brief publication. Risk of bias: Some concern due to missing outcome data
How was the study funded?	Funding not reported.

Kamalvand 1997	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with the HeartWatch cardiac event monitor compared with the Cardiomemo ECG event recorder in 24 patients who had undergone cardioversion for chronic AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield:** Neither device detected a cardiac arrhythmia. **Minimal disruption to patients' daily activities:** acceptability scores were higher for the Cardiomemo worn over the sternum than the HeartWatch wrist event monitor.

Kamalvand 1997	
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: crossover RCT; Limitations: small study and no arrhythmias detected; patient compliance was low, which may have led to delay in recording symptomatic episodes. Risk of Bias: Low risk
How was the study funded?	Funding was not reported

Wasserlauf 2019	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with the HeartWatch AF-sensing Apple watch with Kardia band worn during waking hours for a mean 110 days compared with the Reveal LINQ implantable loop recorder in 24 patients who had a history of paroxysmal AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Greater diagnostic accuracy**: AliveCor Smart Watch had a sensitivity and specificity of 83% compared with the Reveal LINQ ILR.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: small study; smartwatches had battery life of 24 hours and needed charging for 1 to 2 hours a day, during which time recordings could not be made; most patients did not wear the watch when sleeping; AF episodes of 1 hour or more were analysed, so shorter episodes were not evaluated, which affected accuracy – when a 30 minute threshold was applied, the PPV decreased; the true positive rate from the smartwatch was greater than the total number of episodes on the ICM, but the ICM was used as the gold standard, so might have missed some episodes, which will have reduced the perceived accuracy of the smartwatch; interpretation of smartwatch recordings was by algorithm and not by clinical experts. Risk of Bias: Low risk

Wasserlauf 2019	
How was the study funded?	AliveCor provided the Kardiaband monitors. Two authors were employed by the manufacturer AliveCor and owned stock in the company and one author had received other financial support from the manufacturer.

Makowska 2000	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with a Hertcard cardiac event monitor used for 4 weeks compared with 48-hour Holter monitor in 33 patients who had undiagnosed palpitations. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Greater diagnostic accuracy**: more patients had the cause of their palpitations diagnosed with the Hertcard event monitor than with the 48-hour Holter monitor. **Earlier diagnosis**: 50% of patients who were able to record an ECG trace during an episode with the Hertcard event monitor submitted a diagnostic trace by day 4, 100% by day 18.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: crossover RCT; Limitations: small study; Holter monitoring was short-term to minimise patient discomfort and costs but longer monitoring may have increased AF detection rates. Risk of Bias: Some concern due to missing outcome data
How was the study funded?	The study was funded by a research grant from the Medical Center of Postgraduate Education.

De Asmundis 2014	
How are the findings relevant to the decision problem?	The study assessed detection rates of arrhythmias with a 15-day OMRON HeartScan patient-activated cardiac event monitor compared with 24-hour Holter monitor in 625 patients who had paroxysmal palpitations or dizziness. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators.

De Asmundis 2014	
the technology? If so, which?	**Improved diagnostic yield**: the HeartScan event recorder led to a diagnosis of arrhythmia in significantly more patients than the 24-hour Holter monitor.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: very large prospective study with both devices used simultaneously in the same patients; Limitations: Patients used the HeartScan until a diagnostic event was recorded so yield may be lower in a less selective group. Risk of Bias: Some concern as method of confirming the outcome was not reported and patients who were not capable of using the device were also excluded.
How was the study funded?	The study was funded by a research grant from the manufacturer OMRON.

Tan 2010	
How are the findings relevant to the decision problem?	The study assesses detection rates of arrhythmias with the HeartWave500 ambulatory ECG event monitor used for 2 weeks compared with a standard RhythmCard telephonic event recorder for 2 weeks in 120 patients who had palpitations, presyncope or syncope. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: rates of arrhythmia detection were not significantly different between the HeartWave ambulatory ECG monitor and the RhythmCard telephonic event recorder. **Earlier diagnosis**: similar arrhythmia detection rate per patient per week.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: RCT; Limitations: Delay in interpretation of trans-telephonic signals via fixed telephone lines was longer than HeartWave signals transmitted by email with SMS alerts, which may have added bias. Risk of Bias: Low risk

Tan 2010	
How was the study funded?	The study was funded by the Enterprise Challenge but supported by the manufacturer NextWave Biomedical Pte Ltd.

Sivakumaran 2003	
How are the findings relevant to the decision problem?	The study assessed detection rates of arrhythmias with the King of Hearts express loop recorder used for up to 1 month compared with 48-hour Holter monitor in 100 patients who had syncope or presyncope. This is both a relevant population and comparators for the Zio XT Service.

Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield** and **greater diagnostic accuracy**: significantly more patients had an arrhythmia either diagnosed or excluded with the King of Hearts loop recorder than the 48-hour Holter monitor. **Earlier diagnosis**: shorter time to diagnosis with 48-hour Holter monitor than King of Hearts loop recorder. **Minimal disruption to patients' daily activities**: more patients were willing to switch to the King of Hearts loop recorder than to the Holter monitor.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: RCT with limited crossover to the second device that increased the sample size for each device; Limitations: patients and physicians were not blinded to the strategy used; pre-enrolment evaluation was not standardised, leading to a heterogeneous population; baseline data collection was not standardised. Risk of Bias: Low risk
How was the study funded?	The study was funded by a grant from Physician Services Inc. Devices were provided by the manufacturers Baylis Medical Company Inc. and Reynolds Medical.

Senatore 2005	
How are the findings relevant to the decision problem?	The study assessed detection rates of arrhythmias with a trans-telephonic ECG used daily and during symptoms for 90 days compared with 24-hour Holter monitor at 30 and 120 days in 72 patients who were undergoing radiofrequency catheter ablation for AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: significantly more patients were diagnosed with a recurrent arrhythmia with the trans-telephonic ECG than the 24-hour Holter monitor.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: the trans-telephonic ECG lasted only 30 seconds and was triggered when symptoms occurred so asymptomatic episodes may have been undetected; all patients were taking antiarrhythmic drugs during the follow-up period, which may increase the rate of asymptomatic episodes by providing rate control or shortening the duration of the recurrence. Risk of Bias: Low risk
How was the study funded?	The study was partly funded by a manufacturer of a nonfluoroscopic navigation system for ablation, Biosense Webster.

Liu 2010	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with a trans-telephonic ECG device for 12 months compared with a 24-hour Holter monitor in 92 patients who were undergoing catheter ablation for paroxysmal or persistent AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: the trans-telephonic ECG device detected AF in more patients than the 24-hour Holter monitor. **Earlier diagnosis:** recurrent AF was diagnosed more rapidly with the trans-telephonic external loop recorder than the 24-hour Holter monitor.

Liu 2010	
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: assessment of device accuracy depended on the type of AF and ablation strategy used in the heterogeneous population; monitoring was not continuous so may have missed episodes; manual recording avoided skin irritation but means asymptomatic arrhythmias may have been missed. Risk of Bias: Low risk
How was the study funded?	Funding and conflict of interests were not reported.

Chovancik 2019	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF and atrial tachycardia with the Vitaphone episodic card recorder for 12 months compared with the Vitaphone tele-ECG loop recorder for at least 7 days at months 6 and 12 in 105 patients who had undergone a first catheter ablation for paroxysmal AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: Intermittent use of an episodic card recorder during episodes throughout 12 months increased the detection of arrhythmias compared with longer monitoring durations at 6 and 12 months with an episodic loop recorder, despite a shorter wear time.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: relatively low number of arrhythmia recurrences and some patients underwent further ablation during the study period – removal of their data from analysis further reduced the power of the study; intermittent monitoring may mean arrhythmias were missed by both devices. Risk of Bias: Low risk

Chovancik 2019	
How was the study funded?	The study was funded by grant MZ ČR NS10261-3/2009. No conflict of interest was declared by the authors.

Doliwa Sobocinski 2012	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with a Zenicor thumb ECG sensor used intermittently for 30 days compared with a 24-hour Holter monitor in 290 patients who have had an ischaemic stroke or TIA in the previous 14 days and with no prior diagnosis of AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: more patients were diagnosed with AF using the intermittent thumb ECG monitor than with the 24-hour Holter monitor.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: large prospective study with both devices used simultaneously in the same patients; Limitations: withdrawals were high and few participants were diagnosed with AF, potentially leading to bias; protocol was changed during the study to raise minimum age for inclusion; patients disabled after a severe stroke might have found it difficult to use the device. Risk of Bias: Low risk
How was the study funded?	The study was funded by a grant from the Swedish Health and Lung foundation.

Hendrikx 2014	
How are the findings relevant to the decision problem?	The study assessed detection rates of arrhythmias with the Zenicor thumb cardiac event monitor used twice daily plus during symptomatic episodes for 28 days compared with 24-hour Holter monitor in 108 patients who had palpitations or dizziness/ presyncope and no known arrhythmia. This is both a relevant population and comparators for the Zio XT Service.

Hendrikx 2014	
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: more patients had an arrhythmia diagnosed with the Zenicor thumb monitor than with the 24-hour Holter monitor.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: handheld device does not record arrhythmias during physical exertion, sleep or syncope; device has only 1 lead so can be difficult to differentiate atrial flutter from sinus rhythm or regular SVT; recording is for just 30 seconds so can't assess the duration of the episode. Risk of Bias: Low risk
How was the study funded?	The study was funded by grants from Umea University Hospital and Vinnova, the manufacturer Zenicor provided the device at a reduced price.

Poulsen 2017	
How are the findings relevant to the decision problem?	The study assesses detection rates of AF with the Zenicor thumb ECG monitor used twice daily plus during palpitations for 30 days compared with the Lifecard 5-day Holter monitor in 95 patients who had been admitted to hospital with an ischaemic stroke or TIA with no prior diagnosis of AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: there was no significant difference in AF detection rates between the two devices. **Earlier diagnosis**: Faster detection of paroxysmal AF with the 5-day Holter than the Zenicor thumb monitor. **Minimal disruption to patients' daily activities**: more patients preferred to use the thumb ECG device than the Holter monitor.
Is any information from this study likely to be used in the economic model?	No

Poulsen 2017	
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: small study, 22% of patients admitted could not be included in the trial due to cognitive or physical disabilities, which may have increased bias. Risk of Bias: Low risk
How was the study funded?	The study was funded by Herlev Hospital and Carl and Ellen Hertz' grant to Danish medical and natural science.

Studies evaluating external continuous cardiac monitors

Sampaio 2018	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with an ambulatory ECG monitor with mobile data transmission used for 7 days compared with 24-hour Holter monitor in 26 patients who had recent cryptogenic stroke or TIA and in controls with risk factors but no stroke or TIA. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: Significantly more patients with stroke or TIA were diagnosed with atrial tachycardia with the ambulatory ECG monitor than the 24-hour Holter monitor, the difference in AF detection rates was not statistically significant.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: small sample size; difficulty in differentiating between AF and atrial tachycardia from device recordings; mobile phone services have limited coverage and unstable transmission velocity which affects data collection. Risk of Bias: Low risk
How was the study funded?	There were no external funding sources for the study, authors were from the Faculdade Ciências Médicas de Minas Gerais in Brazil and declared no conflicts of interest.

Higgins 2013	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with the Novacor R Test evolution loop recorder at 24, 72 and 168 hours after randomisation compared with standard practice including 24-hour Holter monitor in 100 patients who were in sinus rhythm within 7 days of an ischaemic stroke or TIA and with no history of AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield:** significantly more patients were diagnosed with AF of any duration with the Novacor R Test recorder than with standard care at 14 and 90 days. **Earlier diagnosis and initiation of preventive treatment:** greater use of anticoagulants following Novacor R Test.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: RCT; Limitations: moderately small study based in 2 locations so population may not be generalisable; technical limitations of the R-Test restricted recording time which meant that the total burden of AF could not be determined. Risk of Bias: Low risk
How was the study funded?	The study was funded by grants from the Chief Scientist Office, Scotland and the Scottish Stroke Research Network.

Sejr 2017	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with the R Test Evolution external loop recorder for 7 days compared with 48-hour Holter monitor in 191 patients who had a stroke or TIA in the previous week and no history of AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: significantly more patients were detected as having an arrhythmia with the R Test loop recorder than the Holter monitor but false positives were common and few of the detected arrhythmias from both devices were confirmed by cardiologists.

Sejr 2017	
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; investigators were blinded to the results from the other device; patients were relatively unselected so the results should be wisely generalisable; Limitations: patients thought to be poorly compliant were excluded; the clinical relevance of the 30-second duration of AF threshold is debatable although based on guidelines and different results may have been obtained with a different duration. Risk of Bias: Low risk
How was the study funded?	The project was funded by the Regional Hospital West Jutland, Health Research Fund of Central Denmark Region, Danish Heart Foundation, Aase and Ejner Danielsen Foundation, Fam. Hede Nielsen Foundation Cabinetmaker Sophus Jacobsen and Wife Foundation, Aarhus University Travel Grant and a European Stroke Conference travel grant. One of the authors is supported by the Novo Nordisk Foundation.

Scherr 2008	
How are the findings relevant to the decision problem?	The study assessed detection rates of arrhythmias with the OMRON leadless monitor used for 30 days compared with the PDS Heart event monitor used for 30 days in 18 patients who had palpitations and a negative 24-hour Holter monitor. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: there was no significant difference in arrhythmia detection rates between the OMRON leadless monitor and the PDS Heart event monitor. **Minimal disruption to patients' daily activities**: Most patients preferred the OMRON leadless monitor to the PDS Heart monitor.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: small study, so the non-significant difference may be due to underpowering rather than no true difference in device performance; population included patients with no significant

Scherr 2008	
	resting tremors that might affect the device performance, so the results may not be generalisable to other populations. Risk of Bias; Low risk
How was the study funded?	Funding not reported. Omron Inc. loaned the device to the project and the authors disclosed no conflicts of interest.

Mamchur 2019	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with the Spyder ambulatory monitor used for up to 14 days compared with the Reveal XT implantable loop recorder used for 3 months in 32 patients who were scheduled for catheter ablation for paroxysmal AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Greater diagnostic accuracy**: the accuracy of AF detection was not significantly different with the Spyder non-invasive ambulatory monitor compared with the Reveal XT implantable loop recorder.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: RCT; Limitations: small study so the non-statistical significance of the results may be due to underpowering rather than to no difference in performance. Risk of Bias: Low risk
How was the study funded?	Funding not reported, authors declared no conflict of interest.

Studies evaluating implantable cardiac monitors versus Holter monitors or standard of care

Ciconte 2017	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with the BioMonitor implanted cardiac monitor compared with 48-hour Holter monitor in 66 patients who had documented or symptomatic AF or who were due to have, or had had catheter ablation, and who had an ICM already implanted. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: a greater proportion of patients were diagnosed as having AF with the BioMonitor ICM than with the 48-hour Holter, although statistical significance was not reported. **Greater diagnostic accuracy:** The BioMonitor had a sensitivity of 100% and specificity of 67% compared with the 48-hour Holter.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: small study; did not use permanent pacemaker which is the gold-standard for cardiac rhythm monitoring; only analysed arrhythmia runs lasting >2 minutes which may have missed clinically significant episodes; comparator was only used for 48 hours so relative accuracy may be different with longer follow-up. Risk of Bias: Low risk
How was the study funded?	The study was partly funded by the device manufacturer, Biotronik SE&Co

Lauschke 2016	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with a BioMonitor implantable cardiac monitor for 12 months compared with 48-hour Holter monitor at 6 weeks or 3 months in 152 patients who had a suspected cardiac arrhythmia, previous AF diagnosis, AF ablation or cryptogenic stroke. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: AF detection rates were similar with both devices. **Greater diagnostic accuracy:** sensitivity for detecting AF was 92% with the BioMonitor compared with Holter monitor.

Lauschke 2016	
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: technical issues meant the devices could be compared in only 51% of patients which could add bias; 24% of patients could not be followed up as they were managed by non-participating cardiologists. Risk of Bias: Some concern due to bias in the measurement in the outcome and missing outcome data
How was the study funded?	The study was funded by the manufacturer Biotronic SE&Co.

Piorkowski 2019	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with the BioMonitor 2 implantable cardiac monitor for 3 months compared with a 48-hour Holter monitor in 92 patients who had an indication for ICM insertion such as known AF, unexplained syncope or prior catheter ablation for AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield:** more patients had AF detected with the BioMonitor 2 ICM than the 48-hour Holter monitor but this included false positives. **Greater diagnostic accuracy:** Sensitivity for patients with any arrhythmia and for AF was 100% for the BioMonitor 2 using the 48-hour Holter monitor as gold standard, and specificity was 88.1% for AF.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: Assessment of comparable accuracy was limited to 48 hours with Holter monitor; the device only recorded AF episodes lasting 6 minutes or longer so will have missed shorter episodes; device longevity could not be assessed beyond 3 months. Risk of Bias: Low risk

Piorkowski 2019	
How was the study funded?	The study was funded by the manufacturer Biotronic SE&Co.

Nolker 2016	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with a Confirm implantable cardiac monitor compared with 4-day Holter monitor in 90 patients who had known or suspected paroxysmal AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield:** more patients had AF detected with the Confirm ICM than 4-day Holter monitor but the statistical significance was not reported. **Greater diagnostic accuracy:** Sensitivity of the Confirm ICM was 100% for detection of patients with AF and specificity was 85.7%.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: relatively few AF episodes detected; synchronisation of the clocks on the two devices was necessary but did not always occur, which reduced the sample size; only episodes longer than 2 minutes were detected so AF rate will be underestimated; population were at high risk of AF so unclear how generalisable the results will be in other populations. Risk of Bias: Low risk
How was the study funded?	The study was funded by the manufacturer St Jude Medical Inc.

Sanders 2016	
How are the findings relevant to the decision problem?	The study assesses detection rates of AF with the REVEAL LINQ implantable cardiac monitor compared with 24-hour Holter monitor in 151 patients who had an indication for an ICM or who had a history of AF and were candidates for ablation. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators.

Sanders 2016	
the technology? If so, which?	**Improved diagnostic yield:** more patients had AF detected with the Reveal LINQ ICM than the 24-hour Holter monitor although the statistical significance was not reported. **Greater diagnostic accuracy**: accuracy of the Reveal LINQ ICM was 97.1% overall for diagnosing patients with AF and 99.4% for detecting duration of AF compared with the 24-hour Holter.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: Comparison was only 24 hours and only AF episodes of 2 minutes or longer were analysed so shorter episodes will have been missed; only AF was assessed so accuracy of detecting other atrial arrhythmias was not determined. Risk of Bias: Low risk
How was the study funded?	The study was funded by the manufacturer Medtronic.

Giada 2007	
How are the findings relevant to the decision problem?	The study assesses detection rates of AF with the Reveal Plus implantable loop recorder compared with 24-hour Holter monitor and 4-week ambulatory event recorder if the Holter was negative in 50 patients who had unexplained clinically-significant palpitations. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: significantly higher detection of arrhythmias and AF/ flutter with the Reveal Plus ILR than conventional care with 24-hour Holter ±4-week event recorder. **Earlier diagnosis:** shorter mean time to diagnosis with conventional care than with Reveal Plus ILR.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: randomised controlled trial; Limitations: small study; patients were highly selected and may not be representative of a wiser population; mean time to first

Giada 2007	
	palpitation recurrence was longer than expected, suggesting a placebo effect from device implantation. Risk of Bias: Some concerns due to deviation in one group on final diagnosis and bias in measurement of the outcome.
How was the study funded?	The study was funded in part by the manufacturer Medtronic.

Brachmann 2016 and Sanna 2014	
How are the findings relevant to the decision problem?	The CRYSTAL AF study assessed detection rates of AF with the Reveal XT implantable cardiac monitor for 36 months compared with usual care in 441 patients who had cryptogenic stroke or TIA and a negative 24-hour Holter monitor. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield:** AF detection rates were 10-fold higher with the Reveal XT ICM than the control group at 36 months. **Earlier diagnosis**: median time to diagnosis of AF was longer with the Reveal XT ICM than usual care. **Initiation of preventive treatment**: significantly more patients were taking anticoagulants after the Reveal XT ICM than with usual care. Recurrent stroke rates were similar in both groups.
Is any information from this study likely to be used in the economic model?	Yes (supportive)
What are the strengths and limitations of this evidence?	Strengths: large RCT to compare both devices; Limitations: 2-minute detection window for ICM may miss AF episodes <2mins; algorithm for detecting AF has an accuracy of 98.5% but is not infallible. Risk of bias: Some concern as the method of confirming the outcome was not reported and high withdrawals.
How was the study funded?	The study was funded by the device manufacturer Medtronic Inc.

Damiano 2016	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with the Reveal XT implantable loop recorder compared with 24-hour Holter monitor in 47 patients who were receiving surgical ablation for AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield:** no significant difference in arrhythmia detection rate at 12 months between the Reveal XT ILR and 24-hour Holter monitor. **Minimal disruption to patients' daily activities**: compliance with both devices was similar at 12 months.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: small study; low arrhythmia recurrence rate as the majority of patients had catheter ablation so detection rates may be different on other populations; ECG downloads were intermittent so episodes of arrhythmia may have been missed. Risk of Bias; High risk due to missing outcome data
How was the study funded?	The study was funded by National Institute of health grants and by the device manufacturer Medtronic Inc.

Davtyan 2018	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with the Reveal XT implantable loop recorder compared with 24-hour Holter monitor in 108 patients who were undergoing ablation for AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: more patients were determined to have AF recurrence with the Reveal XT ILR than with 24-hour Holter monitor, but statistical significance was not reported.
Is any information from this study likely to be used in the economic model?	No

Davtyan 2018	
What are the strengths and limitations of this evidence?	Strengths: RCT with both devices used simultaneously in the same patients; Limitations: study was designed to assess effectiveness of 2 ablation techniques, so little data reported on performance of devices. Risk of Bas: Some concern due to bias in measurement of the outcome and deviation from intended intervention.
How was the study funded?	Not reported. The authors stated that they had no conflict of interest.

Hanke 2009	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with the Reveal XT implantable loop recorder for 12 months compared with a 24-hour Holter monitor every 3 months in 45 patients who were undergoing ablation for AF with or without additional cardiac surgery. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield:** significantly higher AF detection with the Reveal XT ILR than with the 24-hour Holter monitor.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: IMD was taken to be the gold standard but may not be 100% accurate; simultaneous 24-hour Holter was not always provided for every time point in the study. Risk of Bias: Low risk
How was the study funded?	Funding was not reported. One author has received honoraria from the manufacturer Medtronic Inc.

Hindricks 2010	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with the Reveal XT implantable loop recorder compared with a 46-hour Holter monitor in 235 patients who were undergoing surgical ablation for frequent

Hindricks 2010	
	or symptomatic AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: similar detection rates of patients with AF and AF burden with both devices.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: Device cannot evaluate AF episodes lasting less than 2 minutes and comparison time was only 46 hours so likely outcomes from a longer follow-up period are unclear; arrhythmias other than AF were defined as false positives. Risk of Bias: Low risk
How was the study funded?	The study was partly funded by the manufacturer Medtronic Inc.

Eitel 2011 (linked publication to Hindricks 2010)	
How are the findings relevant to the decision problem?	The study assesses detection rates of AF with the Reveal XT Implantable loop recorder compared with a 7-day Holter monitor in a subgroup of 64 patients in the XPECT study who had ablation for paroxysmal AF. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: no significant difference in AF detection rates with the Reveal XT ILR and the 7-day Holter monitor.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: Focus of the study is on the impact of software upgrades on arrhythmia detection rate and specificity, so little data reported about the devices themselves.

Eitel 2011 (linked publication to Hindricks 2010)	
	Risk of Bias: Some concern due to missing outcome data in the comparator group and bias in measurement of the outcome.
How was the study funded?	The study was funded by the Volkswagen Foundation and research grants including the Heart Center Leipzig.

Philippsen 2017	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with the Reveal XT implantable loop recorder compared with 72-hour Holter monitor in 97 patients who had no known AF but were aged ≥65 years with hypertension or diabetes mellitus. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield:** more patients had AF detected with the Reveal XT ILR than the 72-hour Holter monitor, but the statistical significance was not reported. **Earlier diagnosis and initiation of preventive treatment:** 17% of patients started oral anticoagulants and 4.8% started rate control antiarrhythmic drugs after the Reveal XT ILR detected AF.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: Storage capacity and detection algorithm limitations mean AF rate was likely to be an underestimate; results may not be generalisable to other populations. Risk of Bias: Low risk
How was the study funded?	Financial support was not specified but was stated not to be by industry.

Ritter 2013	
How are the findings relevant to the decision problem?	The study assessed detection rates of AF with the Reveal XT implantable cardiac monitor compared with a 7-day Holter monitor in 61 patients who were admitted to a stroke unit with cryptogenic

Ritter 2013	
	stroke. This is both a relevant population and comparators for the Zio XT Service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence is not directly relevant to the Zio XT Service but helps to demonstrate the diagnostic accuracy of relevant comparators. **Improved diagnostic yield**: significantly higher detection rates of AF with the Reveal XT ICM than the 7-day Holter monitor.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths: prospective study with both devices used simultaneously in the same patients; Limitations: detection rate of AF was lower than expected, possibly reflecting meticulous patient selection. Risk of Bias: Low risk
How was the study funded?	Funding not reported, authors did not disclose any conflict of interest.

5.3 Results of relevant clinical studies

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Please provide results of all relevant studies in a table format. Example tables are presented below and can be adapted.

Studies evaluating the Zio XT Service

Barrett 2014	**Result with Zio XT Service, N = 146**	**Result with 24-hour Holter, N = 146**	**Company comments**
Wear time	Median 11.1 days (range 0.9 to 14.0 days)	Median 1.0 days (range 0.9 to 1.0 days)	Text
Any of 6 clinically relevant arrhythmias detected over total wear time (AV block, pause >3 seconds, polymorphic SVT >4 beats, SVT >4 beats, VT >4 beats or AF)	65.7% of patients with events detected over total wear time	41.8% of patients with events detected over total wear time, p<0.001	The Zio XT Service detected one of 6 clinically significant arrhythmias in 36 patients who were missed by the Holter monitor over the entire wear time, which was 13 days longer for Zio XT Service
Any of 5 clinically relevant arrhythmias detected over total wear time (AV block, pause >3 seconds, polymorphic SVT >4 beats, VT >4 beats or AF)	28.1% of patients with events detected over total wear time	18.5% of patients with events detected over total wear time, p<0.001	The Zio XT Service detected one of 5 clinically significant arrhythmias in 14 patients who were missed by the Holter monitor over the entire wear time, which was 13 days longer for Zio XT Service

Any of 6 clinically relevant arrhythmias detected at 24 hours	52 events detected during simultaneous 24-hour monitoring period	61 events detected during simultaneous 24-hour monitoring period, p=0.013	Significantly more arrhythmia events were detected by the Holter monitor than the Zio XT Service during the 24 hours of simultaneous monitoring
Any of 5 clinically relevant arrhythmias detected at 24 hours	24 events detected during simultaneous 24-hour monitoring period	27 events detected during simultaneous 24-hour monitoring period, p=0.083	More arrhythmia events were detected by the Holter monitor than the Zio XT Service during the 24 hours of simultaneous monitoring, but the difference was not statistically significant
Rate of missed arrhythmia detection over total wear time	1 patient had event missed that was recorded by Holter monitor	36 patients had event missed that was detected by Zio XT patch	More patients failed to have an event detected with the 24-hour Holter than the Zio XT patch over the total wear time for both devices
Rate of missed arrhythmia detection in first 24 hours	Zio XT Service: 11 patients had events not detected that were detected by 24-hour Holter	Holter: 2 patients had events not detected that were detected by Zio XT Service	More patients failed to have an event detected with the Zio XT patch than the 24-hour Holter over the 24 hours of simultaneous recording
Sensitivity for any of main 6 arrhythmias over total wear time	Zio XT Service = 96/97 = 99%	24-hour Holter = 61/97 = 63%	Gold standard was decision of physician investigators assessing data from both devices Sensitivity calculated from 2x2 tables that do not include gold standard totals
Specificity for any of main 6 arrhythmias over total wear time	Zio XT Service = 49/49 = 100%	24-hour Holter = 49/49 = 100%	
PPV for any of main 6 arrhythmias over total wear time	Zio XT Service = 96/96 = 100%	24-hour Holter = 61/61 = 100%	
NPV for any of main 6 arrhythmias over total wear time	Zio XT Service = 49/50= 98%	24-hour Holter = 49/85 = 58%	

Patient satisfaction	Patch was comfortable to wear = 93.7% Preferred Patch to Holter monitor = 81%	Holter monitor was comfortable to wear = 51.7%	More patients reported that the Zio XT patch than the Holter monitor was comfortable to wear and 81% would choose the patch over the Holter monitor.

Eysenck 2019	**Result with Zio XT Service, N = 21**	**Result with Carnation ambulatory monitor, N = 21; NUUBO Vest, N = 21, Novacor R-Test, N = 21**	**Company comments**
Odds ratio for detecting presence or absence of AF compared with Novacor R Test	OR =12.3 (95%CI 1.4 to 110.3)	Carnation Ambulatory Monitor: OR = 5.8 (95%CI 1.1 to 32.1) NUUBO Vest: OR = 2.0 (95%CI 0.5 to 7.5)	Primary outcome is AF burden but this is only reported as fit plots with limited data reported numerically in the paper. The Zio XT Service and CAM were more accurate in detecting the presence or absence of AF than the Novacor R Test.

Relative risk of detection of AF episodes >6 minutes compared with pacemaker	RR = 0.809, 95%CI 0.757 to 0.864, p<0.0001	Novacor R Test: RR = 0.773, 95%CI 0.502 to 1.191, p=0.2274 Carnation Ambulatory Monitor: RR = 0.953, 95%CI 0.931 to 0.977, p=0.0007 NUUBO Vest: RR = 0.897, 95%CI 0.757 to 1.062, p=0.1923	The Zio XT Service and CAM were less accurate than the permanent pacemaker gold standard at detecting AF episodes lasting > 6 minutes. Differences between the Novacor R Test and CAM were not statistically significant from the pacemaker.
Relative risk of detection of AF episodes >30 seconds compared with pacemaker	RR = 0.867, 95%CI 0.804 to 0.935, p= 0.0008	Novacor R Test: RR = 0.508, 95%CI 0.281 to 0.918, p=0.027 Carnation Ambulatory Monitor: RR = 0.999, 95%CI 0.980 to 1.109, p=0.9372 NUUBO Vest: RR = 0.970, 95%CI 0.945 to 0.995, p= 0.0224	The Zio XT Service, Novacor R Test and NUUBO Vest were significantly less accurate than the pacemaker at detecting AF episodes lasting >30 seconds. Differences between the CAM and the pacemaker were not significant.
Mean wear time	307 hours	Novacor R Test = 224 hours CAM = 268 hours NUUBO Vest = 186 hours	Mean wear time was longer with the Zio XT Service than the other external monitors.
Patient mean discomfort attaching the device (0 to 5 scale)	1.59, 95%CI 1.16 to 2.03	Novocor R Test = 1.86, 95%CI 0.66 to 3.06 CAM = 0.57, 95%CI 0.004 to 1.10 NUUBO Vest = 2.51, 95%CI 2.06 to 2.95	Scores for Zio XT Service and NUUBO Vest have been derived from chart in paper

Patient discomfort wearing the device (0 to 5 scale)	1.86, 95%CI 1.19 to 2.52	Novocor R Test = 2.84, 95%CI 2.18 to 3.51 CAM = 0.95, 95%CI 0.29 to 1.61 NUUBO Vest = 3.95, 95%CI 3.28 to 4.62	All scores have been derived from chart in paper
Mean total patient time expenditure	26.5 minutes, 95%CI 20.1 to 36.0	Novocor R Test = 53 minutes CAM = 24 minutes, 95%CI 20.9 to 35.3 NUUBO Vest = 31 minutes, 95%CI 20.6 to 36.6	Mean patient time was shorter with the Zio XT Service, CAM and NUUBO Vest than for the Novocor R Test, p<0.0001

Kaura 2019	**Result with Zio XT Service, N = 43**	**Result with 24-hour Holter monitor, N = 47**	**Company comments**
AF detection rate at 28 days	14.0% patients	2.1% patients, p=0.051	Text
AF detection rate at 90 days	16.3% patients	2.1%, p= 0.026	Significantly higher AF detection rate with the Zio XT Service than 24-hour Holter monitor at 90 days
Mean daily AF burden at 90 days	4.2 ±6.2 hours	NR	
Mean maximum time spent in AF at 90 days	44.6 ±78.6 hours	NR	
Mean wear time	283 ± 88.7 hours (11.8 days)	25.0 ± 25.0 hours	

Compliance	76.8% completed 90 days of follow-up 18% refused Holter monitor 2% Zio XT patch could not be successfully applied	78.3% had successful monitor placement during the 90 days 22% refused Holter monitor	Most protocol violations were due to patients refusing to be fitted with Holter monitors, which were sued for 24 hours in both treatment arms
Second ischaemic stroke or TIA at 90 days	2.3%	2.1%, p=1.00	No significant difference in recurrent stroke or TIA at 90 days
Mortality at 90 days	2.3%	0%, p=0.48	No significant difference in mortality at 90 days
Anticoagulation therapy at 90 days	16.3%	2.1%, p=0.026	Significantly greater use of anticoagulants at 90 days with Zio XT Service

Rosenberg 2013	**Result with Zio XT Service, N = 74**	**Result with 24-hour Holter monitor, N = 74**	**Company comments**
AF detection rate	38/75 = 50.7%	21/75 = 28.0%	Significantly greater AF detection rate with Zio XT Service than 24-hour Holter monitor
Mean wear time	10.8 ± 2.8 days, range 4 to 14 days	22.5 ± 1.8 hours	Mean wear time was significantly longer with Zio XT Service.

Mean AF burden detected in first 24 hours	54.7 ± 41.2%	58.4 ± 42.7%	The two groups are described as comparable, but statistical significance quoted as p<0.0001
Mean AF burden over whole wear time	28.4% ± 31.2%	58.4% ± 42.7%	
Incidence of AF over 14 days	0.095 events/person-day	NR	Text
Median time to detection of AF	1 day (range 1 to 12 days) overall 3.7 ± 3.0 days for those with arrhythmia detected after first 24 hours	NR	Text
Change in management due to detection of arrhythmia	28.4% overall 17.3% had change in antiarrhythmic medication 5.3% had change in oral anticoagulation 28.4% had a change in the classification of AF	NR	21 of the 75 patients had a change in classification of their AF and had their management changed as a result of using the Zio XT Service.

Studies evaluating external event recorders

Kinlay 1996	**Result with Aerotel event monitor, N = 45**	**Result with 48-hour Holter monitor, N = 45**	**Company comments**
AF / flutter detection rate	6% of recordings	0% of recordings	More recordings identified AF with the Aerotel event monitor than the 48-hour Holter monitor
Clinically significant arrhythmia detection rate	19%	0, p<0.005	Significantly higher detection of clinically-relevant arrhythmia with the Aerotel event recorder
Compliance with sending 2 recordings within 3 months	69%	NR	Text
Mean wear time	34 days	2 days	Text
Proportion of patients with at least 1 recording during symptoms that could be interpreted	67%	35%, p<0.001	Significantly increased chance of having an interpretable recording with the Aerotel event monitor

Halcox 2017	**Result with AliveCor smartphone monitor, N = 500**	**Result with standard of care, N = 501**	**Company comments**
AF detection rate at 12 months	3.8%	1.0%, p=0.007	Significantly greater AF detection rate with AliveCor than standard care at 12 months
Signal quality	2.2% of recordings were unreadable		

Estimated detection probability at 10 weeks	0.8%	0%	Shorter time to diagnosis with AliveCor Text Text Text Text
Estimated detection probability at 20 weeks	1.59%	0.2%	
Estimated detection probability at 30 weeks	2.99%	0.39%	
Estimated detection probability at 40 weeks	2.99%	0.79%	
Estimated detection probability at 50 weeks	3.8%	0.79%	
TIAs or strokes	6 events	10 events, p=0.34	
Patient reported likelihood of visiting physician about heart rhythm (mean score on 1 to 10 scale)	7.1	7.5, p=0.04	Visits significantly less likely with AliveCor than usual care
Patient reported preference for switching to the other device (mean score on 1 to 10 scale)	1.9	6.2	Patients more likely to want to switch to AliveCor than to standard care

Narasimha 2018	**Result with AliveCor Kardia smartphone monitor, N = 38**	**Result with external loop recorder, N = 38**	**Company comments**
Total arrhythmia detection rate (patients)	92.1%	84.2%, p=0.287	No significant difference in overall arrhythmia detection rate
Symptomatic arrhythmia detection rate (total)	89.5% of patients	68.4% of patients, p=0.024	Significantly higher detection of symptomatic arrhythmias with AliveCor

Symptomatic AF detection rate	15.8% of patients	10.5% of patients	Text
Asymptomatic arrhythmia detection rate	7.9% of patients	68.4% of patients, p<0.001	Significantly higher detection of asymptomatic arrhythmias with external loop recorder
Asymptomatic AF detection rate	0%	7.9%	Text
Proportion of days when diagnosis of symptomatic arrhythmia was made	33.7%	20.4%, p<0.001	Significantly greater number of days with at least one diagnostic recording with the AliveCor Kardia monitor than the external loop recorder
Compliance with sending recordings (% of days with at least one recording)	91.2%	52.7%, p<0.01	Significantly greater compliance with AliveCor
Patient satisfaction: mean ease of use (1= very easy to 5 = very hard)	1.4	2.7, p<0.01	AliveCor was significantly easier to use
Patient satisfaction: patients reporting they would use the device at work or socially	87.1%	29.0%	More patients would be happy to use the AliveCor
Patient satisfaction: patients reporting they found the device very accessible at start of symptoms	87.1%	NR	

Reed 2019	Result with AliveCor smartphone monitor, N = 125	Result with standard care, N = 117	Company comments
Symptomatic arrhythmia detection rate at 90 days = (patients)	8.9%	0.9%, p=0.006	Significantly higher arrhythmia detection rate with AliveCor
Mean time to symptomatic arrhythmia detection	9.9 days	48 days, p=0.0004	Significantly shorter time to detection of symptomatic arrhythmia with AliveCor
Resource use due to palpitations/ presyncope	Subsequent ED visit = 1.6% GP visit = 0 Inpatient hospital days = 1.6%	Subsequent ED visit = 0.8% GP visit = 1.7% Inpatient hospital days = 0.9%	No significant difference in resource use
Mean total healthcare and intervention costs	£108 (IQR 99.0 to 246.5)	£0 (IQR 0 to £120), p=0.0001	Significantly greater healthcare plus device costs with AliveCor
Proportion of patients reporting the device is easy to use	87.0%	NR	Text

Tarakji 2015	Result with AliveCor smartphone monitor, N = 55	Result with trans-telephonic monitor, N = 55	Company comments
Sensitivity for AF/ flutter detection	97%	NR	Gold standard was trans-telephonic monitor
Specificity for AF/ flutter detection	100%	NR	Gold standard was trans-telephonic monitor

PPV for AF/ flutter detection	97%		Calculated from 2x2 table, trans-telephonic monitor as gold standard
NPV for AF/ flutter detection	100%		Calculated from 2x2 table, trans-telephonic monitor as gold standard
Proportion of readings that were noninterpretable	0.8% of all recordings 1.0% of simultaneous recordings	0.2% of simultaneous recordings	Statistical significance not reported
Proportion of patients who prefer the device	92%	NR	Text

Gussak 2012	**Result with CardioBip wireless monitor, N = 23**	**Result with 24-hour Holter, N = 25**	**Company comments**
AF/Flutter detection rate (patients) at 2 months	84%	32%, p<0.01	Significantly higher AF/ flutter detection with CardioBip
AF/Flutter detection rate (patients) at 6 months	84%	32%, p<0.01	Significantly higher AF/ flutter detection with CardioBip
Compliance with requested 2 or 3 transmissions a day	64.7% at 2 months 83.5% at 6 months	NA	Text
Sensitivity for AF/ flutter detection	100%	NR	Sensitivity calculated using CardioBip + Holter as gold standard

Time to diagnosis	Mean 27.2± 5.8 days earlier than with 24-hour Holter at 2 months Mean 23.6 ± 4.9 days earlier than with 24-hour Holter at 6 months		Significantly faster time to AF/ flutter detection with CardioBip
Mean number of days monitored at 1-2 months	55.1 (90%CI 4.8 days)		
Mean number of days monitored at 6 months	28.0 (90%CI 0.7 days)		

Rothman 2007	**Result with CardioNet mobile cardiac outpatient telemetry, N = 134**	**Result with External loop event monitor, N = 132**	**Company comments**
Clinically significant arrhythmia detection rate at 15 days	29% of patients	11% of patients	Text
Patients with clinically significant arrhythmia	41.4%	14.6%, p<0.001	Significantly higher arrhythmia detection rate with CardioNet MCOT than external loop event recorder
Patients with non-clinically significant arrhythmia	84.2%	51.5%, p<0.001	Significantly higher arrhythmia detection rate with CardioNet MCOT than external loop event recorder
Arrhythmia diagnosis confirmed /excluded overall	88%	75.4%, p=0.008	Significantly higher confirmation or exclusion of diagnosis with CardioNet MCOT

Arrhythmia diagnosis confirmed/ excluded in patients with syncope/presyncope	88.7%	68.6%, p=0.008	Significantly higher confirmation or exclusion of diagnosis with CardioNet MCOT
Proportion of patients completing at least 25 days of monitoring	85.3%	89.2%	Statistical significance not reported
Non-compliance – proportion not using the device	8.3%	4.7%	Statistical significance not reported
Median time to diagnosis	7 days (95%CI 3 to 16 days)	9 days (95%CI 7 to 21 days)	Statistical significance not reported

Kimura 2017	**Result with Cardiophone telemonitoring ECG, N = 30**	**Result with 24-hour Holter monitor, N = 30**	**Company comments**
AF/ tachycardia detection rate during 1st month	32.1%	7.4%	Detection of AF or tachycardia was higher with telemonitoring ECG than 24-hour Holter monitor Text Text Text Text Text
AF/ tachycardia detection rate during 2nd month	25.0%	8.3%	
AF/ tachycardia detection rate during 3rd month	25.0%	12.5	
AF/ tachycardia detection rate during 4th month	17.9%	15.4%	
AF/ tachycardia detection rate during 5th month	28.6%	4.3%	
AF/ tachycardia detection rate during 6th month	17.9%	5%	

Sensitivity for AF detection when detection rate of telemonitoring ECG = 25.7%		78.6%	Gold standard = physician confirmation of arrhythmia from ECG recording
Sensitivity for AF detection when detection rate of telemonitoring ECG = 61%		50%	Gold standard = physician confirmation of arrhythmia from ECG recording
Specificity for AF detection when detection rate of telemonitoring ECG = 25.7%		97%	Gold standard = physician confirmation of arrhythmia from ECG recording
Specificity for AF detection when detection rate of telemonitoring ECG = 61%		100%	Gold standard = physician confirmation of arrhythmia from ECG recording
Proportion of patients taking anticoagulants	100% at month 1 to 4 92.9% at 5 months 85.7% at 6 months		Anticoagulation was discontinued in patients with no documented AF and CHADS2 score <2
Proportion of patients taking antiarrhythmic drugs	57.1% at 1 month 53.6% at 2 months 32.1% at 3 to 5 months 25.0% at 6 months		Antiarrhythmic drugs were gradually discontinued.

Gladstone 2014	**Result with 30-day event recorder, N = 284**	**Result with 24-hour Holter monitor, N = 285**	**Company comments**

AF (>30 seconds) detection rate within 90 days	16.1%	3.2%, p<0.001	Significantly greater detection of AF episodes lasting>30 seconds with the 30-day event recorder than the 24-hour Holter monitor
AF (>30 seconds) detection rate overall	15.5%	2.5%, p<0.001	Significantly greater detection of AF episodes lasting>30 seconds with the 30-day event recorder than the 24-hour Holter monitor
AF (>2.5 minutes) detection rate	9.9%	2.5%, p<0.001	Significantly greater detection of AF episodes lasting>2.5 minutes with the 30-day event recorder than the 24-hour Holter monitor
Sensitivity for AF detection	15.7%	6.0%	Gold standard unclear
Patients switching from antiplatelet to anticoagulation therapy at randomization	13.6%	4.7%, p<0.001	Significantly greater use of anticoagulants after use of 30-day event recorder than 24-hour Holter
Anticoagulation therapy at 90 days	18.6%	11.1%, p=0.01	Significantly greater use of anticoagulants after use of 30-day event recorder than 24-hour Holter
Patients switching from anticoagulation to antiplatelet therapy	1.1%	0.7%, p=0.66	Non-significant difference in switch rates from anticoagulants to antiplatelets

Antiplatelet therapy at 90 days	79.6%	88.2%, p=0.006	Significantly more patients remaining on antiplatelets after 24-hour Holter than 30-day event recorder
Compliance (completed 3 or more weeks of monitoring)	82.0%	NR	
AF diagnosis rate	2.2% at 24 hours 7.4% at 1 week 11.6% at 2 weeks 12.3% at 3 weeks 14.8% at 4 weeks		

Ad 2009	**Result with 5-day event recorder, N = 76**	**Result with 24-hour Holter monitor or standard ECG, N = 76**	**Company comments**
Sinus rhythm diagnostic rate	84% 12% more patients were identified as having atrial arrhythmias than with 24-hour Holter, p<0.535.	Standard ECG: 96% 24-hour Holter :91%, p<0.046	Significantly more patients were diagnosed with an arrhythmia with 5-day monitoring device than with standard ECG or 24-hour Holter monitor.

Scalvini 2005	**Result with event recorder, N = 155**	**Result with 24-hour Holter monitor, N = 155**	**Company comments**

Proportion of patients with arrhythmia detected	68%	72%	No significant difference

Kamalvand 1997	**Result with HeartWatch smartwatch monitor N = 24**	**Result with Cardiomemo trans-telephonic monitor, N = 24**	**Company comments**
AF detection rate	0	0	Text
Proportion of traces that were nondiagnostic	5.0%	8.0% p=NS	
Patient preference for the device	45% preferred the HeartWatch	55% preferred the Cardiomemo	Text
Patient satisfaction (5 very poor to 25 excellent)	19 ± 3.6	21 ± 2.8, p=0.02	Patient satisfaction was significantly higher with the Cardiomemo worn over the sternum than the HeartWatch worn on the wrist

Wasserlauf 2019	**Result with HeartWatch smartwatch monitor, N = 26**	**Result with LINQ implantable cardiac monitor, N = 26**	**Company comments**
AF (> 1 hour) detection rate	80 episodes	Reveal LINQ ICM: 82 episodes	Text
Sensitivity for detection of AF ≥ 1 hour (patients)	83.3%	Text	Gold standard is LINQ ICM
Specificity for detection of AF ≥ 1 hour (patients)	83.3%	Text	Gold standard is LINQ ICM
Positive predictive value for detection of AF ≥ 1 hour (patients)	93.8%	Text	Gold standard is LINQ ICM

Negative predictive value for detection of AF ≥ 1 hour (patients)	62.5%	Text	Gold standard is LINQ ICM
Mean monitoring time	1306 hours Mean 11.3 hours/patient/day	2647 hours	Text
AF burden (duration of all AF episodes)	84% of all monitored hours	43% of all monitored hours	

Makowska 2000	**Result with Hertcard event recorder, N = 33**	**Result with 48-hour Holter monitor, N = 33**	**Company comments**
Arrhythmia detection rate (patients)	64%	33%, p=0.0138	Significantly higher AF detection rate with the Hertcard event monitor than 48-hour Holter
Proportion of recordings inadequate for interpretation	1/117 = 0.8%	NR	Text
Time to diagnosis of symptomatic palpitations in those able to record during episodes	50% by day 4 100% by day 18	NR	Text

De Asmundis 2014	**Result with OMRON HeartScan patient-activated ECG monitor, N = 625**	**Result with 24-hour Holter monitor, N = 625**	**Company comments**

Total arrhythmia detection rate (patients)	89%	1.8%, p<0.01	Significantly more patients received a diagnosis after the HeartScan than the 24-hour Holter.
Mean Time to Diagnosis	9.1±3.5 days	NR	Text

Tan 2010	**Result with HeartWave500 ambulatory ECG monitor, N = 87**	**Result with RhythmCard trans-telephonic event recorder, N = 33**	**Company comments**
Arrhythmia detection rate (patients)	49.4%	88%	Greater arrhythmia detection rate with RhythmCard trans-telephonic event recorder than HeartWave monitor, significance not reported
AF detection rate (patients)	2%	3%	Text
Proportion of attempted recordings that were unreadable/ unsuccessfully transmitted	33.5%	18%	81% of recording attempts were successful with HeartWave but only 405 of 609 attempts were transmitted and usable
Time to diagnosis	0.62 diagnoses/patient/week in week 1 0.34 diagnoses/patient/week in week 2	0.55 diagnoses/patient/week in week 1, p= 0.6253 0.58 diagnoses/patient/week in week 2, p=0.066	No significant difference in time to diagnosis
Agreement between physician and computer-generated diagnosis	74% of cases	NR	Text

Proportion of patients with diagnosis at end of week 2	67.8%	66.7%	Text

Sivakumaran 2003	**Result with King of Hearts loop recorder, N = 49**	**Result with 48-hour Holter monitor, N = 51**	**Company comments**
Arrhythmia detection rate	2%	0%, p=0.35	No significant difference
Arrhythmia rule out rate (patients)	55%	22%, p<0.001	Significantly more patients had arrhythmia ruled out with King of Hearts loop recorder than 48-hour Holter
Arrhythmia diagnostic yield	56%	22%, p<0.0001	Significantly greater diagnostic yield with King of Hearts loop recorder
Median time to record symptom-rhythm correlation	16 days 13% of patients who had symptom-rhythm correlation had this confirmed by 2 days, 39% in 2 weeks, 87% by 1 month	92% of those who had arrhythmia excluded had this confirmed by 24 hours	Shorter time to diagnosis with 48-hour Holter monitor, significance not reported
Proportion of patients with non-diagnostic recording	23% of those with symptom recurrence 26.5% overall	NR	Text
Proportion of patients willing to cross over to second device	22%	57%	Statistical significance not reported

Senatore 2005	**Result with trans-telephonic ECG, N = 72**	**Result with 24-hour Holter monitor, N = 72**	**Company comments**

Arrhythmia recurrence detection rate (patients)	27.8%	13.9%, p=0.001	Significantly greater arrhythmia recurrence detection with the trans-telephonic ECG

Liu 2010	**Result with trans-telephonic external loop recorder, N = 92**	**Result with 24-hour Holter monitor, N = 92**	**Company comments**
AF recurrence diagnosed	42.4%	29.2%, p=0.032	Significantly greater detection of AF with the trans-telephonic external loop recorder than 24-hour Holter
AF not detected at 10 days	100%	100%	Text
AF not detected at 30 days	83.56%	100%	Text
AF not detected at 50 days	66.10%	84.93%	Text
AF not detected at 70 days	60.79%	70.72%	Text
AF not detected at 90 days	57.53%	70.72%	Significantly greater detection of AF with the trans-telephonic external loop recorder than 24-hour Holter at 90 days
Proportion of effective TTECG recordings received	96.1%		

Chovancik 2019	**Result with episodic card recorder, N = 105**	**Result with episodic loop recorder, N = 105**	**Company comments**
AF/ tachycardia detection rate at 12 months	29.5% of patients	11.4% of patients	Significantly fewer patients had arrhythmias detected by the ELR than the ECR at 12 months

Sensitivity for AF/ tachycardia detection	NR	35%	Gold standard unclear
Compliance: days with ECG sent at 12 months	89% ±12%	98% ±7%	Statistical significance not reported
Wear time (active monitoring hours) at 12 months	6.0±1.9 hours	221±64 hours	
Signal quality (proportion of ECG recordings non-interpretable) at 12 months	5.0% ± 8.1%	3.0% ± 5.5%	
Time to diagnosis: cumulative arrhythmia-free survival	90 days = 99.9% 180 days = 82.3% 268 days = 77.3% 360 days = 76.2%	90 days = 99.9% 180 days = 97.8% 268 days = 94.7% 360 days = 91.7%	Shorter time to detection of arrhythmia with ECR than ELR, log rank p <0.01.
Antiarrhythmic medication during monitoring phase	Months 4 to 6: 25.7% taking antiarrhythmics Months 7 to 12: 19% taking antiarrhythmics		Antiarrhythmic medication was taken throughout the monitoring period to avoid inherent bias in the study outcome so difficult to interpret these results.

Doliwa Sobocinski 2012	**Result with Zenicor intermittent thumb monitor, N = 249**	**Result with 24-hour Holter, N = 249**	**Company comments**
AF detection rate	6% of patients	2% of patients	Text

Mean wear time	NR	22.6 hours	Text
Time to diagnosis (AF episodes detected within first 20 days)	94%	NR	Text
Sensitivity for AF detection	88%	29%	Sensitivity calculated from data in paper, using the combined positives from both devices as the gold standard

Hendrikx 2014	**Result with Zenicor EKG thumb monitor, N = 95**	**Result with 24-hour Holter, N = 95**	**Company comments**
Arrhythmia detection rate	13.7%	3.2%, p=0.0094	Significantly greater arrhythmia detection rate with Zenicor thumb monitor
Compliance	74.7% completed 50 registrations 8.4% made <28 registrations	99% completed 24-hour recordings	Compliance greater with 24-hour Holter monitor, significance not reported
Signal quality (proportion not analysable quality)	1.6%	1.3%	Text
Time to diagnosis	53.8% of all diagnoses at 7 days 69.2% of all diagnoses at 14 and 21 days 100% of all diagnoses at 28 days	NR	Text
Sensitivity for arrhythmia detection	100%	15%	Sensitivity calculated from data in paper taking sum of all positives as gold standard

Poulsen 2017	Result with Zenicor thumb ECG monitor, N = 95	Result with 5-day Holter monitor, N = 95	Company comments
Paroxysmal AF detection rate	21.1% of patients	17.9% of patients, p=0.63	No significant difference in detection rates
Sensitivity for paroxysmal AF detection	59%	100%	Gold standard = 5-day Holter
Specificity for paroxysmal AF detection	87%	100%	Gold standard = 5-day Holter
Positive predictive value for paroxysmal AF detection	50%	Text	Gold standard = 5-day Holter
Negative predictive value for paroxysmal AF detection	91%	Text	Gold standard = 5-day Holter
Time to diagnosis of paroxysmal AF	16% of patients by day 10 21% of patients by 20 days	12% of patients in first day 17% of patients by 2 days	Shorter time to diagnosis with 5-day Holter
Proportion of recordings not useable	13%	NR	
Proportion of patients who preferred the device	76%	2%	More patients preferred the Zenicor thumb monitor

Studies evaluating external continuous ambulatory monitors

Sampaio 2018	Result with PoIP ambulatory monitor, N = 52 overall, 26 after stroke/TIA	Result with 24-hour Holter monitor, N = 52 overall, 26 after stroke/TIA	Company comments

AF detection rate: proportion of patients after stroke/TIA	23.1%	3.8%, p=0.099	No significant difference in detection rates of AF in patients after stroke or TIA
Atrial tachycardia detection rate: proportion of patients after stroke/TIA	84.6%	61.5%, p=0.004	Significantly higher detection of atrial tachycardia with PoIP ambulatory monitor in patients after stroke or TIA
Mean recording time: patients after stroke/TIA	148.8 hours	23.4 hours	Text
Recording time lost due to artefacts	30.1%	2.6%	Text

Higgins 2013	**Result with Novacor R-Test Evolution loop recorder plus 24-hour Holter, N = 50**	**Result with standard care including 24-hour Holter monitor, N = 50**	**Company comments**
Paroxysmal AF detection rate (any duration) at 14 days (patients)	44%	4%, p = 0.001	Significantly greater AF detection with Novacor R-Test
Paroxysmal AF detection rate (any duration) at 90 days (patients)	48%	10%, p = 0.001	Significantly greater AF detection with Novacor R-Test
Sustained paroxysmal AF detection rate at 14 days (patients)	18%	2%, p = 0.05	Significantly greater AF detection with Novacor R-Test
Sustained paroxysmal AF detection rate at 90 days (patients)	22%	8%, p = 0.09	No significant difference

Compliance (successful completion or download)	94% at 24 hours 90% at 72 hours 82% at 168 hours	84% at 24 hours 82% at 72 hours	Text
Anticoagulant use for any indication, 14 days	18%	0%, p<0.01	Significantly greater use of anticoagulants after Novacor R-Test
Anticoagulant use for any indication, 90 days	26%	10%, p<0.05	Significantly greater use of anticoagulants after Novacor R-Test
Anticoagulant use for AF thromboembolism prophylaxis 14 days	16%	0%, p<0.01	Significantly greater use of anticoagulants after Novacor R-Test
Anticoagulant use for AF thromboembolism prophylaxis 90 days	22%	6%, p<0.05	Significantly greater use of anticoagulants after Novacor R-Test
Combined stroke, TIA, MI and/or death	8%	8%	No significant difference

Sejr 2017	**Result with R-Test Evolution external loop recorder, N = 191**	**Result with 48-hour Holter monitor, N = 191**	**Company comments**
AF detection rate: patients with AF-positive recordings	26.2%	2.1%	Statistical significance not reported
AF detection rate: patients confirmed to have AF by cardiologist at end of wear time	4.7% at 7 days	1.6% at 2 days, p=0.031	Significantly more patients detected as having AF with the R-Test ELR

Compliance	Patients with >6 days of recording = 74%	Patients with >47 hours of recording = 81%	Text
Total wear time	Mean = 145 hours (range 0.2 to 356) 84% of patients >96 hours 74% of patients >144 hours	98% of patients >24 hours 81% of patients >47 hours	
Duration of analysable recording	120 hours (range 0.17 to 203)	47 hours (range 7 to 50)	Only Holter monitor showed P waves

Scherr 2008	**Result with OMRON ECG monitor, N = 18**	**Result with event recorder, N = 18**	**Company comments**
Symptomatic arrhythmia detection rate (patients)	72%	57%, p=NS	No significant difference between groups, event recorder detection rate calculated for 14 patients who were compliant
Sensitivity for detection of arrhythmia at 30 days	100%	80%	Text
Patients compliant with use of device	100%	78%, p=0.10	No significant difference
Proportion of recordings classified as poor	3%	1.7%, p=NS	No significant difference
Patient satisfaction: proportion finding the device easier to use than the comparator	94%	6%	Text

Mamchur 2019	Result with Spyder non-invasive ambulatory monitor, N = 17	Result with Reveal XT ILR, N = 15	Company comments
Assessment of AF burden during 14-day period	6.8%	7.1%, p=0.187	No significant difference in AF burden
Sensitivity for paroxysmal AF detection	80.1%	78.6%	Gold standard = physician confirmation of arrhythmia from ECG recording
Specificity for paroxysmal AF detection	73.1%	69%	Gold standard = physician confirmation of arrhythmia from ECG recording
Positive predictive value for paroxysmal AF detection	74.1%	71%	Gold standard = physician confirmation of arrhythmia from ECG recording
Negative predictive value for paroxysmal AF detection	79.2%	77%	Gold standard = physician confirmation of arrhythmia from ECG recording

Studies evaluating implantable cardiac monitors versus Holter monitors or usual care

Ciconte 2017	Result with BioMonitor implantable loop recorder, N = 66	Result with 48-hour Holter monitor, N = 66	Company comments
AF detection rate	71% of patients	62% of patients	Statistical significance not reported
Sensitivity for AF detection (patients)	100%	Text	Gold standard is Holter monitor

Specificity for AF detection (patients)	67%		Calculated from data in 2x2 table, Gold standard is Holter monitor
Positive predictive value for AF detection	83%	Text	Gold standard is Holter monitor
Negative predictive value for AF detection	100%	Text	Gold standard is Holter monitor
AF burden (% of time spent in AF)	27.4±28.9%,	28.0±35.3%, p=0.076	No significant difference in detected AF burden

Lauschke 2016	**Result with BioMonitor implantable cardiac monitor, N = 153**	**Result with 48-hour Holter monitor, N = 153**	**Company comments**
AF detection rate from total wear time	46% of recordings		
AF detection rate during simultaneous recordings in 77 patients	44% of recordings	48% of recordings	Statistical significance not reported
Sensitivity for AF episode detection	92%	Text	Gold standard is 48-hour Holter
Positive predictive value for AF episode detection	59%	Text	Gold standard is 48-hour Holter

Piorkowski 2019	**Result with BioMonitor 2 implantable cardiac monitor, N= 90**	**Result with 48-hour Holter monitor, N = 90**	**Company comments**

AF detection rate	28.0% patients	18.3% patients	Higher with BioMonitor ICM, statistical significance not reported
Sensitivity for arrhythmia detection (patients)	100%	Text	Gold standard is 48-hour Holter
Sensitivity for AF detection (patients)	100%		Gold standard is 48-hour Holter
Specificity for AF detection (patients)	88.1%	Text	Gold standard is 48-hour Holter
Positive predictive value for AF detection	65.2%	Text	Gold standard is 48-hour Holter
Negative predictive value for AF detection	100%	Text	Gold standard is 48-hour Holter
Accuracy for AF detection (patients)	90.2%		Gold standard is 48-hour Holter
Sensitivity for AF duration detection	93.6%		Gold standard is 48-hour Holter
Specificity for AF duration detection	99.2%		Gold standard is 48-hour Holter
Positive predictive value for AF duration detection	93.4%		Gold standard is 48-hour Holter
Negative predictive value for AF duration detection	99.3%		Gold standard is 48-hour Holter
Accuracy for AF duration detection	98.7%		Gold standard is 48-hour Holter
Compliance with message transmission	94.9%	Text	Text

Nolker 2016	Result with Confirm implantable cardiac monitor, N = 90	Result with 4-day Holter monitor, N = 90	Company comments
AF detection rate in patients with usable data	31.6%	20.2%	Statistical significance not reported
Mean monitoring time	NR	87.3 hours	
Proportion of patients with unusable data	NR	12%	
Sensitivity rate for AF detection (patients)	100%	Text	Gold standard is 4-day Holter monitor
Positive predictive value for AF detection (patients)	64%	Text	Gold standard is 4-day Holter monitor
Negative predictive value for AF detection (patients)	100%	Text	Gold standard is 4-day Holter monitor
Specificity rate for AF detection (patients)	85.7%	Text	Gold standard is 4-day Holter monitor
AF burden (% of time spent in AF)	9.2%	NR	Text
Sensitivity rate for AF burden detection	83.9%	Text	Gold standard is 4-day Holter monitor
Positive predictive value for AF burden detection	97.3%	Text	Gold standard is 4-day Holter monitor
Negative predictive value for AF burden detection	98.5%	Text	Gold standard is 4-day Holter monitor
Specificity rate for AF burden detection	99.4%	Text	Gold standard is 4-day Holter monitor

Sanders 2016	Result with Reveal LINQ implantable cardiac monitor, N = 151	Result with 24-hour Holter monitor, N = 151	Company comments
AF detection rate (patients with usable recordings)	26.5% of 151 patients	27.5% of 138 patients	More patients were diagnosed with AF with the Reveal LINQ ICM
Sensitivity for AF detection (patient)	97.4%	Text	Gold standard is 24-hour Holter monitor
Specificity for AF detection (patient)	97%	Text	Gold standard is 24-hour Holter monitor
Positive predictive value for AF detection (patient)	92.5%	Text	Gold standard is 24-hour Holter monitor
Negative predictive value for AF detection (patient)	99%	Text	Gold standard is 24-hour Holter monitor
Accuracy for AF detection (patient)	97.1%	Text	Gold standard is 24-hour Holter monitor
Mean analysable time	NR	23.1 hours	Text
Sensitivity for AF duration detection (patient average)	93.7%		Gold standard is 24-hour Holter monitor
Specificity for AF duration detection (patient average)	99.6%		Gold standard is 24-hour Holter monitor
Positive predictive value for AF duration detection (patient average)	90.6%		Gold standard is 24-hour Holter monitor
Negative predictive value for AF duration detection (patient average)	96.4%		Gold standard is 24-hour Holter monitor
Overall, duration of AF burden accuracy	99.4%		Gold standard is 24-hour Holter monitor

Proportion of patients with non-usable recordings	NR	6%	

Giada 2007	**Result with Reveal Plus implantable loop recorder, N = 26 before crossover, 35 after crossover**	**Result with 24-hour Holter ± 4-week event recorder, N = 24**	**Company comments**
Total arrhythmia detection rate, before and after crossover	Before crossover = 73% of patients After crossover = 71%	21% of patients, p<0.001	Significantly higher detection of arrhythmias with Reveal Plus ILR
AF/ Flutter detection rate	23% of patients	4% of patients	Higher detection rate of AF/ Flutter with Reveal Plus ILR
Mean time to Diagnosis	279 ±228 days	36 ±26 days	Longer mean time to diagnosis with Reveal Plus ILR
Mean duration of monitoring	321 ±235 days	Event recorder: 40 ±25 days	

Philippsen 2017	**Result with Reveal XT implantable cardiac monitor, N = 82**	**Result with 72-hour Holter monitor, N = 82**	**Company comments**
AF detection rate	20.7% of patients	2.4%	Statistical significance not reported
Median time to first detected episode	91 days (IQR 41 to 251 days)	NR	Text

Patients with AF ≥6 minutes duration starting oral anticoagulants	17%	Text	Text
Patients with AF ≥6 minutes duration starting rate control antiarrhythmics	4.8%		

Brachmann 2016 and Sanna 2014	**Result with Reveal XT Implantable monitor, N = 221**	**Result with Standard of care, N = 220**	**Company comments**
AF detection rate at 1 month (patients)	3.7%	0.5%	Text
AF detection rate at 6 months (patients)	8.9%	1.4%	Text
AF detection rate at 12 months (patients)	12.4%	2%	Text
AF detection rate at 24 months (patients)	21.1%	3%	Text
AF detection rate at 36 months (patients)	30%	3%, p<0.0001	Significantly higher AF detection rate with Reveal XT ICM than standard care
Median time to detection of AF at 36 months	8.4 months	2.4 months	Longer median time to detection of AF with the Reveal XT ICM

AF burden	Median maximal % of time spent in AF per day = 10.5 hours (IQR 2.9 to 23.8) 94.9% of patients had >6 minutes AF/day	NR	
Use of Oral Anticoagulant therapy at 6 months	10.1% of all patients 94.7% of patients with detected AF	4.6% of all patients	
Prescribed Oral Anticoagulant therapy at 12 months	14.7% of all patients 96.6% of patients with detected AF	5.9% of all patients	
Prescribed Oral Anticoagulant therapy at 36 months	38.5% of all patients 90.5% of patients with detected AF	8.3% of all patients, p=0.02	Significantly greater use of anticoagulants in Reveal XT ICM group
Recurrent stroke at 3 years	9.0%	10.9%	Statistical significance not reported

Damiano 2016	**Result with Reveal XT implantable loop recorder, N = 47**	**Result with 24-hour Holter monitor or ECG, N = 47**	**Company comments**
Freedom from arrhythmia at 3 months (patients)	72%	Holter: 92% ECG: 95%	Greater arrhythmia detection with Reveal XT ILR than 24-hour Holter monitor, significance not reported
Freedom from arrhythmia at 6 months (patients)	78%	Holter: 87% ECG: 95%	Greater arrhythmia detection with Reveal XT ILR than 24-hour Holter monitor, significance not reported

Freedom from arrhythmia at 12 months (patients)	95% or 88%	Holter: 94%, p=0.451 ECG:95%	No significant difference in arrhythmia detection with Reveal XT ILR versus 24-hour Holter monitor, ILR detection rate described differently in different sections of the paper
Atrial tachycardia detection rate	46% of recordings		Text
Compliance at 6 months	96%	Holter: 81%, p=0.073 ECG: 83%	No significant difference in compliance
Compliance at 12 months	91% or 93%	Holter: 85%, p=0.067 ECG: 76%	ILR compliance described differently in different sections of the paper
Signal quality	11% (2249) out of 20,878 recordings were available for analysing.		Storage limitations restricted the number of episodes that could be adjudicated
Mean ATA burden (% of time spent in AF) at 1 year follow up	0.63% (range 0.48% to 0.85%)	Text	AF burden calculated from patients with both ILR and 24-hour Holter data at 12 months

Davtyan 2018	**Result with Reveal XT implantable loop recorder, N = 89**	**Result with 24-hour Holter monitor, N = 89**	**Company comments**
Freedom from AF recurrence at 3 months, all patients	58.4%	70.8%	Data calculated from detection rates with the 2 ablation techniques, significance of difference for devices not reported

Freedom from AF recurrence at 12 months, all patients	58.4%	71.9%	Data calculated from detection rates with the 2 ablation techniques, significance of difference for devices not reported
Compliance with follow-up	100% of patients	100% of patients	Text

Hanke 2009	**Result with Reveal XT implantable loop recorder, N = 45**	**Result with 24-hour Holter monitor, N = 45**	**Company comments**
AF detection rate during 85 simultaneous recordings	60%	37%, p<0.0001	Significantly higher detection rate with Reveal XT ILR
Sensitivity for AF detection	Text	60%	Compared to ILR
Negative predictive value for AF detection	Text	64%	Compared to ILR
Mean total monitoring time per patient	4906 hours	45 hours	Calculated from total recording time for 45 patients
AF burden (% of time spent in AF)	37±43%	Text	Text

Hindricks 2010	**Result with Reveal XT implantable loop recorder, N = 235**	**Result with 46-hour Holter monitor, N = 235**	**Company comments**
AF detection rate	31.1%	32.3%	Statistical significance not reported
Sensitivity for AF detection	96.1%	Text	Gold standard was clinician-validated 24-hour Holter monitor trace

Specificity for AF detection	85.4%	Text	Gold standard was clinician-validated 24-hour Holter monitor trace
Positive predictive value for AF detection	79.3%	Text	Gold standard was clinician-validated 24-hour Holter monitor trace
Negative predictive value for AF detection	97.4%	Text	Gold standard was clinician-validated 24-hour Holter monitor trace
Accuracy for detecting AF	98.5%	Text	Gold standard was clinician-validated 24-hour Holter monitor trace
AF burden (% of time in AF)	Mean absolute difference from Holter = 1.4% ±6.4%	14.5%	Absolute value of AF burden on ILR not reported
Sensitivity for AF burden	98.1%		Gold standard was clinician-validated 24-hour Holter monitor trace
Specificity for AF burden	98.5%		Gold standard was clinician-validated 24-hour Holter monitor trace
Positive predictive value for AF burden	95%		Gold standard was clinician-validated 24-hour Holter monitor trace
Negative predictive value for AF burden	95%		Gold standard was clinician-validated 24-hour Holter monitor trace
Recordings not suitable for analysis	NR	1.2%	

Eitel 2011 (linked publication to Hindricks 2010)	Result with Reveal XT ILR, N = 51	Result with 7-day Holter monitor, N = 51	Company comments
AF detection rate (patients)	31%	24%, P=0.125	No significant difference
Sensitivity for AF detection	100%	75%	Calculated from data in paper using all positives as gold standard

Ritter 2013	Result with Reveal XT implantable cardiac monitor, N = 60	Result with 7-day Holter monitor, N = 60	Company comments
AF detection rate (patients)	17%	1.7%, p=0.0077	Significantly higher diagnostic yield with Reveal XT ICM
Mean time to diagnosis of AF	64 days (range 1 to 556 days)	NR	Text
Recurrent stroke	0	0	

6 Ongoing use and data collection

Briefly describe any ongoing or planned data collection which is aimed at demonstrating the effectiveness of the technology. Provide details of the patients included and the setting where these data are collected and the planned duration. Provide details of any NHS partners involved in the data collection.

Briefly describe if data is collected on an ongoing basis to demonstrate usage of the technology in the target population and improvement in user outcomes or user satisfaction with the technology, where applicable. Provide details of the patients included and the setting where these data are collected and comment on whether ongoing usage data reflects usage required to achieve outcomes reported in the clinical evidence (no more than 1000 words).

On a quarterly basis across every customer site globally, iRhythm reviews commercial Zio XT Service performance. The Zio XT Service Evaluation Tool produces a thorough summary of important performance metrics such as indications for monitoring, monitor wear time compared to prescription duration, analysable time and percentage, and arrhythmia yield (rule in and rule out).

Ongoing commercial usage reflects the outcomes reported in the clinical evidence across these metrics, taking into such variations as patient selection, indications for monitoring and prescribed monitor wear time. For examples of these reports, please see Zio XT Service Evaluation Tools in Appendix D.

Additionally, iRhythm's clinical operations team performs ongoing reviews to ensure quality of the final Zio XT technical reports and urgent notifications. Quality Clinical Managers oversee the Cardiac Technicians and review the following on a daily basis:

- 50% of urgent notifications to prescribing physicians (95% validation rate)
- 100% of physicians' final interpretations of Zio XT technical reports completed online (99% validation rate)
- High risk ECG outliers including heart rate below 20 beats per minute or over 300 beats per minute; age over 99 years; ventricular tachycardia rates under 100 beats per minute (95% validation rate)
- 100% of the reports completed by new Cardiac Technicians prior to competency
- 1-3% of all reports completed by all Cardiac Technicians (95% validation rate)

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7 Adverse events

Describe any adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude). Please describe the search in appendix B and provide links and references.

A search for regulatory documents and other reports on adverse events identified no relevant data.
The manufacturer recommends that the Zio XT Patch is not applied to patients with known allergic reaction to adhesives or hydrogels or with a family history of adhesive skin allergies.

Describe any adverse events and outcomes associated with the technology in the clinical and data usage evidence.

A total of 24 studies reported data associated with adverse events.

The Zio XT Service is very well tolerated. Of the four studies included in the systematic review that evaluated the Zio XT Service, only two reported adverse event data. In a single-arm trial comparing simultaneous monitoring of the Zio XT Service and 24-hour Holter in 75 people there were 25 discontinuations (34%), 16 (21%) due to the device falling off, 6 (8%) due to patients removing the device, 1 (1%) due to battery malfunction in the comparator arm, 1 due to the need for other cardiac intervention, and 1 for an unknown cause (Rosenberg et al. 2013). An RCT of the Zio XT Service compared with a 24-hour Holter monitor reported a mortality rate of 2.3% in the Zio XT group (one death due to pneumonia) compared with 0% in the Holter group, a non-significant difference (Kaura et al. 2019). Withdrawals were high in this RCT, with 26 protocol failures out of the 116 randomised patients. In addition to the one death, 24 of the protocol failures were due to patients refusing to have the Holter monitor applied and one was due to an inadequate Zio XT Patch signal due to obesity.

Five studies evaluating other external devices reported adverse event data. In one RCT (Halcox et al. 2017), there were 2 clinically significant bleeds in 500 participants randomised to the AliveCor Kardia smartphone ECG monitor compared with 1 bleed in the 501 participants randomised to standard care. Serious adverse event rates were reported in a second RCT in which there were 11 (8%) serious adverse events in 125 people randomised to the AliveCor monitor compared to 2 (1%) serious adverse events in 117 people randomised to standard care (Reed et al. 2019). Adverse skin reactions associated with the devices were reported by 1 participant out of 287 (<1%) randomised to the ER910AF 30-day event trigger recorder (Gladstone et al. 2014), and by 7 participants out of all 266 (3%) randomised to either the CardioNet Mobile cardiac outpatient telemetry system (MCOT) or unspecified external loop monitors (Rothman et al. 2007). Rothman et

al. (2007) also reported 7 (3%) complaints of the devices being too cumbersome and 6 (2%) complaints of devices interfering with work or travel.

Kamalvand et al. (1997) did not report any adverse events but did note that participants were reluctant to wear the HeartWatch device. Two studies, one evaluating the Novacor R-test (Higgins et al. 2013), and one evaluating Aerotel (Kinlay et al. 1996), reported no incidence of adverse events associated with these devices. However, Kinlay et al. (1996) report 2 discontinuations (4%) prior to monitoring with the Aerotel device due to complaints of the Holter being too uncomfortable.

Seven studies evaluating an implantable cardiac monitoring device reported adverse event data. The most serious adverse events were infections as a result of the implantation procedures. Lauschke et al. (2016) reported that 2 out of 152 participants (1%) had an infection related to implantation of the BioMonitor, 3 patients (2%) complained of pain at the implantation site, and there was 1 haemorrhage (<1%). Brachmann et al. (2016, also reported in Sanna et al. 2014) reported data on the Reveal XT device, in which 5 out of 208 participants (2%) were discontinued due to infection at the insertion site, 3 additional participants (1%) had an infection related to implantation, there were 3 (1%) complaints of pain associated with the device, and 4 (2%) complaints of irritation or inflammation.

Piorkowski et al. (2019) reported that, of 92 people enrolled to receive the BioMonitor ICM, there were 2 (2%) serious adverse events. In a single-arm trial of the Reveal XT ICM, 12 of the 247 (5%) participants withdrew from the study due to long-term burden (Hindricks et al. 2010). In a single-arm trial of the Reveal XT ICM there were 4 reported deaths (9%) out of 45 participants (Hanke et al. 2009). Two studies, one evaluating the CONFIRM implantable cardiac monitor (Nolker et al. 2016), and one evaluating the Reveal Plus implantable loop recorder (Giada et al. 2007), reported no incidence of any adverse events.

8 Evidence synthesis and meta-analysis

If a quantitative evidence synthesis is not considered appropriate, please instead complete the section on qualitative review.

8.1 Quantitative review

If a quantitative evidence synthesis is appropriate, describe the methods used. Include a rationale for the studies selected.

Not conducted.

Report all relevant results, including diagrams if appropriate.

Not applicable.

Explain the main findings and conclusions drawn from the quantitative evidence synthesis.

Not applicable

8.2 Qualitative review

Please only complete this section if a quantitative evidence synthesis for all relevant outcomes is not appropriate.

Explain why a quantitative review is not appropriate for all relevant outcomes.

The evidence for the efficacy and safety of the Zio XT Service and relevant comparators is extremely heterogeneous, in terms of populations, methodology, devices used and outcomes reported. As such, any attempt at conducting a meta-analysis or network meta-analysis is unfeasible and, if it were to be conducted, would be misleading in the estimates of comparative efficacy and safety.

Provide a qualitative review for outcomes where a quantitative review is not appropriate. This review should summarise the overall results of the individual studies with reference to the information in Section 5.

Four studies compared the performance of the Zio XT Service with other cardiac monitoring technologies. Three studies used the 24-hour Holter monitor as the comparator in 150 patients under evaluation for cardiac arrhythmias in the USA (Barrett et al., 2014), 120 patients with ischaemic stroke or TIA in the previous 72 hours in the UK (Kaura et al., 2019) and 75 patients with paroxysmal AF in the USA (Rosenberg et al., 2013). The fourth compared the Zio XT Service, Novocor R-Test external loop recorder, Carnation Ambulatory Monitor and NUUBO Vest in 21 patients with implanted pacemakers in the UK (Eysenck et al., 2019).

One of the studies was a randomised controlled trial with a high withdrawal rate due to 20% of participants refusing the use the 24-hour Holter monitor (Kaura et al., 2019). The other three studies compared the monitors at the same time in the same participants, although Eysenck et al. (2019) allocated each participant to the four external ambulatory monitors in turn for 2 weeks at a time, comparing each external monitor simultaneously to the implanted pacemaker.

The Zio XT Service increases the diagnostic yield for arrhythmia
Compared with the 24-hour Holter monitor, the Zio XT Service significantly increased the detection of cardiac arrhythmias over the 24-hour simultaneous monitoring period, (Barrett

et al., 2014; Rosenberg et al., 2013) and of paroxysmal AF at 28 and 90 days (Kaura et al., 2019). Overall, 65.7% of patients had one of the six most clinically significant arrhythmias detected and 28.1% the five most important arrhythmias (excluding supraventricular tachycardia), compared with 41.8% and 18.5% respectively with the 24-hour Holter monitor, p<0.001 (Barrett et al., 2014). The proportion of patients with AF detected in patients after ischaemic stroke or TIA was 14% at 28 days and 16.3% at 90 days with the Zio XT Service compared with 2.1% at both timepoints with the 24-hour Holter monitor, a statistically significant difference at 90 days, p=0.026 (Kaura 2019). Half (58.1%) of patients with paroxysmal AF had the arrhythmia identified with the Zio XT Service compared with 28% with the 24-hour Holter monitor, reported as statistically significant (Rosenberg et al., 2013).

The Zio XT Service has greater diagnostic accuracy and efficiency in detecting clinically-relevant arrhythmias

The sensitivity of the Zio XT Service for detection of any of the 6 most clinically-significant arrhythmias was 99%, specificity was 100%, positive predictive value (PPV) was 98% and negative predictive value (NPV) was 98% taking the gold standard to be the decision of physician investigators assessing recordings from both monitors. This compared with a sensitivity of 63%, specificity of 100%, PPV of 100% and NPV of 58% with the 24-hour Holter monitor (Barrett et al. 2014). In the study where four external monitors were compared with implanted pacemakers to determine the gold standard, the Zio XT Service was significantly more likely to detect the presence or absence of AF than the Novacor R-Test (odds ratio 12.3, 95%CI 1.4 to 110.3), compared with an OR of 5.8 (95%CI 1.1 to 32.1) with the Carnation ambulatory monitor and OR 2.0 (95%CI 0.5 to 7.5) with the NUUBO Vest (Eysenck et al., 2019).

The Zio XT Service leads to earlier diagnosis and initiation of preventative treatment

A significantly higher proportion of patients randomised to the Zio XT Service were taking anticoagulants at 90 days, 16.3% compared with 2.1% of patients who only had 24-hour Holter monitoring (Kaura et al., 2019). The short duration of this trial meant that no significant difference was seen in clinical outcomes, with one death in the Zio XT Service group due to pneumonia on day 4 that was not considered to be due to the monitor, and similar numbers of recurrent ischaemic strokes or TIAs. In a second study, 28.4% of patients with paroxysmal AF in the USA had a change in their classification of AF and subsequent medication change after assessment with both the Zio XT Service and the 24-hour Holter monitor, with 17.3% having a change in their antiarrhythmic medication and 5.3% changing oral anticoagulant use (Rosenberg et al., 2013).

The Zio XT Service causes minimal disruption to patients' daily activities leading to improved patient compliance and data collection

Median wear time for the Zio XT Service was 10.8 days (Rosenberg et al., 2013), 11.1 days (Barrett et al., 2014), 11.8 days (Kaura et al., 2019) and 12.8 days (Eysenck et al., 2019) out of the scheduled 14 days. This was, not surprisingly, longer than the mean 22.5 to 25 hours' wear time for the 24-hour Holter monitor in these three studies. However, in the one study where the Zio XT Service was compared with other longer-term continuous cardiac monitors, the mean wear time with the Zio XT Service (12.8 days) was higher than with the Novacor R-Test (9.3 days), Carnation ambulatory monitor (11.2 days) and

NUUBO Vest (7.75 days), when all four monitors were intended to be used for 14 days (Eysenck et al., 2019).
Most (93.7%) patients found the Zio XT Patch was comfortable to wear, compared with 51.7% of patients who thought the Holter monitor was comfortable, and 81% of patients preferred the Zio XT Patch to the 24-hour Holter monitor (Barrett et al., 2014). Although the Zio XT Patch could not be successfully applied in only 2% of patients in the UK-based RCT, 20% of participants refused to have the 24-hour Holter monitor applied, leading to high withdrawal rates (Kaura et al., 2019). In the direct comparison study with other long-term external monitors (Eysenck et al., 2019), mean patient discomfort scores (on a 0 to 5 scale where 5 is worst) were 1.59 for attaching the Zio XT Patch compared with 1.86 for attaching the Novacor R-Test, 2.51 for the NUUBO Vest and 0.57 for the Carnation ambulatory monitor. Similarly, mean patient discomfort score on the same 0 to 5 scale while wearing the Zio XT Patch was 1.86, compared with 2.84 while wearing the Novocor R test, 3.95 for the NUUBO Vest and 0.95 for the Carnation ambulatory monitor. These results are displayed graphically in the paper with p values not reported. Total patient time required during the monitoring was significantly shorter for the Zio XT Service (26.5 minutes) than the Novocor R-Test (53 minutes, $p<0.0001$), with the other two devices requiring similar time to the Zio XT Service (Eysenck et al., 2019).

The populations and types of cardiac monitor assessed in the other studies identified in the systematic review are very heterogeneous, making a valid indirect comparison against the Zio XT Service impossible. The overall accuracy for detecting arrhythmias from these different devices are summarised in the table below. Sensitivity and specificity of arrhythmia detection was often determined using the Holter monitor as the gold standard. The table below only reports accuracy data for the Holter monitors where these have been adjudicated against a higher gold standard such as clinician judgement from comparing the recordings from both technologies.

Summary of efficacy data from studies included in the systematic literature review

Technology Outcome	Zio XT Service	External event recorders	External continuous monitors	Implanted monitors	Holter monitor
Arrhythmia detection rates	**65.7%** (Barrett 2014)	**0%** (Kamalvand 1997) **2%** (Sivakumaran 2003) **13.7%** (Hendrikx 2014) **16%** (Ad 2009) **27.8%** (Senatore 2005) **29%** (Rothman 2007) **49%** (Tan 2010) **64%** (Makowska 2000) **68%** (Scalvini 2005) **88%** (Tan 2010) **89%** (De Asmundis 2014) **92.1%** (Narasimha 2018)	**6.8%** (Mamchur 2019) **72%** (Scherr 2008)	**7.1%** (Mamchur 2019) **46%** (Damaino 2016) **73%** (Giada 2007)	**41.8%** (Barrett 2014) **0%** (Sivakumaran 2003) **3.2%** (Hendrikx 2014) **9%** (Ad 2009) **13.9%** (Senatore 2005) **33%** (Makowska 2000) **72%** (Scalvini 2005) **1.8%** (De Asmundis 2014) **21%** (Giada 2007)
AF detection rates	**16.3%** (Kaura 2019 at 90 days) **50.7%** (Rosenberg 2013)	**2%** (Tan 2010) **3.8%** (Halcox 2017) **6%** (Doliwa Sobocinski 2012) **8.9%** (Reed 2019) **15.5%** (Gladstone 2014) **15.8%** (Narasimha 2018)	**23.1%** (Sampaio 2018) **26.2%** (Sejr 2017) **48%** (Higgins 2013)	**17%** (Ritter 2013) **20.7%** (Philippsen 2017) **23%** (Giada 2007) **26.5%** (Sanders 2016) **28%** (Piorkowski 2019)	**2.1%** (Kaura 2019) **28%** (Rosenberg 2013) **2%** (Doliwa Sobocinski 2012) **2.5%** (Gladstone 2014) **0%** (Kinlay 1996)

		19% (Kinlay 1996) **21.1%** (Poulsen 2017) **29.5%** (Chovancik 2019) **32.1%** (Kimura 2017) **42.4%** (Liu 2010) **84%** (Gussak 2012)		**30%** (Brachmann 2016) **31.1%** (Hindricks 2010, Eitel 2011) **31.6%** (Nolker 2016) **41.6%** (Davtyan 2018) **60%** (Hanke 2009) **71%** (Ciconte 2017)	**17.9%** (Poulsen 2017) **7.4%** (Kimura 2017) **29.2%** (Liu 2010) **32%** (Gussak 2012) **3.8%** (Sampaio 2018) **2.1%** (Sejr 2017) **10%** (Higgins 2013) **1.7%** (Ritter 2013) **2.4%** (Philippsen 2017) **4%** (Giada 2007) **27.5%** (Sanders 2016) **18.3%** (Piorkowski 2019) **32.3%** (Hindricks 2010, Eitel 2011) **20.2%** (Nolker 2016) **29.2%** (Davtyan 2018) **37%** (Hanke 2009) **62%** (Ciconte 2017)
Sensitivity for arrhythmia detection	**99%** (Barrett 2014)		**100%** (Scherr 2008)	**100%** (Piorkowski 2019)	**63%** (Barrett 2014) **100%** (Piorkowski 2019)
Specificity for arrhythmia detection	**100%** (Barrett 2014)			**88.1%** (Piorkowski 2019)	**100%** (Barrett 2014) **100%** (Piorkowski 2019)

Sensitivity for AF detection		**15.7%** (Gladstone 2014) **35%** (Chovancik 2019) **59%** (Poulsen 2017) **83%** (Wasserlauf 2019) **88%** (Doliwa Sobocinski 2012) **97%** (Tarakji 2015) **100%** (Gussak 2012)	**80.1%** (Mamchur 2019)	**78.6%** (Mamchur 2019) **96.1%** (Hindricks 2010) **97%** (Sanders 2016) **100%** (Ciconte 2017, Nolker 2016)	**6.0%** (Gladstone 2014) **29%** (Doliwa Sobocinski 2012)
Specificity for AF detection		**83%** (Wasserlauf 2019) **87%** (Poulsen 2017) **100%** (Tarakji 2015)	**73.1%** (Mamchur 2019)	**67%** (Ciconte 2017) **69%** (Mamchur 2019) **85.4%** (Hindricks 2010) **85.7%** (Nolker 2016) **97%** (Sanders 2016)	
Mean time to detection of arrhythmia	Median **1 day** (Rosenberg 2013)	**7 days** (Rothman 2007) **9.1 days** (De Asmundis 2014) **9.9 days** (Reed 2019) **16 days** (Sivakumaran 2003)		**64 days** (Ritter 2013) **91 days** (Philippsen 2017) **8.4 months** (Brachmann 2016, Sanna 2014)	
Clinical impact	**OAC use** 16.3**%** (Kaura 2019) 5.3% change (Rosenberg 2013) **Antiarrhythmic use**	**OAC use** **26%** (Higgins 2013) **Decreased from 100% to 85.7%** (Kimura 2017) **18.6%** (Gladstone 2014)		**OAC Use** **38.5%** (Brachmann 2016, Sanna 2014)	**OAC use = 2.1%** (Kaura 2019) **10%** (Higgins 2013) **11.1%** (Gladstone 2014)

	17.3% change (Rosenberg 2013) **Recurrent stroke/ TIA 2.3%** (Kaura 2019)	**Antiarrhythmic use Decreased from 57.1% to 25%** (Kimura 2017) **Recurrent stroke/ TIA 1.2%** (Halcox 2017)		**Recurrent stroke/ TIA** **9.0%** (Brachmann 2016, Sanna 2014)	**8.3%** (Brachmann 2016, Sanna 2014) **Recurrent stroke/ TIA** **2.1%** (Kaura 2019) **10.9%** (Brachmann 2016, Sanna 2014)

9 Summary and interpretation of clinical evidence

Summarise the main clinical evidence, highlighting the clinical benefits and any risks relating to adverse events from the technology.

The evidence reported in the previous sections shows the value of the Zio XT Service compared with 24-hour Holter monitors and other long-term external ambulatory monitors, in terms of improved arrhythmia and AF detection rate, more accurate diagnosis of arrhythmias, improved wear time due to lower discomfort and higher preference rates and an increase in the use of preventative medications. Few adverse events have been reported for the Zio XT Service, and sensitivity to the adhesive is the main adverse event experienced.

The comparative efficacy of other external and internal cardiac monitors is difficult to determine precisely due to the heterogeneity of the evidence. However, the qualitative summary table above shows that the performance of the Zio XT Service compares well with other external event recorders, external continuous ambulatory monitors and implantable loop recorders.

There are several issues regarding the efficacy and safety evidence. Although some studies were traditional RCTs, many studies directly compared two devices in the same person at the same time, which is likely to produce more accurate comparisons of their performance, especially when detecting infrequent paroxysmal arrhythmias.

The Holter monitor was used as the comparator in most of the included studies, which reflects current clinical practice. However, the Holter recording was often taken to be the gold standard against which the newer technologies were compared. In the smaller number of studies where the judgement of a clinical expert was taken to be the gold standard, such as the Zio XT Service studies by Barrett et al., 2014 and Rosenberg et al., 2013, the fallibility of the Holter monitors was clear. This means that there has to be some doubt about the findings of the studies that assumed the Holter monitor was 100% accurate, as the conclusions might be biased against the new technology. Additionally, not all studies blinded the investigators assessing the ECG recordings to the device that had been used, unlike, for example, the Zio XT Service study by Rosenberg et al., 2013. This may have biased the findings against the comparator in these unblinded studies.

The technologies with the longer wear times were more likely to detect a higher proportion of patients as having an arrhythmia. However, in some studies, this was associated with a longer mean time to detection of arrhythmia with the longer-duration monitors than with 24-hour Holter monitors. This again may lead to apparent bias against some of the longer-term technologies.

Several issues relate to the use of hand-held external event recorders to detect paroxysmal arrhythmias. These devices may be difficult for some patients to use, such as patients who have reduced manual dexterity after a stroke. The devices are unlikely to record episodes when the patient is asleep, busy or during episodes of syncope or

asymptomatic arrhythmia, and devices that only record intermittently cannot be used to determine the burden of arrhythmia over a 24-hour period. Devices that only record episodes of arrhythmia lasting longer than 30 seconds or 2 minutes will miss shorter episodes, although the clinical significance of these is unclear. The Zio XT Service, by being applied to the chest and left for 14 days, does not suffer from these disadvantages.

Implantable cardiac monitors are also able to monitor patients continuously and so have some advantages over hand-held event recorders. However, they require minor surgery to implant them, which can be painful and lead to bleeding and infections.

Briefly discuss the relevance of the evidence base to the decision problem. This should focus on the claimed benefits proposed by the company and the quality and quantity of the studies in the evidence base.

The decision problem for this submission is broad in terms of the population and the interventions and comparators. There are multiple reasons why patients might be suspected of having a cardiac arrhythmia, and a wide number of ECG monitoring interventions have been assessed.

The evidence base identified by the systematic literature review is also broad and, as such, is relevant to the decision problem, although the results of each individual study may not be generalisable to the whole of the target population. Although some studies included participants who had any reason to be suspected of having an arrhythmia, most focused on specific populations such as those who had had ablation for previous AF, patients with cryptogenic stroke or TIAs, or those with palpitations and syncope.

Of note, the majority of the included studies compare the diagnostic yield and clinical utility of monitoring devices only. The comparator in the decision problem encompasses the full patient pathway in which these devices are employed, which is not adequately compared in existing studies.

Identify any factors which might be different between the patients in the presented evidence and patients having routine care in the NHS in England.

The countries in which the studies were conducted were predominantly Europe and North America, with populations who are likely to resemble the UK population in terms of demographics and risk factors.

Generally, there are no significant differences between the patients in the study populations of the presented evidence and patients having routine care in the NHS in England. In 8 of the studies included in the systematic evidence review, there was a slight

unintended gender bias to either male or female in the population demographic. In a few studies there was an ethnic mix that would be less reflective of NHS patient populations in some parts of the country.

As such, it is reasonable to extrapolate the findings of the studies identified by the systematic review to the UK population.

Describe any criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate.

The Zio XT Service is intended for use in people, aged 18 and over, who are suspected of having cardiac arrhythmia and in whom ambulatory ECG monitoring is indicated to diagnose or rule out arrhythmia. Specifically, the greatest value from the the Zio XT Service is likely to be in those people who may be asymptomatic or who may suffer from symptoms of suspected arrhythmic episodes occurring with a frequency of more than 24 hours.

These transient symptoms may include palpitations, shortness of breath, dizziness, light-headedness, pre-syncope, syncope, fatigue, or anxiety.

It will also include people previously diagnosed with AF (or other arrhythmia) who require ambulatory ECG monitoring to monitor their rate control treatment.

Briefly summarise the strengths and limitations of the clinical evidence for the technology.

The four comparative trials of the Zio XT Patch had a good methodology, with three having a low risk of bias on the Cochrane Risk of Bias 2 tool, and the fourth (Kaura et al., 2019) having some concerns only because of the high refusal rate for the Holter monitor from participants. One study (Kaura et al., 2019) was an otherwise well-conducted RCT while the other three studies compared the Zio XT Service with either a 24-hour Holter monitor or with a permanent pacemaker, with patients providing simultaneous recordings from both technologies at the same time.

The issues of investigator bias were addressed in the study by Rosenberg et al. (2013), where the experts who determined whether the ECG traces showed AF or not were blinded to the source technology. Issues about whether the Holter monitor was an appropriate gold standard did not apply in the studies by Barratt et al. (2014) and Rosenberg et al. (2013), where a clinical expert determined the true arrhythmia rate for both technologies.

The evidence shows that, compared with the 24-hour Holter monitor, the Zio XT Service provides greater diagnostic accuracy for the five or six most clinically significant arrhythmias overall and for AF specifically. The diagnostic yield was significantly higher than with the 24-hour Holter monitor and in those studies where experts determined the true arrhythmia rate, the accuracy of the Zio XT Service was higher than the 24-hour Holter monitor. Use of the Zio XT Service increased the proportion of patients who started oral anticoagulants in the one RCT (Kaura et al., 2019) while 28.4% of participants in a single-arm trial had their anticoagulation and/or antiarrhythmia medication altered as a result of a change in the classification of their AF. Patient preference was greater for the Zio XT Service than the 24-hour Holter monitor, compliance was good, and most patients found the device comfortable to wear.

Limitations of the evidence base for the Zio XT Service are that the four comparative trials were of variable size, with a total of 366 participants, and the populations were heterogeneous, so the number of patients from each population relevant to the decision problem was small.

10 Outline of economic evidence

10.1 Population benefiting

Provide an estimate of the numbers of people likely to benefit from use of the technology in year 1 and how uptake will change over time to year 5. Explain assumptions and evidence sources informing your estimate.

The number of patients currently undergoing cardiac rhythm monitoring is uncertain, as recording of outpatient procedures is not mandatory under PbR regulations. Hospital Episode Statistics for 2017-18 documents 271,007 outpatient attendances for rhythm monitoring (Procedure codes U19.1, U19.2, U19.3, U19.5, U19.6), so this can reasonably be regarded as a minimum estimate for current service use.

There are currently no English NHS trusts that routinely use the Zio XT Service, although some are using it in special circumstances, so we can effectively say that baseline usage of the system is zero.

Clearly, the future uptake of the system is an unknown. However, if we make the arbitrary assumption that over the next five years, uptake of the Zio XT Service rises to 20% at a constant year-on-year rate, one would anticipate the following number of patients benefiting from the system:

Year 1: 10,800
Year 2: 16,200
Year 3: 21,600
Year 4: 27,000
Year 5: 54,000

10.2 List price of technology

Provide the unit list price(s) for the technology, including all related charges such as licence fees and subscription charges (all charges excluding VAT). The cost of the technology used in the base case of the economic modelling must be publicly available. Companies can present additional economic analyses using other technology costs to support their case for adoption. Please highlight any confidential information as explained at the start of the user guide.

The full NHS list price for the system is £295 per patient per diagnostic cycle.
This includes the cost of:

- The hardware component (Zio XT biosensor)
- Accessories required to prepare patient's skin for biosensor (razor, abrader, alcohol wipe)
- Freepost return of the biosensor by the patient to iRhythm UK data analysis centre
- Analysis of the results based on cardiac physiologist interpretation of the output of the ZEUS analytical algorithm
- Provision of detailed technical report to the referring clinician
- Urgent notifications of higher risk arrhythmias
- iRhythm 24-hour customer service for providers and patients
- Delivery of quarterly Zio XT Service Evaluation Tool
- Continually improved AI algorithm following each regulated update
- Implementation specialists and ongoing staff training as needed

10.3 Value of patient and system benefits

Section 2.2 describes the patient and system benefits. Where possible, provide an estimate of the impact of these changes on NHS annual costs. Explain assumptions and evidence sources informing your estimate. If no financial estimate is possible, describe the anticipated resource savings and related supporting evidence.

At this stage in the appraisal process, our financial modelling is incomplete, so we are unable to provide precise quantitative estimates of the value of the Zio XT Service to the NHS. We can however, provide a qualitative assessment of the likely impact, based on our preliminary budget impact modelling.

1) The Zio XT Service is expected to be cost neutral relative to current pathways using current technologies, when considered at a system level. This reflects the following cost drivers attributable to the current pathways using existing technologies, which need to be set against a single charge of £295 for the Zio XT Service:
   a) The unit cost per patient of hardware, maintenance and consumables
   b) The cost of out-patient attendance for fitting and removal of the standard device (single attendance assumed for the Zio XT pathway)
   c) The cost of a cardiac physiologist to analyse and report on the result (typical average 45 minutes per test – bundled into Zio XT Service charge)
   d) The cost of repeat testing – the diagnostic yield of existing technologies is substantially lower than for the Zio XT Service, necessitating repeat testing for many patients, with consequent repeat costs, as detailed above
   e) Evidence for the evaluation of system-level costings is based on a combination of data from clinical evaluation, nationally published statistics (HES) and expert input from clinicians and trusts.

2) Thanks to its improved diagnostic yield, use of the Zio XT Service is likely to result in earlier diagnosis and greater detection of intermittent arrhythmias. This is particularly important for patients with undiagnosed atrial fibrillation, in whom prompt treatment with anticoagulation can be expected to yield a reduction in stroke risk. At this stage, there is no long-term follow-up data for the Zio XT Service to support this outcome, but we intend to model the long-term savings based on published and established data from epidemiological studies and the results of randomised controlled trials of anticoagulants.

We anticipate that, by virtue of cost-neutrality demonstrated in step 1, the Zio XT Service will cross the health economic threshold expected by NICE for this type of appraisal. Although step 2 is necessarily more speculative, we believe it will show the potential for long-term savings for the NHS.

10.4 Training and pathway costs

Section 2.3 describes training requirements, section 3 describes the changes in the clinical pathway(s) and section 3.3 other system changes associated with the technology. Where possible provide an estimate of the impact of these changes on NHS annual costs. Explain assumptions and evidence sources informing this estimate. If no financial estimate is possible, describe the anticipated resource changes that will cause costs to increase. Please provide supporting evidence for any anticipated changes to resource use.

The answer to section 10.3 above includes some elements of pathway savings, consequent on reductions in the requirement for the in-house analytical service required by conventional rhythm monitoring systems currently in use. However, because this analysis is integral to the Zio XT Service currently under evaluation, we have incorporated this element into our previous answer. There are no resource-relevant training implications for the new technology.

10.5 Other annual NHS costs and savings

Are there any other material costs or savings which have not been described earlier? If so, where possible, provide an estimate the impact of these changes on NHS annual costs. Explain assumptions and evidence sources informing the estimate. If no financial estimate is possible, describe the anticipated resource changes which will cause costs to change. Please provide supporting evidence for any anticipated changes to resource use.

None.

10.6 Total costs and savings

Given the responses to section 10.2 to 10.5, where possible estimate the annual total costs to implement and operate the technology and the associated annual savings to the NHS. If the total costs and savings will change over time, describe the expected changes. Conclude with a sentence summarising the expected net lifetime savings (that is after all costs have been deducted) to the NHS from using this technology. If no financial estimate is possible please describe the anticipated net lifetime savings and related supporting evidence.

This response should be the consistent with that used in Section 2.2 'Cost benefits'.

Our worst-case estimate for this technology would be cost neutrality, with the possibility for long term savings attributable to more effective diagnosis and therefore greater detection of arrhythmias. At this stage in the appraisal process we are unable to provide a quantitative estimate of the magnitude of these long-term savings.

Because the Zio XT Service is charged on a per-patient basis, with no infrastructure or disinvestment implications, the effect of its adoption is entirely scalable. Costs for Zio XT are only incurred for those patients in whom it is used, with offset savings being made from pathway changes achieved through reduced use of older technology. This means that introduction can be phased, with the Zio XT Service being introduced in a phased fashion, as existing technology wears out or is otherwise no longer usable. There is therefore no asset wastage involved.

The reduction in requirement for in-house interpretation generates a theoretical disinvestment saving in direct proportion to the reduction in use of old technologies. In reality, it is unlikely that a significant staff reductions would occur, as NHS cardiac physiology resources are currently significantly overstretched (source: clinician input). Release of higher band cardiac physiology staff from the need to analyse monitoring traces will allow them to be redeployed in other areas of cardiac physiology that are under pressure and particularly helping to meet demands such as 7-day working.

In summary, the anticipated financial impact of the Zio XT Service will therefore be an improvement in patient diagnostic services at a similar cost to the existing service, while freeing up professional resources that can be better deployed elsewhere. The potential for improvements in clinical outcomes offers the additional potential for long term savings, although the magnitude of these are currently speculative.

10.7 Economic evidence

Summarise any existing economic evidence.

Economic evaluations

Kaura et al (2019) conducted a randomised open-label trial to compare the Zio XT Service to Holter monitoring for the monitoring of paroxysmal AF. 43 patients were successfully fitted with the Zio XT patch, and 47 with a 24-hour Holter monitor. The rate of detection of PAF at 90 days was 16.3% in the Zio XT Service group, compared with 2.1% in the 24-hour Holter monitor group (odds ratio 8.9, p=0.026). A budget impact model demonstrated that implementation of the Zio XT Service would result in 10.8 strokes being avoided per year at one UK hospital compared with current Holter monitoring, and a saving of £113,630 in the first year, increasing to £162,491 over 5 years.

A Health Technology Assessment by Health Quality Ontario assessed the effectiveness and costs associated with long-term ECG monitors (LTCM) compared to loop recorders in Canada (Anon 2017). As part of this HTA a budget impact analysis was conducted. It was estimated that the total cost of funding long-term ambulatory ECG testing in Ontario would range from $29.1 million in 2016 to $38.4 million in 2020. The net budget impact of increasing the use of LTCM and decreasing the use of loop recorders would range from $0.13 million in 2016 to $0.37 million in 2020. The budget impact analysis showed that the use of LTCM grew steadily over time since the introduction in 2006, and faster since 2011 when 14 day monitoring became publicly funded, causing a corresponding decline in loop recorder use. The analysis suggested that if the trends continued, publicly funding both devices would result in additional costs ranging between $130,000 to $370,000 per year over the next 5 years. Sensitivity analyses show that the greatest cost savings occur in a scenario where only tests via loop recorders are publicly funded.

Diamantopoulos et al. (2015) completed a cost effectiveness analysis of the Reveal XT implantable cardiac monitor compared with standard of care in the UK from an NHS perspective using a lifetime Markov model, populated using data from the CRYSTAL-AF study. Scenario analyses using CHADS2 scores were performed, and probabilistic and deterministic sensitivity analyses were performed. All costs and benefits were discounted at a rate of 3.5%. Monitoring with an ICM was associated with fewer recurrent strokes in the patient's lifetime and increased QALYs compared to standard of care. Due to the reduction in recurrent strokes, costs related to stroke were reduced in the ICM model, but remained higher overall than standard care. The ICER was £17,175 per QALY gained, compared to standard of care in the base-case scenario. This figure is below the established QALY willingness to pay threshold and so was deemed cost-effective. If warfarin was used instead of non-vitamin-k oral anticoagulants, the ICER decreased to £13,296 per QALY.

Kinlay et al. (1996) enrolled 45 patients into a randomised crossover trial of an event monitor for 3 months compared with a 48-hour Holter monitor. AF or flutter was detected in 6% of patients with the event recorder and no patients with 48-hour Holter. Clinically significant arrhythmias were detected in 19% of patients with the event recorder and no patients with the 48-hour Holter monitor. A cost-effectiveness analysis from a societal

perspective in Australia concluded that the ICER was -$213 per additional ECG recorded during symptoms and -$373 per additional clinically significant arrhythmia detected with the event recorder compared with the 48-hr Holter monitor. The event recorder dominated in all the scenario analyses conducted.

Levin et al (2014) conducted a cost-effectiveness analysis of 24-hour Holter monitoring compared with hand-held ECG or no screening for the detection of silent AF in Sweden. The long-term (20 year) costs and effects were estimated using a decision analytic model based on a clinical study and epidemiological data in Sweden. All costs were in 2013 Euros. Continuous 24-hour Holter monitoring was less cost-effective than intermittent handheld ECG monitoring due to its lower sensitivity and higher costs. Base-case analysis compared the intermittent handheld ECG screening with no screening in patients with recent stroke. Implementing a screening programme for 1000 patients resulted in 11 avoided strokes and the gain of 29 life-years or 23 QALYs and cost savings of €55,400 over a 20-year period. Continuous 24- hour Holter monitoring was dominated by the hand-held ECG due to its lower sensitivity and higher cost (€4,255,000/1000 patients). After 7 years, the screening programme with handheld ECG would become cost-saving compared with no screening.

Quiroz et al. (2017) developed a cost-utility model to assess the cost-effectiveness of an implantable cardiac monitor versus standard of care in patients following a cryptogenic stroke in the Netherlands. Few details are reported in this conference abstract. Health states related to the presence of, and diagnosis of AF, cerebrovascular and bleeding events and death. The Markov model had a lifetime horizon and a 3-month cycle time, with costs discounted at 4% and QALYs at 1.5% per year. The base-case analysis showed an ICER of €24,715 per QALY gained with the ICM compared with standard of care, which ranged from € 22,011 for a CHADS2 score of 4 to 6 to € 29,795 for a CHADS2 score of 2. Probabilistic sensitivity analysis suggested that ICM had a probability of 91% of being cost-effective at a threshold of € 80,000 per QALY gained.

Rinciog et al (2019) completed a cost-utility analysis of ICMs compared to standard of care for detecting atrial fibrillation in patients who are at high risk of stroke (CHADS2 score >2) in the UK from an NHS perspective. Patient characteristics and data were taken from the REVEAL AF trial and the Markov model developed by Diamantopoulos et al. (2016) was used. Costs and benefits were extrapolated across the patient's lifetime. Events including ischaemic and haemorrhagic stroke, bleeding and the cost of anticoagulants were included in the model. Costs and health outcomes were presented as QALYS and were discounted at a rate of 3.5% per year, and both deterministic and probabilistic sensitivity analysis were completed. The total cost of ICM was higher than SoC (£13,360 vs £11,936). ICM generated more QALYs than SoC (6.5 vs 6.3) and the ICER was £7140/QALY gained. In the probabilistic sensitivity analyses, ICM was cost-effective in 77.4% of the simulations.

Rockx et al. (2005) assessed the cost-effectiveness of a loop recorder compared to 48-hour Holter monitoring in a prospective randomised trial of 100 patients who were referred for ambulatory monitoring. 49 patients received the loop recorder and 51 the Holter monitor. After enrolment, 63% of patients in the loop recorder group had symptom recurrence compared to 24% in the 48-hour Holter group (p=<0.0001). The loop recorder

costs $533.56 compared to $177.64 for the Holter monitor, but cost of diagnosis in the two groups was similar (Holter= $745, loop=$843). The ICER of the loop recorder was $901.74 per extra successful diagnosis. If patients received 48-hour Holter monitoring followed by the loop recorder, the overall cost ($481+/-267) was lower than if they received the devices the other way round ($551 +/-$83), but had a lower diagnostic yield (49% vs 63%), and an overall higher cost of diagnosis ($982 vs $871, p=0.08). Analyses showed that 90% of cost-effectiveness ratios were less than $1250.

Yong et al (2016) completed a long-term (lifetime horizon) cost effectiveness analysis of a handheld ECG vs repeat Holter monitoring for 30 days, 14 days or 7 days. Patients were >55 years and had a recent cryptogenic stroke and negative 24-hour ECG. A Markov model was created for observed rates of AF detection, and published literature was used to estimate costs. Lifetime costs, lifetime effectiveness, QALYs, life years gained and incremental costs were calculated. Prolonged ECG monitoring prevented more ischaemic strokes and decreased mortality, as well as improving QALYs. If combined with anticoagulant treatment known to reduce stroke risk by 50% then 30-day ECG (cost $447) becomes highly cost-effective at $2000 per QALY gained, in patients whose annual stroke recurrence risk was 4.5%. Cost-effectiveness was affected by stroke recurrence risk, and the effectiveness and presence of anticoagulants. Shorter duration (7 or 14 days ECG) monitoring was cost-saving and more effective than 24-hour Holter monitoring, and its cost-effectiveness was less sensitive to changes in stroke risk and anticoagulant use. Per 1,000 people, the 30-day ECG would prevent 16 ischaemic strokes and 2 intracranial haemorrhages, with a life gain of 17 years, a QALY gain of 13 and an additional cost of $28,000.

Zimetbaum et al. (1998) completed a prospective cohort study of 105 patients in the USA to determine the yield, timing and incremental cost-effectiveness of each week of monitoring for palpitations using the continuous loop event recorder. The loop recorder recorded 1.04 diagnoses per patient in the first week, 0.15 in the second and 0.01 diagnoses per patient in week 3 and beyond. The cost-effectiveness ratio per new diagnosis was $98 in week 1, $576 in week 2 and $5832 in week 3. If a patient received a diagnosis and it was considered "meaningful", the cost-effectiveness ratio for week 1 of event monitoring was $98 (CI $82 to $121) per diagnosis. This increased to $576 (CI $383 to $1066) during week 2, and to $5832 (CI $1975 to infinity) during week 3 and beyond.

Other studies reporting relevant cost data for the UK

A medtech innovation briefing from NICE determined the costs of use and monitoring with the Zio XT Service in the UK. The purchase cost of the Zio XT patch is lower than the Holter monitor but the costs per patient are higher. These costs may be offset if the Zio XT Service leads to more accurate diagnosis and better treatment of arrhythmias (NICE MIB141, 2018).

A second NICE medtech innovation briefing report determined the costs of use and implantation of the Reveal LINQ implantable cardiac monitor in the UK. The costs of the LINQ are higher than for standard ECG monitoring or stress-testing but these costs may be offset if its use leads to a greater detection of AF and initiation of preventive therapy.

Costs are also lower if the device can be fitted outside a catheter laboratory (NICE MIB101, 2017).

Ali et al. (2015) reported on the direct medical costs of acute stroke care for patients with atrial fibrillation from a UK hospital. The majority of patients had ischaemic strokes, 37.3% of whom had AF, 56 were known to have AF before the stroke, 8 of whom were anticoagulated and 33 were taking antiplatelets. The overall mean cost of ischaemic stroke per patient was £9,084 in those with AF compared with £5,729 in those with no AF. The difference in costs of haemorrhagic stroke was not significantly different in those with or without AF, £7,058 vs. £8,790, p = 0.764. The presence of AF independently increased acute care costs of ischaemic stroke by £2,173 (95%CI £91 to £4,255, p=0.041), with a history of congestive cardiac failure and NIHSS stroke score the only other independent predictors of costs. The increase in costs with AF was significantly higher than for patients in sinus rhythm for hospital admissions and bed-days, pathology tests, feeds, fluids, medications, ward consumables, therapist rehabilitation and specialist referrals and procedures.

Boggon et al., (2010) reported the resource use for a UK cohort of patients with atrial fibrillation, as well as breaking down this resource use according the NICE stroke risk score of the patients. Of the 15,373 patients with diagnosed AF, 18.6% were aged 18 to 64 years, 23.3% were aged 65 to 74 years, 36.5% were aged 75 to 84 years and 21.6% were aged 85 years and older. Almost half (48.8%) were female and 43.8% had never smoked. Most (64.8%) had a high NICE stroke risk. Patients with AF had significantly more drug prescriptions than controls in the past 6 months and had significantly higher numbers of contacts, referrals, tests and hospitalisations per year than controls. All-cause mortality rate was 107.6/1,000 person-years with AF compared with 35.0/1,000 person-years in the control group, a relative risk of 3.11 (95%CI 2.92 to 3.31).

Stewart et al., (2004) calculated resource use and costs for all patients with AF in the UK in 1995 and extrapolated the data to estimate the likely resource use for 2000 based on the aging population. Total NHS costs in 1995 were £243.9 million and this was estimated to increase to £459.0 million in 2000, or £1307.4 million if nursing home care and admissions where AF was a secondary diagnosis are included. Of this total, 50% of the costs were for hospital admissions, 20% for drug treatments, 13% for GP visits, 12% for GP outpatient referrals and 6% for post-discharge outpatient visits.

Yiin et al. (2014) assessed 1-year hospitalisation costs and 5-year residential care costs for the 454 people in Oxfordshire who had an AF-related ischaemic stroke or systemic embolism in 2002 to 2012 and extrapolated the data to estimate the likely costs for the UK in 2050. Mean total care costs of AF-related ischaemic stroke at 2008-09 costs were £22,423, of which £12,417 was due to hospital care and £10,007 was due to long-term institutionalisation. Mean costs were higher in patients aged 80 years and older compared with younger patients. Mean hospital and total costs of systemic emboli were £13,720 and were slightly higher in the older age-group. By 2050, the estimated care costs, at 2008 prices, of AF-related incident ischaemic stroke would be £1.7 billion, and £221 million for systemic emboli.

Ghosh et al. (2018) assessed 30 patients undergoing monitoring for arrhythmias after a minor stroke or TIA in the UK. AF was detected in 1 patient using the Zio XT patch and none using a 24-hour Holter. Patients were fitted with the Zio XT patch in the clinic but had to wait a median of 59 days for the Holter monitor. Costs of the investigation plus follow up were £367 for the 24-hour Holter and £440 with the Zio XT patch. Few other details are reported in this conference abstract.

Halcox et al (2017) randomised 1001 patients with CHADS-VASc score of 2 or more who were aged >65 years but with no prior diagnosis of AF to routine care or the AliveCor Kardia iPod/smartphone wireless ECG monitor for 12 months to assess the costs, satisfaction, efficacy and diagnostic ability. Outcomes were assessed at 12, 32 and 52 weeks. 19 patients in the AliveCor group were diagnosed with AF compared with 5 in the standard care group (HR 3.9, 95%CI= 1.4 to 10.4, p=0.007). No significant differences in adverse event rates were seen between groups. The estimated detection rate of the two interventions was recorded at 10, 20, 30, 40 and 50 weeks. Patients in the AliveCor group were significantly more likely to receive a diagnosis than those receiving usual care (p=0.004).

Chandratheva et al. (2017) assessed 80 patients with TIA attending a TIA clinic in London, AF was detected in 1 of 20 patients with a Zio XT patch, 2 of 20 patients with an E-patch, 1 of 20 patients with in-clinic monitoring with Apoplex and none of 20 patients with 72-hour Holter. The costs of each device were cheapest for the Zio XT patch (£300), compared with £569 for the 72-hour Holter, £651 for the 30-day E-patch and £670 for in-clinic monitoring. Few other details are reported in this conference abstract.

Reed et al. (2019) compared the AliveCor smartphone case and app with standard care in 243 patients over the age of 16 years who presented at an emergency department in the UK with palpitations or presyncope and with a nondiagnostic ECG. There were more emergency department presentations after the index event for palpitations or presyncope in the AliveCor group (9.7% compared with 2.6% of the control group, p=0.031) but no significant differences in hospital admissions, outpatient visits, GP visits or ECGs performed due to palpitations or presyncope. Median overall healthcare costs were higher with AliveCor (£108 vs £0 with standard care) but the cost per symptomatic rhythm diagnosis was lower with AliveCor (£474 versus £1395 with standard care).

Summarise the planned economic analysis detailing likely model structure, relevance to clinical pathway, decision problem and time horizon.

The plan is to construct a two-stage cost-consequences model to separately capture the costs associated with short term process changes and the medium-term costs associated with a reduction in adverse clinical outcomes associated with earlier, more comprehensive diagnosis of arrhythmias, with particular focus on atrial fibrillation.

The first stage of the model will use a decision-tree structure that will be constructed around a typical care-flow pathway. This will capture the diagnostic pathway undergone by a typical patient, and will capture the technologies used, the diagnostic yield, frequency of re-testing and onward consequences of both positive and negative tests. We are still in the process of determining the most representative care pathways to model, but clinical pathways described in Section 3.1 give an example of the potential approach. For each decision point in the flow diagram, transition probabilities and costs will be captured, to allow aggregate expected costs to be estimated for both Zio XT and control arms.

Loop-backs, to reflect repeat testing for negative results, will be built into the flow diagrams.

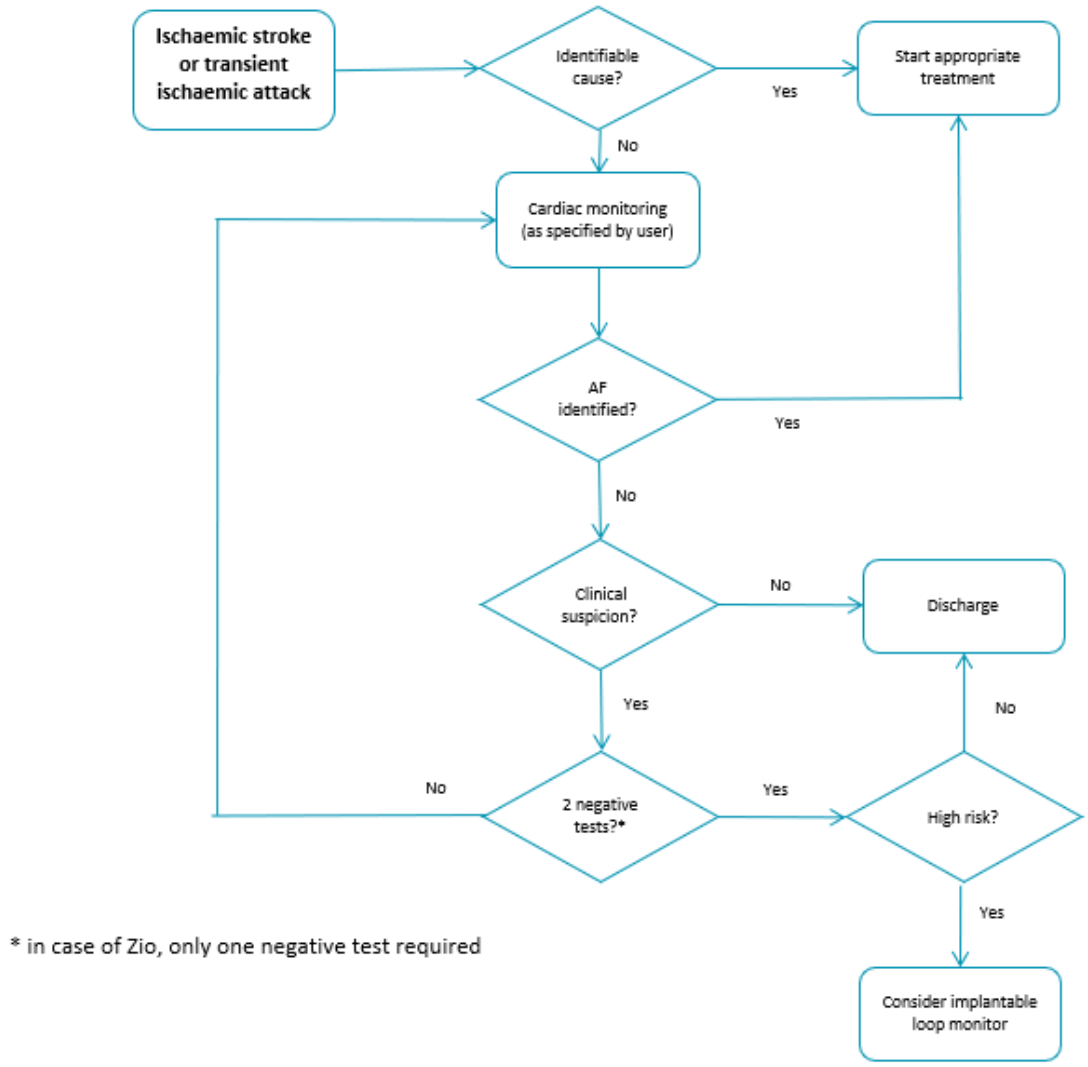
The time horizon for the process stage will be 1 year, on the basis that most patients will have been given a definitive diagnostic decision over this time period.

The second stage of the model aims to capture two components:

- ◊ The excess risk of stroke associated with a delayed diagnosis of atrial fibrillation.
- ◊ The excess risk of stroke associated with a missed diagnosis of atrial fibrillation.

In the absence of clinical outcomes evidence for the Zio XT System, the element of the model will use published epidemiological data to estimate the risk of excess risk of stroke for each three-month period during which time AF has not been diagnosed and treatment has not been initiated. Appropriate costs will be appended to these figures, to estimate the cost consequences of the missed diagnostic opportunity.
Given that we must assume that those patients with a missed AF diagnosis will ultimately be diagnosed, we will limit this stage of the model to 5-years.

Once again, the development of this step in the model is still a work in progress. The flow diagram below explores a possible flow structure for stage 2. At this stage we are inclined to use a simple decision tree approach, although a Markov state-transition model has not been ruled out.



The results of the overall model will be presented as both stage 1 alone and stage 1+2 combined, reflecting the differing approaches and budget heads against which the potential savings will be assessed.

Describe the main parameters in the planned economic analysis and the key sources of uncertainty.

Test performance (diagnostic yield)

For each technology, we will need to capture:

a) The proportion of patients who had a positive/negative result in the presence of symptoms during the monitoring period
b) The proportion of patients who had a positive/negative result in the absence of symptoms during the monitoring period

This information is available for the Zio XT Service but is very limited for the comparator technologies. A series of assumptions will have to be made and explored within a sensitivity analysis.

Test use/re-use

In the presence of a negative test result, particularly if the patient was asymptomatic during the monitoring period, it is likely that patients will return for re-testing, thereby incurring an additional cost. Whilst we are attempting to characterise this phenomenon using HES data, limited coding quality for out-patient procedures makes the results quite uncertain. This will have to be explored carefully, given its impact on overall costs in the comparator arm.

Cost of comparator technologies

Information on the true cost per test of comparator technologies is absent. Although there is a tariff associated with cardiovascular monitoring, it is a flat rate that does not reflect differing costs associated with different technologies – both with regard to hardware costs and technical analytical services. The same is true for PLICS costs that are available for cardiovascular monitoring. We will endeavour to use a ground-up costing approach to arrive at fair estimates for this true costs, but this will inevitably be anecdotal in nature. This parameter will therefore also need to be explored in sensitivity analyses

Care pathways

We have undertaken extensive research to understand different patient care pathways within the NHS and have identified a wide range of possible pathways, incorporating for instance differences in access (Direct vs via consultant), context (community vs hospital), response to positive/negative results and technology used. We intend to model a representative sample of the possible approaches, but it is inevitable that our conclusions will not relate universally to all trusts.

Clinical outcomes

The risks of stroke associated with delayed or missed diagnosis will be derived from the published literature. Whilst there is an extensive accepted evidence base in the field, one must accept that a) there are no direct RCT-derived data for the benefit of the Zio XT System in this regards and b) it is possible that the historic literature-derived estimates will not reflect clinical outcomes moving forward. This is a problem inherent, to some extent, in almost any economic model. Other than acknowledging it and being aware of the potential limitations that it inflicts on the result, there is little that can be done to rectify it.

11 References

Please include all references below using NICE's standard referencing style.

Ad, N., Henry, L., Hunt, S., et al. (2009). "The Cox-Maze III Procedure Success Rate: Comparison by Electrocardiogram, 24-Hour Holter Monitoring and Long-Term Monitoring." Annals of Thoracic Surgery 88(1): 101-105.

Ali, A. N., Howe, J., Abdel-Hafiz, A et al. (2015). "Cost of acute stroke care for patients with atrial fibrillation compared with those in sinus rhythm." Pharmacoeconomics 33(5): 511-520.

Anonymous (2017). Long-term continuous ambulatory ECG monitors and external cardiac loop recorders for cardiac arrhythmia: a health technology assessment. Ontario Health Technology Assessment series.

Barrett, P. M. Komatireddy, R. Haaser, S. et al. (2014). "Comparison of 24-hour Holter monitoring with 14-day novel adhesive patch electrocardiographic monitoring." American Journal of Medicine 127(1): 95.e11-95.e17.

Boggon, R., Gregory Y.H. Lip, Arlene M. Gallagher, et al. (2012). "Resource utilization and outcomes in Patients with AF." Appl Health Econ Health Policy (10 (4): 249-259 1175-5652/12/0004-0249/$49.95/0).

Brachmann, J, Morillo, Ca, Sanna, T et al. (2016) "Uncovering Atrial Fibrillation Beyond Short-Term Monitoring in Cryptogenic Stroke Patients: three-Year Results From the Cryptogenic Stroke and Underlying Atrial Fibrillation Trial". Circulation. Arrhythmia and electrophysiology 9, e003333 10.1161/CIRCEP.115.003333.

Bravo, Y., Martí, B., Grifols, M. A. (2012). "Cost analysis of an implantable loop recorder, reveal© XT, for the diagnosis of atrial fibrillation in patients who underwent cryptogenic stroke from the perspective of a tertiary Spanish Hospital." Value in Health 15(7): A351.

Camm, J., Talajic, M, Komajda, M., et al. (2014). "Cardiac safety of the sino atrial node f channel blocker ivabradine in chronic heart failure: An ECG-holter sub-study." Journal of cardiac failure 20(8): S38.Wineinger, N. E., Barrett, P. M., Zhang, Y. et al. (2019). "Identification of paroxysmal atrial fibrillation subtypes in over 13,000 individuals." Heart Rhythm 16(1): 26-30.

Chandratheva A., Pleming J., Dados A., et al. (2017). "New versus conventional non-invasive cardiac monitoring for atrial fibrillation detection in TIA clinic." Presented at the European Stroke Organisation conference, 2017.

Chen, L.Y., Agarwal, S.K., Norby, F.L., et al. (2015). "Premature atrial contraction frequency is not associated with cerebral infarcts: The atherosclerosis risk in communities (ARIC) study." Circulation 132.

Chovancik, J., Bulkova, V., Wichterle, D., et al. (2019). "Comparison of two modes of long-term ECG monitoring to assess the efficacy of catheter ablation for paroxysmal atrial fibrillation." Biomedical papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia 163(1): 54-60.

Ciconte, G., Saviano, M, Giannelli, L., et al. (2017). "Atrial fibrillation detection using a novel three-vector cardiac implantable monitor: The atrial fibrillation detect study." Europace 19(7): 1101-1108.

Coutinho Cruz, M., Almeida Morais, L., Antunes, E., et al. (2017). "An innovative miniature patch ambulatory electrocardiographic recorder." European Heart Journal 38: 1178.

Damiano, R. J., Jr. Lawrance, C. P., Saint, L. L. et al. (2016). "Detection of Atrial Fibrillation After Surgical Ablation: Conventional Versus Continuous Monitoring." Ann Thorac Surg 101(1): 42-47; discussion 47-48.

Davtyan, K., Shatakhtsyan, V., Poghosyan, H., et al. (2018). "Radiofrequency versus Cryoballoon Ablation of Atrial Fibrillation: An Evaluation Using ECG, Holter Monitoring, and Implantable Loop Recorders to Monitor Absolute and Clinical Effectiveness." BioMed Research International 2018.

De Asmundis, C., Conte, G., Sieira, J., et al. (2014) "Comparison of the patient-activated event recording system vs. traditional 24 h Holter electrocardiography in individuals with paroxysmal palpitations or dizziness". Europace 16, 1231-1235 10.1093/europace/eut411.

Doliwa Sobocinski, P., Änggårdh Rooth, E., Frykman Kull, V., et al. (2012). "Improved screening for silent atrial fibrillation after ischaemic stroke." Europace 14(8): 1112-1116.

Eisenberg, E., Carlson, S.K., Doshi, R.N., et al. (2014) " Chronic Ambulatory Monitoring: Results of a Large Single-Center Experience ". The Journal of Innovations in Cardiac Rhythm Management, 5 (2014), 1818–1823

Eitel, C., Husser, D., Hindricks, G., et al. (2011). "Performance of an implantable automatic atrial fibrillation detection device: Impact of software adjustments and relevance of manual episode analysis." Europace 13(4): 480-485.

Eysenck, W., Freemantle, N., Sulke, N. et al. (2019). "A randomized trial evaluating the accuracy of AF detection by four external ambulatory ECG monitors compared to permanent pacemaker AF detection." Journal of Interventional Cardiac Electrophysiology.

Francisco Pascual, J., Santos Ortega, A., Mila Pascual, L., et al. (2017). "Systematic use of an external loop recorder to evaluate patients with palpitations: A cost-benefit study." Europace 19: iii216.

Garcia Quintana, A., Mendoza-Lemes, H., Garcia Perez, L., et al. (2011). "Diagnostic yield of a new ambulatory ECG telemonitoring system (HOLTIN) and conventional Holter in patients with unexplained palpitations or syncope." Europace 13.

Giada, F, Gulizia, M, Francese, M et al. (2007) "Recurrent unexplained palpitations (RUP) study comparison of implantable loop recorder versus conventional diagnostic strategy". Journal of the American College of Cardiology 49, 1951-1956 10.1016/j.jacc.2007.02.036.

Gladstone, D. J., Spring, M., Dorian, P. et al. (2014) "Atrial fibrillation in patients with cryptogenic stroke". New England Journal of Medicine 370, 2467-2477 10.1056/NEJMoa1311376.

Go, A. S., Reynolds, K., Yang, J., et al. (2018). "Association of Burden of Atrial Fibrillation With Risk of Ischemic Stroke in Adults With Paroxysmal Atrial Fibrillation: The KP-RHYTHM Study." JAMA Cardiol 3(7): 601-608.

Gussak, I., Vukajlovic, D., Vukcevic, V., et al. (2012). "Wireless remote monitoring of reconstructed 12-lead ECGs after ablation for atrial fibrillation using a hand-held device." Journal of Electrocardiology 45(2): 129-135.

Halcox, J. P. J., Wareham, K., Cardew, A.et al. (2017). "Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation: The REHEARSE-AF Study." Circulation 136(19): 1784-1794.

Hanke, T., Charitos, E. I., Stierle, U. et al. (2009). "Twenty-four - hour holter monitor follow-up does not provide accurate heart rhythm status after surgical atrial fibrillation ablation therapy up to 12 months experience with a novel permanently implantable heart rhythm monitor device." Circulation 120(SUPPL. 1): S177-S184.

Hannun, A. Y. Pranav, R., Masoumeh, H. et al. (2019). "Cardiologist-level arrhythmia detection and classification in ambulatory electrocardiograms using a deep neural network." Nature Medicine 25(1): 65-69.

Hart R, Pearce L., Aquilar M. (2007). “Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation.” Annals of Internal Medicine 146: 857-67.

Heckbert, S. R., Austin, T. R., Jensen, P. N. et al. (2018). "Yield and consistency of arrhythmia detection with patch electrocardiographic monitoring: The Multi-Ethnic Study of Atherosclerosis." Journal of Electrocardiology 51(6): 997-1002.

Hendrikx, T., Rosenqvist, M., Sandström, H., et al. (2012). "Comparing efficacy of Holter ECG and Handheld ECG in detecting relevant arrhythmias-the Primarytm study." Cerebrovascular Diseases 33: 838-839.

Hendrikx, T., Rosenqvist, M., Wester, P., et al. (2014). "Intermittent short ECG recording is more effective than 24-hour Holter ECG in detection of arrhythmias." BMC Cardiovascular Disorders 14.

Higgins, P., MacFarlane, P.W., Dawson, J., et al. (2013). "Noninvasive cardiac event monitoring to detect atrial fibrillation after ischemic stroke: A randomized, controlled trial." Stroke 44(9): 2525-2531.

Hindricks, G., Pokushalov, E., Urban, L. et al. (2010). "Performance of a new leadless implantable cardiac monitor in detecting and quantifying atrial fibrillation results of the XPECT trial." Circulation: Arrhythmia and Electrophysiology 3(2): 141-147.

Howlett, P. J., Morritt, J., Jabr, R. et al. (2014). "Targeted screening for paroxysmal atrial fibrillation: Prolonged monitoring significantly increases diagnostic yield." Europace 16: iii26.

Howlett, P., Morritt, J., Greswell, L.., et al. (2014). "Symptom frequency is a poor predictor of onset of paroxysmal atrial fibrillation in a population presenting with palpitations." Europace 16: iii31.

Interian, A., Garcia, P.V., Chanda, A., et al. (2011). ""“economic impact in the early usage of implantable loop recorders in patients with syncope and structural normal hearts”." Journal of Cardiovascular Electrophysiology 22: S84-S85.

Kamalvand, K, Tan, K, Kotsakis, A et al. (1997) "Ambulatory patient-activated arrhythmia monitoring: comparison of a new wrist-applied monitor with a conventional precordial device". Journal of Electrocardiology 30, 127-131.

Kaura, A., Sztriha, L., Chan, F. K. et al (2019)Early prolonged ambulatory cardiac monitoring in stroke (EPACS): an open-label randomised controlled trial

Kimura, T., Aizawa, Y., Kurata, N., et al. (2017). "Assessment of atrial fibrillation ablation outcomes with clinic ECG, monthly 24-h Holter ECG, and twice-daily telemonitoring ECG." Heart and Vessels 32(3): 317-325.

Kinlay, S., Leitch, J. W., Neil, A. et al. (1996) "Cardiac event recorders yield more diagnoses and are more cost-effective than 48-hour Holter monitoring in patients with palpitations. A controlled clinical trial". Annals of Internal Medicine 124, 16-20 10.7326/0003-4819-124-1_part_1-199601010-00003.

Lauschke, J, Busch, M, Haverkamp, W et al. (2016) "New implantable cardiac monitor with three-lead ECG and active noise detection". Herz 1-8 10.1007/s00059-016-4492-7.

Levin, L. A., Husberg, M., Sobocinski, P. D. et al. (2014). "A cost-effectiveness analysis of screening for silent atrial fibrillation after ischaemic stroke." Europace 17(2): 207-214.

Liu, J., Fang, P. H., Hou, Y. et al. (2010) "The value of transtelephonic electrocardiogram monitoring system during the "Blanking Period" after ablation of atrial fibrillation". Journal of Electrocardiology 43, 667-672 10.1016/j.jelectrocard.2010.06.007.

Locati, E., Ardito, C., Llorca, D., et al. (2016). "Wearable wireless prolonged ECG monitoring in clinical practice: Diagnostic yield of 7-day versus 21-day recordings in patients with suspected arrhythmias." Europace 18: i172.

Locati, E.T., Ardito, C., Cecchi, F., et al. (2017). "Diagnostic yield of 7-days versus 21-days recordings by using a new wearable wireless continuous ambulatory ECG recorder." European Heart Journal 38: 1176.

Lutsey, P., Chen, Ly, Eaton, A, et al. (2018) A Pilot Randomized Trial of Oral Magnesium Supplementation on Supraventricular Arrhythmias. Nutrients 10, DOI: 10.3390/nu10070884

Maervoet, J., Bossers, N., Borge, R. P. et al. (2017). "Clinical and economic value of device-based detection of atrial fibrillation in patients with cryptogenic stroke." Value in Health 20(9): A584.

Makowska, E, Szymot, J, Soszynska, M et al. (2000) "Evaluation of patients with palpitations: cardiac event recorder versus 48-hour Holter monitoring". Annals of Noninvasive Electrocardiology 5, 315-321.

Mamchur, S.E., Khomenko, E.A., Chichkova, T.Y., et al. (2019). "Noninvasive long-term ECG monitoring vs. loop recorder implantation for the atrial fibrillation management." Annals of Noninvasive Electrocardiology.

Mullis, A. H., Ayoub, K. , Shah, J. et al. (2019). "Fluctuations in premature ventricular contraction burden can affect medical assessment and management." Heart Rhythm.

Muse, E. D., Wineinger, N. E., Spencer, E. G. et al. (2018). "Validation of a genetic risk score for atrial fibrillation: A prospective multicenter cohort study." PLoS Med 15(3): e1002525.

Narasimha, D., Hanna, N., Beck, H., et al. (2018). "Validation of a smartphone-based event recorder for arrhythmia detection." PACE - Pacing and Clinical Electrophysiology 41(5): 487-494.

NICE (2017). "Zio XT Service for detecting cardiac arrhythmias." National Institute for Health and Care Excellence.

NICE (2018). "Reveal LINQ insertable cardiac monitor to detect atrial fibrillation after cryptogenic stroke."

NÖLker, G., Mayer, J., Boldt, L. H., et al. (2016). "Performance of an Implantable Cardiac Monitor to Detect Atrial Fibrillation: Results of the DETECT AF Study." Journal of Cardiovascular Electrophysiology 27(12): 1403-1410.

Philippsen, T., Christensen, L. S., Hansen, M. G. et al. (2017). "Detection of Subclinical Atrial Fibrillation in High-Risk Patients Using an Insertable Cardiac Monitor." JACC: Clinical Electrophysiology 3(13): 1557-1564.

Piorkowski, C., Busch, M., Nölker, G. et al. (2019). "Clinical evaluation of a small implantable cardiac monitor with a long sensing vector." PACE - Pacing and Clinical Electrophysiology.

Poulsen, M.B., Binici, Z., Dominguez, H., et al. (2017). "Performance of short ECG recordings twice daily to detect paroxysmal atrial fibrillation in stroke and transient ischemic attack patients." International Journal of Stroke 12(2): 192-196.

Proesmans, T., Desteghe, L., Berti, D., et al. (2019). "Impact and cost-effectiveness of long-term intermittent PPG monitoring in stroke patients." Europace 21: ii540.

Quiroz, M., Wolff, C., Eggington, S., et al. (2017). "Insertable cardiac monitor versus standard of care for detection of atrial fibrillation in patients following cryptogenic stroke: A Dutch cost-effectiveness analysis." Value in Health 20(9): A588.

Reed, M.J., Grubb, N.R., Lang, C.C., et al. (2019). "Multi-centre Randomised Controlled Trial of a Smartphone-based Event Recorder Alongside Standard Care Versus Standard Care for Patients Presenting to the Emergency Department with Palpitations and Pre-syncope: The IPED (Investigation of Palpitations in the ED) study." EClinicalMedicine 8: 37-46.

Reed, M.J., Grubb, N.R., Lang, C.C., et al. (2019). "The investigation of palpitations in the emergency department study." Academic Emergency Medicine 26: S160.

Reiffel, J.A., Verma, A., Kowey, P., et al. (2018). "A comparison of atrial fibrillation monitoring strategies in patients at high risk for atrial fibrillation and stroke: Results from the reveal AF study." Journal of the American College of Cardiology 71(11).

Rinciog, C. I., Sawyer, L. M., Diamantopoulos, A, et al. (2019). "Cost-effectiveness of an insertable cardiac monitor in a high-risk population in the UK." Open Heart 6(1).

Ritter, M. A., Kochhäuser, S., Duning, T., et al. (2013). "Occult atrial fibrillation in cryptogenic stroke: Detection by 7-day electrocardiogram versus implantable cardiac monitors." Stroke 44(5): 1449-1452.

Rockx, M. A., Hoch, J. S., Klein, G. J. et al. (2005). "Is ambulatory monitoring for "community-acquired" syncope economically attractive? A cost-effectiveness analysis of a randomized trial of external loop recorders versus Holter monitoring." American Heart Journal 150(5): 1065.e1061-1065.e1065.

Rosenberg, M. A., Samuel, M., Thosani, A. et al. (2013). "Use of a noninvasive continuous monitoring device in the management of atrial fibrillation: A pilot study." PACE - Pacing and Clinical Electrophysiology 36(3): 328-333.

Rothman, Sa, Laughlin, Jc, Seltzer, J et al. (2007) "The diagnosis of cardiac arrhythmias: a prospective multi-center randomized study comparing mobile cardiac outpatient telemetry versus standard loop event monitoring". Journal of Cardiovascular Electrophysiology 18, 241-247.

Sampaio, R.F., Gomes, I.C. and Sternick, E.B. (2018). "Cryptogenic acute ischemic stroke: Assessment of the performance of a new continuous long-term monitoring system in the detection of atrial fibrillation." Arquivos Brasileiros de Cardiologia 111(2): 122-131.

Sanders, P, Purerfellner, H, Pokushalov, E et al. (2016). "Performance of a new atrial fibrillation detection algorithm in a miniaturized insertable cardiac monitor: Results from the Reveal LINQ Usability Study." Heart Rhythm 13(7): 1425-1430.

Sanna, T., Diener, H. C., Passman, R. S, et al. (2014). "Cryptogenic stroke and underlying atrial fibrillation." New England Journal of Medicine 370(26): 2478-2486.

Scalvini, S., Zanelli, E., Martinelli, G., et al. (2005). "Cardiac event recording yields more diagnoses than 24-hour Holter monitoring in patients with palpitations." Journal of Telemedicine and Telecare 11(SUPPL. 1): 14-16.

Scherr, D., Dalal, D., Henrikson, C. A.et al. (2008). "Prospective comparison of the diagnostic utility of a standard event monitor versus a "leadless" portable ECG monitor in the evaluation of patients with palpitations." Journal of Interventional Cardiac Electrophysiology 22(1): 39-44.

Schreiber, D., Sattar, A., Drigalla, D., & Higgins, S. (2014). Ambulatory Cardiac Monitoring for Discharged Emergency Department Patients with Possible Cardiac Arrhythmias. Western Journal of Emergency Medicine: Integrating Emergency Care with Population Health, 15(2).

Schultz, K. E., Lui, G. K., McElhinney, D. B. et al. (2019). "Extended cardiac ambulatory rhythm monitoring in adults with congenital heart disease: Arrhythmia detection and impact of extended monitoring." Congenital Heart Disease 14(3): 410-418.

Sejr, M. H., Nielsen, J. C., et al., Damgaard, D. (2017). "Atrial fibrillation detected by external loop recording for seven days or two-day simultaneous Holter recording: A comparison in patients with ischemic stroke or transient ischemic attack." J Electrocardiol 50(3): 287-293.

Senatore, G., Stabile, G., Bertaglia, E.et al. (2005). "Role of transtelephonic electrocardiographic monitoring in detecting short-term arrhythmia recurrences after radiofrequency ablation in patients with atrial fibrillation." J Am Coll Cardiol 45(6): 873-876.

Shah, A. P., and Rubin, S. A. (2007) “Errors in the computerized electrocardiogram interpretation of cardiac rhythm”. Journal of Electrocardiology 40(5): 385-390.

Sivakumaran, S., Krahn, A. D., Klein, G. J.et al. (2003). "A prospective randomized comparison of loop recorders versus Holter monitors in patients with syncope or presyncope." American Journal of Medicine 115(1): 1-5.

Solomon, M. D., Yang, J., Sung, S. H. et al. (2016). "Incidence and timing of potentially high-risk arrhythmias detected through long term continuous ambulatory electrocardiographic monitoring." BMC Cardiovascular Disorders 16(1).

Steinhubl, S. R., Waalen, J., Edwards, A. M. et al. (2018). "Effect of a home-Based wearable continuous ECG monitoring patch on detection of undiagnosed atrial fibrillation the mSToPS randomized clinical trial." JAMA - Journal of the American Medical Association 320(2): 146-155.

Stewart, S., Murphy, N., Walker, A.et al. (2004). "Cost of an emerging epidemic: An economic analysis of atrial fibrillation in the UK." Heart 90(3): 286-292.

Sutton, B., Bermingham, S., Diamantopoulos, A. et al. (2019). "COST-EFFECTIVENESS OF IMPLANTABLE CARDIAC MONITOR FOR THE DETECTION OF ARRHYTHMIA IN UNEXPLAINED SYNCOPE PATIENTS IN THE UNITED STATES." Journal of the American College of Cardiology 73(9 Supplement 1): 303.

Tan, B. Y., Ho, K. L., Ching, C. K. et al. (2010). "Novel electrogram device with web-based service centre for ambulatory ECG monitoring." Singapore medical journal 51(7): 565-569.

Tarakji, K. G., Wazni, O. M., Callahan, T., et al. (2015). "Using a novel wireless system for monitoring patients after the atrial fibrillation ablation procedure: The iTransmit study." Heart Rhythm 12(3): 554-559.

Thijs, V., Guarnieri, C., Makino, K. et al. (2018). "Cost-effectiveness of long-term continuous monitoring with an insertable cardiac monitor to detect atrial fibrillation in patients with cryptogenic stroke: An Australian payer perspective." Journal of Neurology, Neurosurgery and Psychiatry 89(6): e6.

Tung, C. E., Su, D., Turakhia, M. P., et al. (2015). "Diagnostic yield of extended cardiac patch monitoring in patients with stroke or TIA." Frontiers in Neurology 6(JAN).

Turakhia, M. P., Hoang, D. D., Zimetbaum, P.., et al. (2013). "Diagnostic utility of a novel leadless arrhythmia monitoring device." American Journal of Cardiology 112(4): 520-524.

Turakhia, M. P., Ullal, A., Than, C. et al. (2014). "Feasibility of outpatient ambulatory ECG monitoring to screen for silent atrial fibrillation: Findings from the screening trial for undiagnosed atrial fibrillation (study-AF)." Heart Rhythm 11(5): S312-S313.

Wasserlauf, J., You, C., Patel, R., et al. (2019). "Smartwatch Performance for the Detection and Quantification of Atrial Fibrillation." Circulation. Arrhythmia and electrophysiology 12(6): e006834.

Weerathunga, J., Kausar, S., Blann, A., et al. (2014). "Finding atrial fibrillation in acute stroke patients: Just keep looking, just keep looking (with prolonged ECG monitoring)." Cerebrovascular Diseases 37: 224.

Wineinger, N. E., Barrett, P. M., Zhang, Y. et al. (2019). "Identification of paroxysmal atrial fibrillation subtypes in over 13,000 individuals." Heart Rhythm 16(1): 26-30.

Witte, K., Thijs, V., Tsintzos, S. et al. (2018). "Clinical and economic burden of oral anticoagulation (OAC) in embolic stroke of undetermined source (ESUS) without atrial fibrillation (AF): United Kingdom, Spain, Netherlands and

Witte, K., Thijs, V., Tsintzos, S. et al. (2018). "Economic evaluation of insertable cardiac monitors in detecting previously undiagnosed atrial fibrillation and subsequently moderating stoke risk in a high-risk population in the United Kingdom." European Heart Journal 39: 645.

Xu X. M., Vestesson E., Paley L. et al. (2018). “The economic burden of stroke care in England, Wales and Northern Ireland: Using a national stroke register to estimate and report patient-level health economic outcomes in stroke.” European Stroke Journal 3: 82-91.

Yiin, G. S., Howard, D. P.,Paul, N. L.et al. (2014). "Age-specific incidence, outcome, cost, and projected future burden of atrial fibrillation-related embolic vascular events: a population-based study." Circulation 130(15): 1236-1244.

Yinman, W., Xiaochen, T., Yunlong, X., et al. (2011). "The significance of following up after radiofrequency ablation for atrial fibrillation using transtelephonic ECG monitoring system." Heart 97: A184-A185.

Yong, J. H., Thavorn, K., Hoch, J. S.et al. (2016). "Potential Cost-Effectiveness of Ambulatory Cardiac Rhythm Monitoring After Cryptogenic Stroke." Stroke; a journal of cerebral circulation 47(9): 2380-2385.

Yong, J.H.E., Thavorn, K., Hoch, J.S., et al. (2015). "Clinical and cost-effectiveness of 30 day ECG monitoring for atrial fibrillation detection in patients with cryptogenic stroke or TIA." International Journal of Stroke 10: 1.

Zimetbaum, P. J. (1998). "Diagnostic Yield and Optimal Duration of Continuous-Loop Event. Monitoring for the Diagnosis of Palpitations."

12 Appendices

Appendix A: Study identification for clinical and economic evidence

Describe the process and methods used to identify and select the studies relevant to the technology. Include searches for published studies, abstracts and ongoing studies in separate tables as appropriate. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	08 to 29 August 2019
Date span of search:	From 1946 to present day
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
Embase (date span 1947 to 29 August 2019)	

1	('heart arrhythmia'/mj OR arrhythmia:ab,ti OR 'atrial fibrillation'/mj OR 'atrial fibrillation':ab,ti OR 'heart palpitation'/mj OR palpitation*:ab,ti) AND [humans]/lim AND [abstracts]/lim AND [embase]/lim	130255
2	('monitoring'/mj OR 'surveillance'/mj OR 'diagnosis'/mj OR surveillance:ab,ti OR diagnose$:ab,ti OR diagnosis:ab,ti OR detect*:ab,ti) AND [humans]/lim AND [abstracts]/lim AND [embase]/lim	3122905
3	((ecg NEAR/1 (monitor* OR ambulatory)) OR 'holter monitoring'/exp OR 'holter monitoring' OR (event NEAR/1 trigger*) OR 'event recorder' OR 'event near/1 recorder' OR 'external loop recorder'/exp OR 'external loop recorder' OR 'novacor r-test' OR (novacor NEAR/2 (r OR test)) OR 'king of hearts' OR 'cardiomemo' OR 'implantable cardiac monitor'/exp OR 'implantable cardiac monitor' OR (implantable NEAR/2 monitor) OR 'insertable cardiac monitor' OR (insertable NEAR/2 monitor) OR 'injectable loop recorder' OR (injectable NEAR/2 recorder) OR 'internal loop recorder' OR (internal NEAR/2 recorder) OR 'reveal linq' OR 'reveal xt' OR (reveal NEAR/2 (device OR monitor* OR cardiac* OR cardio*)) OR ((cardiac* OR cardio*) NEAR/2 (hour OR day)) OR 'ambulatory electrocardiographic monitor'/exp OR 'ambulatory electrocardiographic monitor') AND [humans]/lim AND [abstracts]/lim AND [embase]/lim	28244
4	1 AND 2 AND 3	3136
5	('economic evaluation'/exp OR 'economic evaluation' OR 'cost of illness'/exp OR 'cost of illness' OR cost*:ab,ti OR budget*:ab,ti OR financ*:ab,ti OR resource*:ab,ti OR 'resource use':ab,ti OR 'length of stay':ab,ti OR admission*:ab,ti OR economic*:ab,ti OR hospitali$ation:ab,ti OR absenteeism:ab,ti OR productivity:ab,ti OR ((value NEAR/1 (money OR monetary)):ab,ti)) AND [humans]/lim AND [abstracts]/lim AND [embase]/lim	1113617

6	('united kingdom':ab,ti OR uk:ab,ti OR 'england':ab,ti OR 'scotland':ab,ti OR 'northern ireland':ab,ti OR 'wales':ab,ti OR london:ab,ti OR 'united kingdom':ad OR uk:ad OR 'england':ad OR 'scotland':ad OR 'northern ireland':ad OR 'wales':ad OR london:ad) AND [humans]/lim AND [abstracts]/lim AND [embase]/lim	1350073
7	1 AND 5 AND 6	2257
8	('pharmacoeconomics'/exp OR 'pharmacoeconomics' OR (((economic* OR cost* OR budget*) NEAR/1 model):ab,ti) OR ((cost NEAR/1 (efficacy OR effective* OR benefit OR utilit*)):ab,ti) OR 'monte carlo':ab,ti OR markov:ab,ti OR 'discrete event simulation':ab,ti OR 'technology assessment':ab,ti) AND [humans]/lim AND [abstracts]/lim AND [embase]/lim	213987
9	1 AND 2 AND 8	648
10	4 OR 7 OR 9	5782

MEDLINE (Via EMBASE, date span 1946 to 29 August 2019)

1	('heart arrhythmia'/mj OR arrhythmia:ab,ti OR 'atrial fibrillation'/mj OR 'atrial fibrillation':ab,ti OR 'heart palpitation'/mj OR palpitation*:ab,ti) AND [humans]/lim AND [abstracts]/lim AND [medline]/lim	75229
2	('monitoring'/mj OR 'surveillance'/mj OR 'diagnosis'/mj OR surveillance:ab,ti OR diagnose$:ab,ti OR diagnosis:ab,ti OR detect*:ab,ti) AND [humans]/lim AND [abstracts]/lim AND [medline]/lim	2310153
3	((ecg NEAR/1 (monitor* OR ambulatory)) OR 'holter monitoring'/exp OR 'holter monitoring' OR (event NEAR/1 trigger*) OR 'event recorder' OR 'event near/1 recorder' OR 'external loop recorder'/exp OR 'external loop recorder' OR 'novacor r-test' OR (novacor NEAR/2 (r OR test)) OR 'king of hearts' OR 'cardiomemo' OR 'implantable cardiac monitor'/exp OR 'implantable cardiac monitor' OR (implantable NEAR/2 monitor) OR 'insertable cardiac monitor' OR (insertable NEAR/2 monitor) OR 'injectable loop recorder' OR (injectable NEAR/2 recorder) OR 'internal loop recorder' OR (internal NEAR/2 recorder) OR 'reveal linq' OR 'reveal xt' OR (reveal NEAR/2 (device OR monitor* OR cardiac* OR cardio*)) OR ((cardiac* OR cardio*) NEAR/2 (hour OR day)) OR 'ambulatory electrocardiographic monitor'/exp OR 'ambulatory electrocardiographic monitor') AND [humans]/lim AND [abstracts]/lim AND [medline]/lim	14114
4	1 AND 2 AND 3	1616
5	('economic evaluation'/exp OR 'economic evaluation' OR 'cost of illness'/exp OR 'cost of illness' OR cost*:ab,ti OR budget*:ab,ti OR financ*:ab,ti OR resource*:ab,ti OR 'resource use':ab,ti OR 'length of stay':ab,ti OR admission*:ab,ti OR economic*:ab,ti OR hospitali$ation:ab,ti OR absenteeism:ab,ti OR productivity:ab,ti OR ((value NEAR/1 (money OR monetary)):ab,ti)) AND [humans]/lim AND [abstracts]/lim AND [medline]/lim	841856

6	('united kingdom':ab,ti OR uk:ab,ti OR 'england':ab,ti OR 'scotland':ab,ti OR 'northern ireland':ab,ti OR 'wales':ab,ti OR london:ab,ti OR 'united kingdom':ad OR uk:ad OR 'england':ad OR 'scotland':ad OR 'northern ireland':ad OR 'wales':ad OR london:ad) AND [humans]/lim AND [abstracts]/lim AND [medline]/lim	1100499
7	1 AND 5 AND 6	1101
8	('pharmacoeconomics'/exp OR 'pharmacoeconomics' OR (((economic* OR cost* OR budget*) NEAR/1 model):ab,ti) OR ((cost NEAR/1 (efficacy OR effective* OR benefit OR utilit*)):ab,ti) OR 'monte carlo':ab,ti OR markov:ab,ti OR 'discrete event simulation':ab,ti OR 'technology assessment':ab,ti) AND [humans]/lim AND [abstracts]/lim AND [medline]/lim	168926
9	1 AND 2 AND 8	362
10	4 OR 7 OR 9	2960

Cochrane Library

1	MeSH descriptor: [Arrhythmias, Cardiac] this term only	1,880
2	MeSH descriptor: [Atrial Fibrillation] explode all trees	4,025
3	palpitation OR "atrial fibrillation" OR arrhythmia	19,642
4	1 OR 2 OR 3	20,768
5	MeSH descriptor: [Electrocardiography, Ambulatory] explode all trees	1,171
6	MeSH descriptor: [Population Surveillance] explode all trees	636
7	MeSH descriptor: [Monitoring, Ambulatory] explode all trees	3,065
8	"reveal linq" OR "reveal xt" OR "king of hearts" OR "novacor" OR "cardiomemo" OR "event recorder" OR "external loop recorder" OR "implantable cardiac monitor" OR "insertable cardiac monitor" OR "injectable loop recorder" OR "internal loop recorder"	356
9	5 OR 6 OR 7 OR 8	4022
10	4 AND 9	**691**

Heoro.com

Disease: Arrhythmias, Cardiac	**Study type:** Economic Models	**679**
Disease: Arrhythmias, Cardiac	**Study type:** Cost and Resource Use	**160**

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

Additional sources searched on 07 and 08 August 2019:

Site	URL	Search strategy	Hits
European Heart Rhythm Association	https://www.escardio.org/Sub-specialty-communities/European-Heart-Rhythm-Association-(EHRA)	("atrial fibrillation" OR "arrhythmia") AND ("holter" OR "Zio XT" OR "Ambulatory" OR "Monitor"), limited to last 2 years	474
Heart Rhythm Congress	http://www.heartrhythmcongress.org/	All abstracts for 2017 and 2018 downloaded and screened	171
British Cardiovascular Society	https://www.bcs.com/pages/default.asp	All abstracts for 2019 conference downloaded and screened. Abstracts for 2017 and 2018 not accessible.	136
American College of Cardiology	https://www.acc.org/#sort=%40fcommonsortdate90022%20descending	("atrial fibrillation" OR "arrhythmia") AND ("holter" OR "Zio XT" OR "Ambulatory" OR "Monitor"), limited to last 3 years	733
NICE	https://www.nice.org.uk/	Search for arrhythmia, atrial fibrillation last 3 years	112
International Stroke Conference	https://professional.heart.org/professional/EducationMeetings/MeetingsLiveCME/InternationalStrokeConference/UCM_316939_Archive-International-Stroke-Conference.jsp	Included in the AHA website content	-
European Stroke Conference	http://www.eurostroke.net/Berlin/index.html	No abstracts accessible	0
European Stroke Organisation	https://journals.sagepub.com/toc/esoa/3/1_suppl	Abstract books for 2017, 2018 and 2019 downloaded and searched by hand.	
American Heart Association	https://aha.scientificposters.com/epsSearchAHA.cfm	Posters for 2019, 2018 and 2017 were searched using the eposters portal for each year in turn (“Diagnosis for stroke etiology” section only)	174

		Stroke journal abstracts were searched by hand for years 2017, 2018 and 2019: "Diagnosis of stroke aetiology" section only	
Clinicaltrials.gov	www.clinicaltrials.gov	Disease: Cardiac arrhythmia OR atrial fibrillation Intervention: device OR monitor OR recorder OR ECG Interventional studies Age: Adult, Older adult	733

Inclusion and exclusion criteria:

Inclusion and exclusion criteria:

Criterion	Inclusion criterion	Exclusion criterion
Disease	Any cardiac arrhythmias in people with cardiovascular disease or no overt disease but reason to think they may have an arrhythmia (including atrial fibrillation).	Arrhythmias associated with congenital or structural heart disorders. .
Population	Adults requiring ambulatory ECG monitoring for suspected arrhythmia; Patients after cryptogenic or other stroke or transient ischaemic attacks; Patients with palpitations, syncope or presyncope; Patients after ablation for known arrhythmias.	Healthy volunteers; Mass screening of general population not known to have CVD; Children or adolescents; Animals; Electronic arrhythmia simulators.
Interventions	Ambulatory ECG monitoring devices; Implantable ECG monitoring devices including defibrillators where diagnosis of arrhythmia is being assessed. • Event recorders • External loop recorders • Novacor r-test • "King of hearts" device • Cardiomemo device • Zio XT device • Insertable cardiac monitor • Injectable loop recorder • Internal loop recorder • "Reveal" device	Short-term ECG recorders; Echocardiographic or other radiological or physiological assessments of heart rhythm or blood pressure; Anticoagulants or other drug treatments for arrhythmias; Ablative techniques; Implantable defibrillators where correction of arrhythmias is being assessed; Resynchronisation interventions.

	The intervention device to be used continuously or at least once daily for more than 24 hours.	Comparisons between different types or monitoring times with Holter monitors Holter monitors vs usual care In-hospital (non-ambulatory) monitoring Comparing diagnostic algorithms for outputs from the same device
Comparators (efficacy studies only)	Other ECG monitoring devices or processes used at the same time in the same patient, or in a randomised control group; Usual care; No intervention. Comparator devices may be used for any duration of time.	Efficacy studies with historical controls only Other devices used in a non-randomised control group
Outcomes	Detection rates of arrhythmias; Diagnostic yield (detection rate); Rule-out rate; Patient satisfaction; Prevention of thromboembolic events including stroke; Adverse events associated with the device; Mortality; Costs or resource use associated with detecting and managing the arrhythmias or their complications (stroke, other thromboembolism, syncope, blackouts, collapse, sudden death); Economic evaluations of relevant devices.	Efficacy, safety, costs associated with irrelevant interventions.
Outcomes	Detection rates of arrhythmias; Diagnostic yield (detection rate); Rule-out rate; Patient satisfaction; Prevention of thromboembolic events including stroke; Adverse events associated with the device; Mortality; Costs or resource use associated with detecting and managing the arrhythmias	Efficacy, safety, costs associated with irrelevant interventions.

	or their complications (stroke, other thromboembolism, syncope, blackouts, collapse, sudden death); Economic evaluations of relevant devices.	
Study methodology	RCTs and controlled trials (for efficacy and safety); Observational studies, single-arm clinical studies, database/registry studies (for costs); Economic evaluations; Systematic reviews of relevant studies; Conference abstracts with sparse data will be indexed as supportive evidence but not included in the main analysis.	Conference abstracts that have a corresponding full text publication; Study protocols with no results reported; Secondary publications with no new data. Duplicate publications.
Study size	10 or more participants.	Case studies with <10 participants
Language	Any	
Publication dates	Any	

Data abstraction strategy:

Data on all outcomes relevant to the decision problem were abstracted into an Excel spreadsheet. Data was extracted by one researcher and checked for accuracy and comprehensiveness by a second researcher.
Sensitivity, specificity, positive and negative predictive values for arrhythmia detection were reported or calculated where possible from 2x2 tables reported in the papers.

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Aste M. Remote monitoring of wearable or implantable long-term ECG monitors: a cost - effectiveness analysis. Presented at the ESC Congress, 2016.	Economic evaluation, Remote monitoring of wearable or implanted ECG recorders	No relevant data reported	
Bravo, Y., et al. (2012). "Cost analysis of an implantable loop recorder, reveal© XT, for the diagnosis of atrial fibrillation in patients who underwent cryptogenic stroke from the perspective of a tertiary Spanish Hospital." Value in Health 15(7): A351.	Economic evaluation, Reveal XT	No relevant data reported	
Burri, H., et al. (2013). "Cost-consequence analysis of daily continuous remote monitoring of implantable cardiac defibrillator and resynchronization devices in the UK." Europace 15(11): 1601-1608.	Economic evaluation, Biotronic home monitoring system	Irrelevant Intervention	
Chovančík, J., Bulková, V., Fiala, M., et al. (2012). "A comparison of two methods of long-term external ECG telemonitoring in patients after ablation for atrial fibrillation." Vnitrni Lekarstvi 58(9): 633-639.		Irretrievable	
Da Costa A., et al. (2013) "Clinical impact of the implantable loop recorder in patients with isolated syncope, bundle branch block and negative workup: a randomized multicentre prospective study". Archives of Cardiovascular Diseases 106, 146-154 10.1016/j.acvd.2012.12.002.	RCT, Reveal ILR implantable loop recorder	Irrelevant comparator	
De Voogt W., et al. (2006) "Verification of pacemaker automatic mode switching for the detection of atrial fibrillation and atrial tachycardia with Holter recording".	St Jude Medical Pacemaker	Irrelevant Intervention	

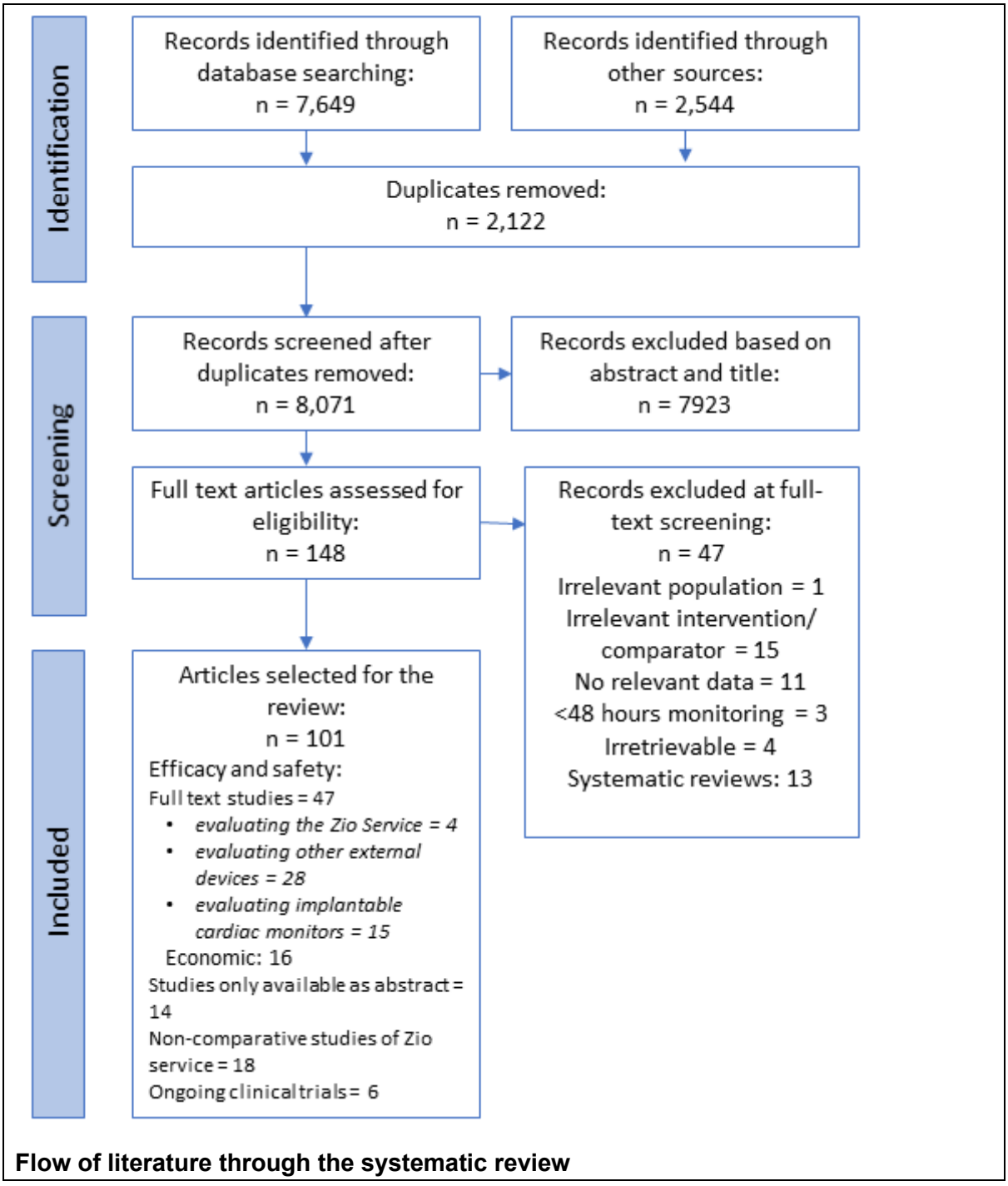
Europace 8, 950-961 10.1093/europace/eul112.			
Dekker, L.R.C., et al. (2016). "Continuous Cardiac Monitoring around Atrial Fibrillation Ablation: Insights on Clinical Classifications and End Points." PACE - Pacing and Clinical Electrophysiology 39(8): 805-813.	LINQ ICM	Irrelevant comparator	
Deshmukh, A., et al. (2016). "Performance of Atrial Fibrillation Detection in a New Single-Chamber ICD." PACE - Pacing and Clinical Electrophysiology 39(10): 1031-1037.	implantable cardioverter defibrillators	Irrelevant Intervention	
Diederichsen, S., et al. (2017) "Complications after implantation of a new-generation insertable cardiac monitor: results from the LOOP study". International journal of cardiology. (no pagination), 2017 Date of Publication: February 12, 10.1016/j.ijcard.2017.03.144.	LINQ ICM	No relevant data reported	
Fensli, R., et al. (2010). "Towards improved healthcare performance: Examining technological possibilities and patient satisfaction with wireless body area networks." Journal of Medical Systems 34(4): 766-775.	wireless ECG based Body Area Networks (BAN)	Irrelevant comparator	
Francisco-Pascual, J., Santos-Ortega, A., Roca-Luque, I., et al. (2019). "Diagnostic Yield and Economic Assessment of a Diagnostic Protocol With Systematic Use of an External Loop Recorder for Patients With Palpitations." Revista Espanola de Cardiologia 72(6): 473-478.	Zenicor EKG thumb intermittent ECG recorder	Irretrievable	
Hobbs, F.D., et al. (2005). "A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study." Health Technol Assess 9(40): iii-iv, ix-x, 1-74.	RCT, targeted screening with ECG	Irrelevant population	
Hoefman, E., et al. (2005). "Diagnostic yield of patient-activated loop recorders for detecting heart rhythm abnormalities in general practice: A randomised clinical trial." Family Practice 22(5): 478-484.	Card Guard loop event recorder	Irrelevant comparator	

Kaleschke, G., et al. (2009). "Prospective, multicentre validation of a simple, patient-operated electrocardiographic system for the detection of arrhythmias and electrocardiographic changes." Europace 11(10): 1362-1368.	OMRON HeartScan	Irrelevant comparator	
Kamel, H., et al. (2010). "Cost-effectiveness of outpatient cardiac monitoring to detect atrial fibrillation after ischemic stroke." Stroke 41(7): 1514-1520.	Economic evaluation, Outpatient monitoring for 7 days	Irrelevant Intervention	
Kamel, H., et al. (2013) "Pilot randomized trial of outpatient cardiac monitoring after cryptogenic stroke". Stroke; a journal of cerebral circulation 44, 528-530 10.1161/STROKEAHA.112.679100.	RCT, Cardionet mobile telemetry monitor	Irrelevant comparator	
Kapa, S., et al. (2013) "Assessing arrhythmia burden after catheter ablation of atrial fibrillation using an implantable loop recorder: the ABACUS study". Journal of Cardiovascular Electrophysiology 24, 875-881 10.1111/jce.12141.	ILR	Irrelevant comparator	
Kollias, A., et al. (2018). "Atrial fibrillation detection during 24-hour ambulatory blood pressure monitoring: Comparison with 24-hour electrocardiography." Hypertension 72(1): 110-115.	Microlife Watch novel 24-hour ambulatory blood pressure (ABP) monitor	Irrelevant Intervention	
Lévy, S., Boccara, G., Dotto, P., et al. (2004). "A multicentre trial of the diagnostic value and cost of electrocardiography in symptoms suggesting arrhythmia with a new event recorder with transtelephonic transmission." Archives des Maladies du Coeur et des Vaisseaux 97(2): 108-112.	AliveCor smartphone ECG recorder	Irretrievable	
Luengo-Fernandez, R., et al. (2013). "Population-based study of acute- and long-term care costs after stroke in patients with AF." Int J Stroke 8(5): 308-314.	Economic evaluation, no intervention	No relevant data reported	
Maervoet, J., et al. (2017). "Clinical and economic value of device-based detection of atrial fibrillation in patients with cryptogenic stroke." Value in Health 20(9): A584.	Biomonitor ICM	No relevant data reported	

Müller, A., et al. (2009). "Reliability of an external loop recorder for automatic recognition and transtelephonic ECG transmission of atrial fibrillation." Journal of Telemedicine and Telecare 15(8): 391-396.	telemonitoring with external loop recorder	<48-hours monitoring	
Nault, I., et al. (2019). "Validation of a novel single lead ambulatory ECG monitor – Cardiostat™ – Compared to a standard ECG Holter monitoring." Journal of Electrocardiology 53: 57-63.	Cardiostat ambulatory ECG	<48-hours monitoring	
Orozco, J.J., Shrivastav, M. and Vilendrer, S. (2015). "Cost-effectiveness analysis of external looping recording compared to holter monitoring for syncope in Colombia." Value in Health 18(3): A44-A45.	Economic evaluation, external loop recorder	No relevant data reported	
Plummer, C., et al. (2001) "The use of permanent pacemakers in the detection of cardiac arrhythmias". Europace 3, 229-232 10.1053/eupc.2001.0178.	pacemaker telemetry	Irrelevant Intervention	
Podd, S., et al. (2016) "Are implantable cardiac monitors the 'gold standard' for atrial fibrillation detection? A prospective randomized trial comparing atrial fibrillation monitoring using implantable cardiac monitors and DDDRP permanent pacemakers in post atrial fibrillation ablation patients". Europace 18, 1000-1005 10.1093/europace/euv367.	RCT, Reveal XT	Irrelevant comparator	
Scalvini, S., Zanelli, E., Martinelli, G., et al. (2004). "Cardiac event recorder yields more diagnoses than 24-hour Holter monitoring in patients with palpitations." Italian heart journal. Supplement : official journal of the Italian Federation of Cardiology 5(3): 186-191.	Cardiac event recorder	Secondary publication with no additional data	
Sutton, B., et al. (2019). "COST-EFFECTIVENESS OF IMPLANTABLE CARDIAC MONITOR FOR THE DETECTION OF ARRHYTHMIA IN UNEXPLAINED SYNCOPE PATIENTS IN THE UNITED STATES." Journal of the American College of Cardiology 73(9 Supplement 1): 303.	Economic evaluation, ICM	No relevant data reported	

Thijs, V., et al. (2018). "Cost-effectiveness of long-term continuous monitoring with an insertable cardiac monitor to detect atrial fibrillation in patients with cryptogenic stroke: An Australian payer perspective." Journal of Neurology, Neurosurgery and Psychiatry 89(6): e6.	Economic evaluation, ICM	No relevant data reported	
Torfs, T., Smeets, C.J.P., Geng, D., et al. (2014). "Clinical validation of a low-power and wearable ECG patch for long term full-disclosure monitoring." Journal of Electrocardiology 47(6): 881-889.		<48-hour monitoring	
Tsintzos S., Witte K., Lip G. et al. 2018. ECONOMIC EVALUATION OF INSERTABLE CARDIAC MONITORS IN THE DIAGNOSIS OF OCCULT AF FOLLOWING CRYPTOGENIC STROKE: RESULTS FROM THE DUTCH HEALTHCARE SETTING USING INPUTS FROM CRYSTAL-AF. Presented at the Europe Stroke Organisation Conference 2018.	Economic evaluation, ICM	No relevant data reported	
Visser, J. and Schuilenburg, R.M. (1984). "Trans-telephonic ECG monitoring in the diagnosis of cardiac arrhythmias: A comparison with Holter electrocardiography." Nederlands Tijdschrift voor Geneeskunde 128(9): 397-401.	Trans-telephonic ECG	Irretrievable	
Wachter, R., et al. (2017). "Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AFRANDOMISED): an open-label randomised controlled trial." The Lancet Neurology 16(4): 282-290.	RCT, 10-day Holter	Irrelevant comparator	
Witte, K.K., et al. (2018). "Economic evaluation of insertable cardiac monitors in detecting previously undiagnosed atrial fibrillation and subsequently moderating stoke risk in a high-risk population in the United Kingdom." European Heart Journal 39: 645.	Economic evaluation, Reveal ICM	No relevant data reported	

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).



Flow of literature through the systematic review

Appendix B: Search strategy for adverse events

Date search conducted:	Enter text.
Date span of search:	Enter text.
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
The search for adverse events was conducted as part of the full systematic review reported in Appendix A.	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
Additional sources searched for data on the safety of the Zio XT Service were as follows: https://www.nice.org.uk/advice/mib101/chapter/Regulatory-information https://www.irhythmtech.com/products-services/zio-xt https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/detail.cfm?mdrfoi__id=4990677 https://www.irhythmtech.com/zio_xt_precautions https://www.fiercebiotech.com/medical-devices/irhythm-wearable-cardiac-monitor-gets-ce-mark-cardiologic-partners-to-sell-it-u-k http://www.thegoodhealthsuite.co.uk/GP/management-staffing/i-t/153-zio-service-cardiac-monitoring-device-launches-in-uk http://www.heartrhythmalliance.org/files/files/A-A%20US/A-A%20USA%20Which%20ECG%20is%20Right%20for%20You%20Booklet.pdf https://www.cardiovascularbusiness.com/topics/technology-management/zio-irhythm-gains-further-recognition-key-diagnostic-cardiac https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm http://www.mhra.gov.uk/public-assessment-reports/ https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/ema_group_types/ema_medicine http://mri.cts-mrp.eu/Human/ https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/ http://www.crd.york.ac.uk/crdweb/Showrecord.asp?LinkFrom=OAI&ID=32016000097 https://www.ncbi.nlm.nih.gov/pubmed/31045463	

Inclusion and exclusion criteria:
Any report of safety concerns or adverse events were included.
Data abstraction strategy:
Relevant studies were to be incorporated into the data extraction tables used for the systematic review.

Adverse events evidence

List any relevant studies below. If appropriate, further details on relevant evidence can be added to the adverse events section.

Study	Design and intervention(s)	Details of adverse events	Company comments
Studies evaluating the Zio XT Service			
Kaura 2019	Randomised controlled trial of Zio XT Service for 14 days versus 24-hour Holter monitor.	Of participants randomised to the Zio XT patch the mortality rate at 90 days was 2.3%, with 24-hour Holter monitor the rate was 0%. No other adverse events were reported.	Difference in mortality was not statistically significant
Studies evaluating other external devices			
Gladstone 2014	Randomised controlled trial of ER910AF 30-day event trigger recorder worn for 30 days or until a diagnosis was made, with telephone transmission of recorded ECG data versus one additional round of 24-hour Holter monitoring.	Of 287 participants in the 30-day event recorder arm 1 (<1%) reported an adverse skin reaction.	
Halcox 2017	Randomised controlled trial of AliveCor Kardia smartphone ECG monitor used twice weekly plus when symptomatic for 12 months versus standard care.	Of 500 participants randomised to the AliveCor diagnostic arm there were 3 (<1%) deaths and 2 (<1%) clinically significant bleeds. In comparison in	

		the 501 patients monitored by SoC there were 5 (1%) deaths and 1 (<1%) clinically significant bleed.	
Hindricks 2010	Prospective single-arm study evaluating the Reveal XT ***implant***able cardiac monitor and 46-hours Holter monitor after 4 to 6 weeks, simultaneously in each participant.	Of the 247 participants 12 (5%) withdrew from the study due to long-term burden.	
Higgins 2013	Randomised controlled trial of the Novacor R-test Evolution loop recorder, used at 24, 72 and 168 hours after randomisation, plus 12-lead ECGs at 24 and 72 hours, plus standard care, versus standard practice (12-lead ECGs, 24-hour Holter monitoring and echocardiography).	No serious adverse events were reported in either group	
Kamalvand 1997	Crossover randomised controlled trial of the HeartWatch event monitor that records for 30 seconds when triggered, ECG data transmitted wirelessly to telephone receiving centre, versus the Cardiomemo ECG recorder, which records for 32 seconds when triggered and ECG data transmitted via telephone.	A comment in the discussion notes that patients were reluctant to wear the HeartWatch.	
Kinlay 1996	Crossover randomised controlled trial of Aerotel event monitor used for 3 months or until 2 recordings were obtained during symptoms, versus 48 hr Holter monitoring	None associated with the Aerotel monitor, 2 participants (4%) withdrew prior to Aerotel monitoring due to complaints regarding the	

	with symptoms recorded in a diary during the recording period.	Holter being too uncomfortable.	
Reed 2019	Randomised controlled trial of the AliveCor smartphone case and app, patients asked to email recordings taken during episodes of palpitations or presyncope, plus symptom diary, versus standard care.	Of 125 people randomised to the AliveCor monitor there was 1 (<1%) death during the trial period and 11 (8%) serious adverse events. Of the 117 people randomised to SoC there were 2 (1%) serious adverse events.	
Rothman 2007	Randomised controlled trial of the CardioNet Mobile cardiac outpatient telemetry system (MCOT) for up to 30 days, versus an external loop monitor.	Of all 266 people randomised there were 7 (3%) complaints of the device being too cumbersome, 7 (3%) complaints of an allergic reaction or skin irritation, and 6 (2%) complaints of devices interfering with work or travel.	
Studies evaluating implantable cardiac monitors versus Holter monitors or standard of care			
Brachmann 2016 (also Sanna 2014)	Randomised controlled trial of the REVEAL XT Insertable cardiac monitor versus standard care.	Of 208 patients with an ICM 5 (2%) patients had the device removed due to infection at the insertion site or pocket erosion. 3 (1%) patients had an additional infection associated with the ICM, 3 (1%) patients reported pain associated with the ICM, and 4 (2%) patients reported irritation/ inflammation associated with ICM.	
Giada 2007	Multicentre crossover RCT of the Reveal Plus implantable loop recorder for at least 12 months, versus 24-h Holter monitor plus 4-week	No adverse events were reported by the participants.	

	ambulatory ECG event recorder if Holter was negative.		
Hanke 2009	Prospective single-arm study evaluating the Reveal XT implantable monitoring device implanted subcutaneously promptly after chest surgery and monitored for 3 years, and 24-hour Holter monitor, simultaneously in each participant.	Of 45 participants there were a total of 4 (9%) deaths and no incidence of stroke.	
Hindricks 2010	Prospective single-arm study evaluating Reveal XT implanted subcutaneously under local anaesthesia, and 46-hr Holter plus expert evaluation of surface ECG recordings from the Holter to give true positive rate, simultaneously in each participant.	Of the 247 participants 12 (5%) withdrew from the study due to long-term burden.	Text
Lauschke 2016	Prospective single-arm study evaluating the BioMonitor Implantable cardiac monitor implanted subcutaneously or epifascially and monitored for 12 months, and 48-hour Holter monitor, simultaneously in each participant.	Of 152 participants there were 2 (1%) incidence of SADE pocket infections, 3 (2%) reported pain at implantation site and 1 (<1%) haemorrhage at implantation site.	
Nolker 2016	Prospective single-arm study evaluating the CONFIRM Implantable cardiac monitor (ICM) fitted with an electronic symptom marker, and Holter monitoring for 4 days, fitted with an electronic symptom marker and used as the	No adverse events were reported.	

	gold standard for accuracy analysis, simultaneously in each participant.		
Piorkowski 2019	Prospective single-arm study evaluating an Implantable Cardiac Monitor (ICM) - BioMonitor 2, standard settings, 3-month follow-up, and continuous 48-h Holter-ECG obtained between the 1-week and 3-month follow-ups, simultaneously in each participant.	Of 92 people enrolled 1 (1%) had a failed insertion. There were 2 (2%) serious adverse events.	

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

See Appendix A.

Appendix C: Checklist of confidential information

Please see section 1 of the user guide for information about identifying confidential information and instructions on how to complete this section. As stated there it is the company's responsibility to highlight any commercial- or academic-in-confidence data clearly and correctly:

- information that is commercial in confidence should be underlined and highlighted in blue
- information that is academic in confidence should be underlined and highlighted in yellow.

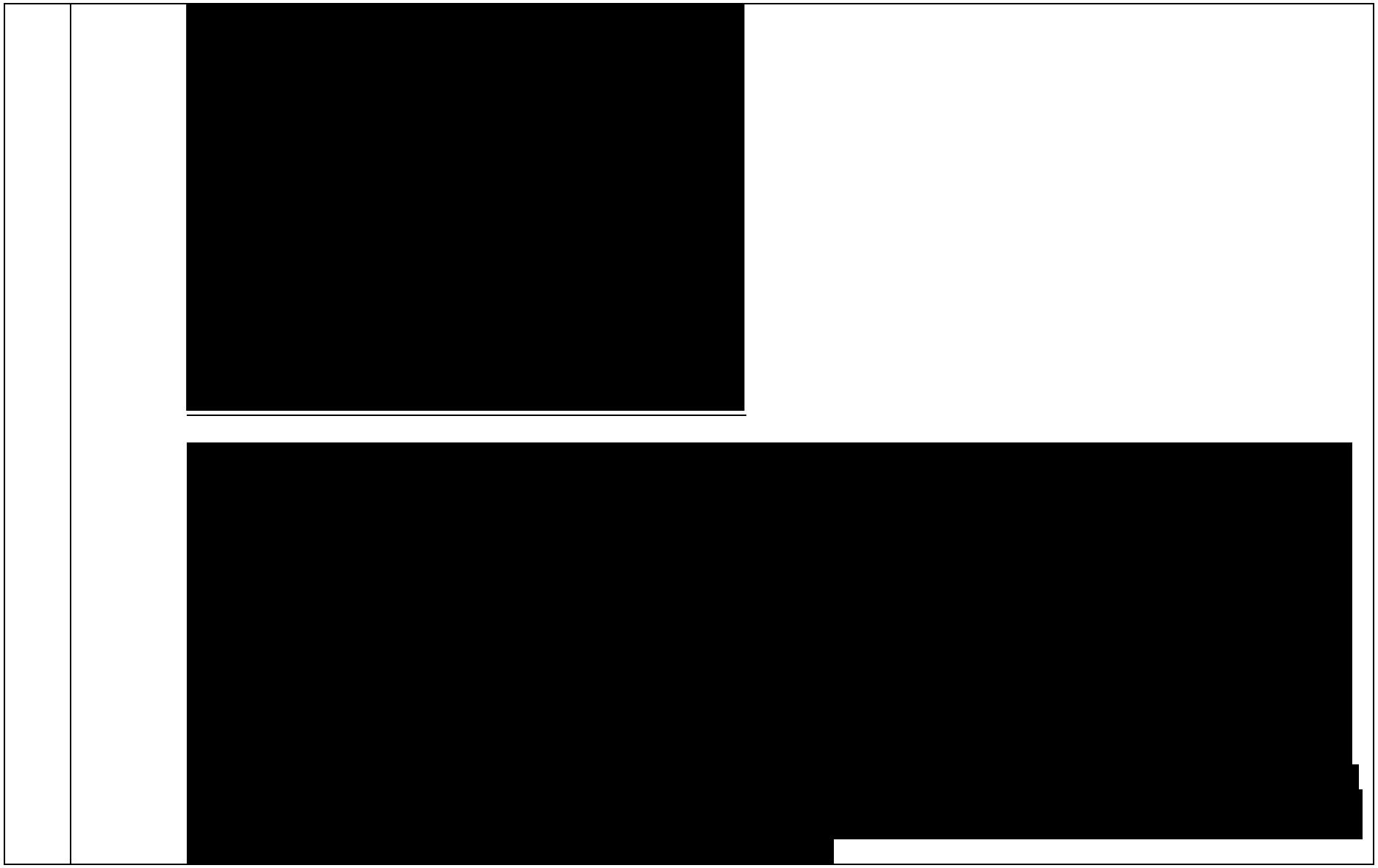
Does your submission of evidence contain any confidential information? (please check appropriate box):

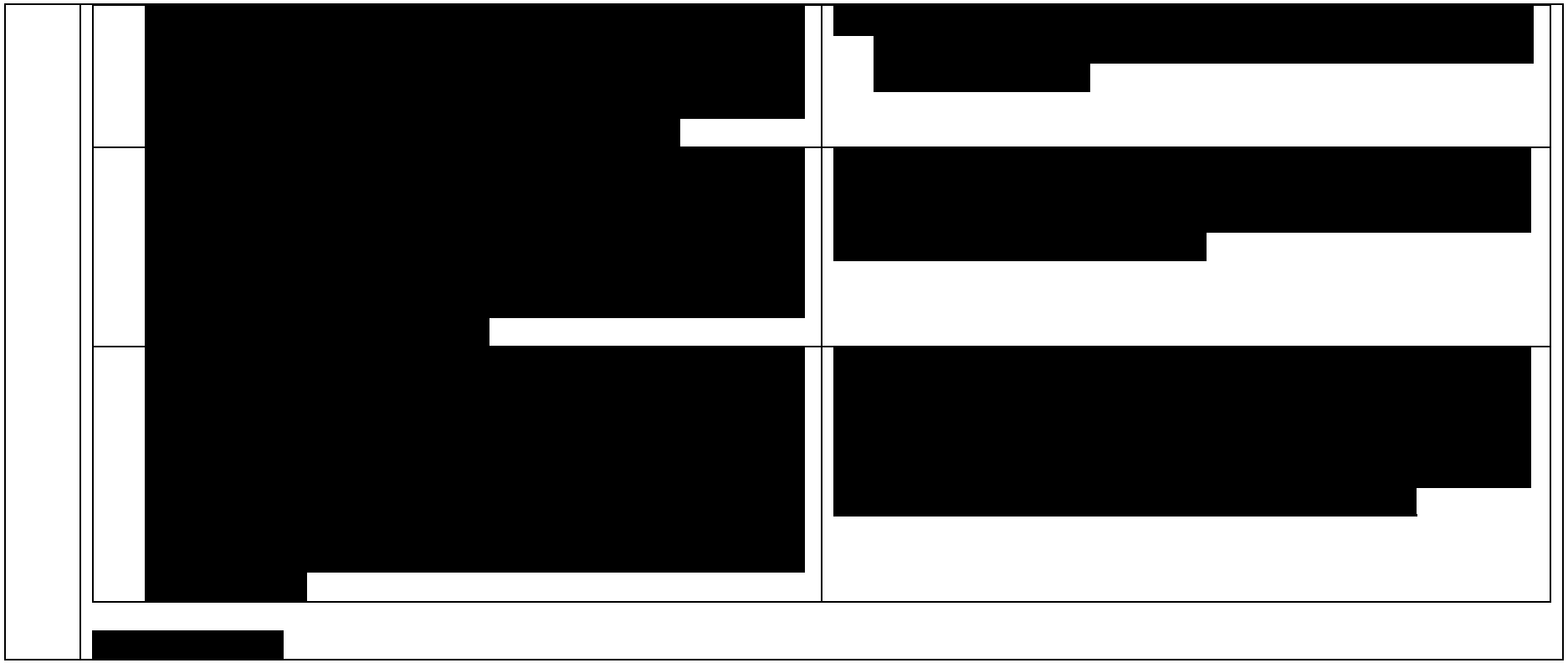
No	☐	If no, please proceed to declaration (below)
Yes	☒	If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document and match the information in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

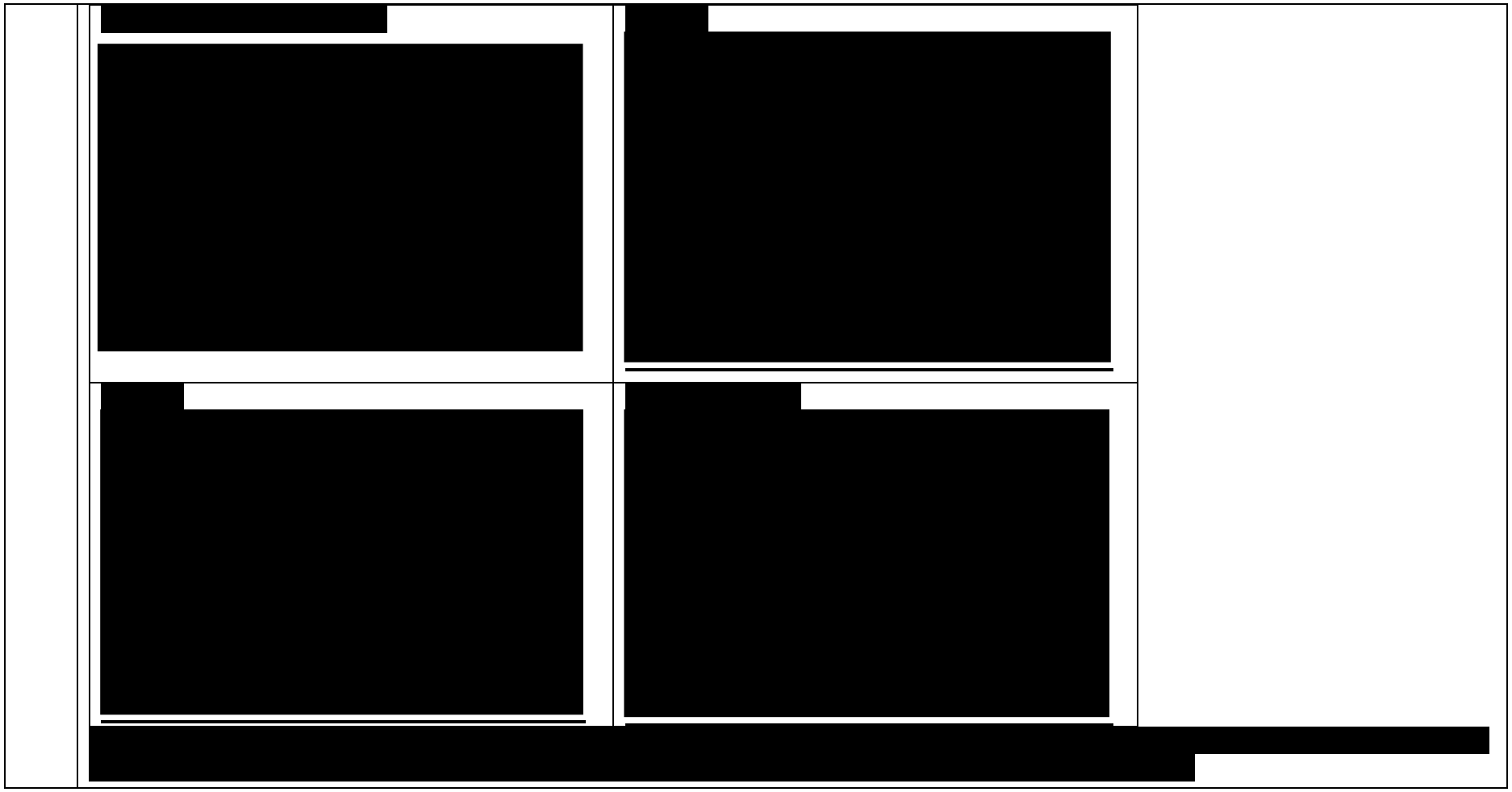
Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
233	☒ Commercial in confidence ☐ Academic in confidence	Zio XT Biosensor Design contains details on the components and design of the monitor, some of which are patented and others are trade secrets. These design elements provide Zio with competitive advantages in ECG signal recording.	Indefinite
Details	[redacted].		
236 & attached	☒ Commercial in confidence ☐ Academic in confidence	Zio XT Service Evaluation Tools contain data on the clinical results of every patient monitored by the Zio Service globally as well as within the UK and at individual NHS accounts. While completely anonymised and shared with explicit permission from our customers, iRhythm only distributes this data on a selective basis for business reasons.	Indefinite
Details	[redacted]		

237-241	☐ Commercial in confidence ☒ Academic in confidence	Zio XT Service in Primary Care outlines the methodology, results and economic modelling of a pilot project which our academic partners intend to publish at a later date.	Until published, date unknown

Details	[redacted]

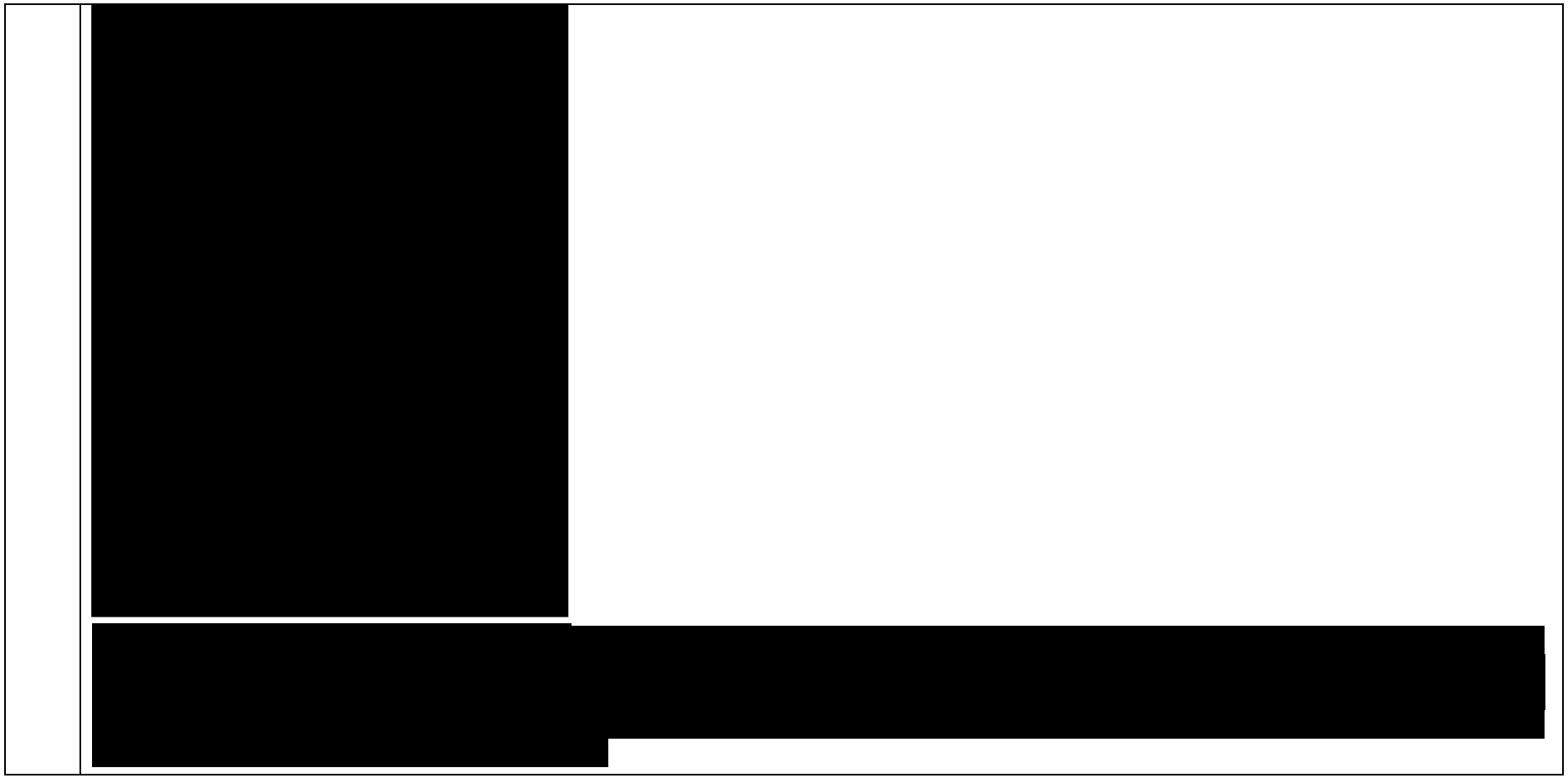






234-236	☒ Commercial in confidence ☐ Academic in confidence	Clinical Operations and UK Scalability includes sensitive and proprietary information about how our clinical technicians are selected and trained, how they work, and how iRhythm intends to roll out our Service across the UK.	Indefinite

Details	[redacted]

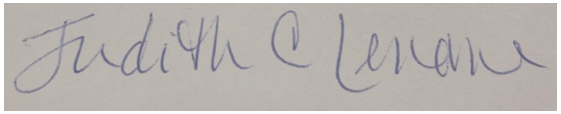


Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	25 September 2019
Print:	Judith C Lenane	**Role / organisation:**	Chief Clinical Officer & Executive Vice President, iRhythm Technologies
Contact email:	[redacted]		

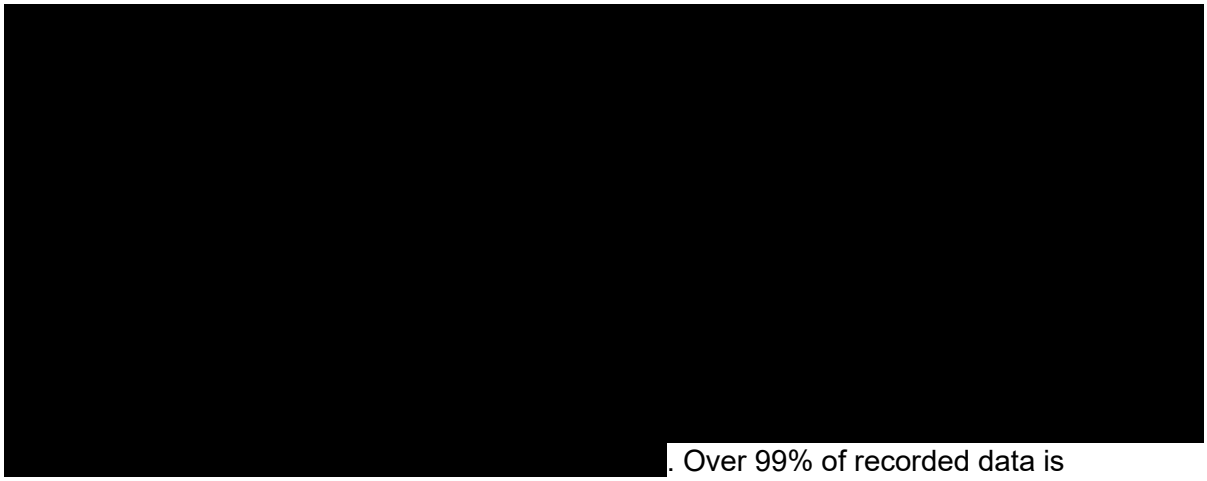
Appendix D: iRhythm Supporting Materials

Contents

1. Zio XT Service Components

1.1. Zio XT Biosensor Design

The Zio XT biosensor is a single-use, wire-free, wearable patch-based biosensor that records a patient's heartbeats and ECG data. The Zio XT biosensor records continuously for an extended monitoring duration of 14 days, unlike Holter monitors which record continuously but for limited durations of 1-2 days or Event monitors, which only record snapshots of data for up to 30 days. The Zio XT's continuous extended recording with high signal fidelity enables greater diagnostic yield and greater likelihood of capturing symptom-rhythm correlation than can be achieved in either Holter or Event monitors. The extended monitoring duration is enabled by two key considerations: 1) ability to adhere and capture good signal for the entire duration and 2) patient centric design that maximizes compliance.



. Over 99% of recorded data is considered analysable in the generation of the technical report (median, global Zio XT Service Evaluation Tool, Appendix D).

High patient compliance is ensured through a design which requires no maintenance by the patient through the entire monitoring period. The electronics and embedded software are considered carefully to allow for a full 14-day recording on a single set of batteries. Similarly, the adhesive and electrode gels are designed to adhere and sense for the entire period. Combined with an unobtrusive, waterproof and comfortable design, these features enable the patient to go about all of the activities of normal life without changing the patch, batteries or electrode elements. In other monitoring modalities, required interventions by the patient translate to opportunities for loss of ECG data or curtailment of monitoring. For example, in traditional Holter and Event monitors, the patient must disconnect the monitor from its electrodes whenever they bathe or shower and electrodes must be changed every few days to maintain their efficacy. Many such monitors also require frequent battery changes or charges. Furthermore, the cumbersome and uncomfortable nature of traditional monitors results in frequent abbreviation of wear periods relative to what is prescribed. For those patients prescribed a Zio XT biosensor for 14 days, the wear time is 13.6 days (median, global Zio XT Service Evaluation Tool, Appendix D).

1.2. Clinical Operations and UK Scalability

iRhythm is committed to maintaining the highest level of quality across the business, including within the clinical operations function. The highly skilled cardiac technicians on the iRhythm team play an important role in the development of the Technical Report; through a demanding hiring process, ongoing training and development and stringent quality controls, iRhythm consistently delivers results that our customers trust.

Quality Policy
iRhythm Technologies, Inc. is a responsive provider of innovative healthcare information services for continuous ambulatory cardiac monitoring that meet or exceed the quality expectations of our customers and industry.

Our Commitments

- Continuously improving our quality management system
- Comply with all applicable regulatory requirements, and
- Deliver excellence to customers through our products, processes, service, and data.

[redacted]

AF Burden and Duration
The Zio XT Patient report includes True Atrial Fibrillation (AF) Burden and Duration, the validated amount of time an episode of AF lasts, on both a daily basis and throughout the full wear time. The availability of AF Burden and Duration data makes the Zio XT Service uniquely capable of providing a comprehensive approach toward AF diagnosis and management.

True AF duration can only be reported if segments of a single episode interrupted by artifact in the recording are "bridged" and timed as a single episode, as performed by the Zio XT Service. The reporting output combines the precision of beat-to-beat analysis with an intelligent bridging approach to provide accurate AF Duration reporting over a patient's entire monitoring prescription period.

Understanding True AF Duration can support the clinical care pathway by helping the clinician determine the risk of stroke, the efficacy and use of anti-coagulants, the efficacy of cardioversion, and rate control or rhythm control.

[redacted]

[redacted]

[redacted]

[redacted]

1.3. Zio XT Service Technical Report Sample – *attached separately*

1.4. Zio XT Service Urgent Notification Form – *attached separately*

1.5. Patient Instructions & Button Press Log – *attached separately*

2. Zio XT Service Evaluation Tools

[redacted]

3. Pilots & Partnerships

3.1. Zio XT Service in Primary Care – A Pilot Project

Project lead: Dr Ravi Assomull, Consultant Cardiologist, London North West University Healthcare NHS Trust

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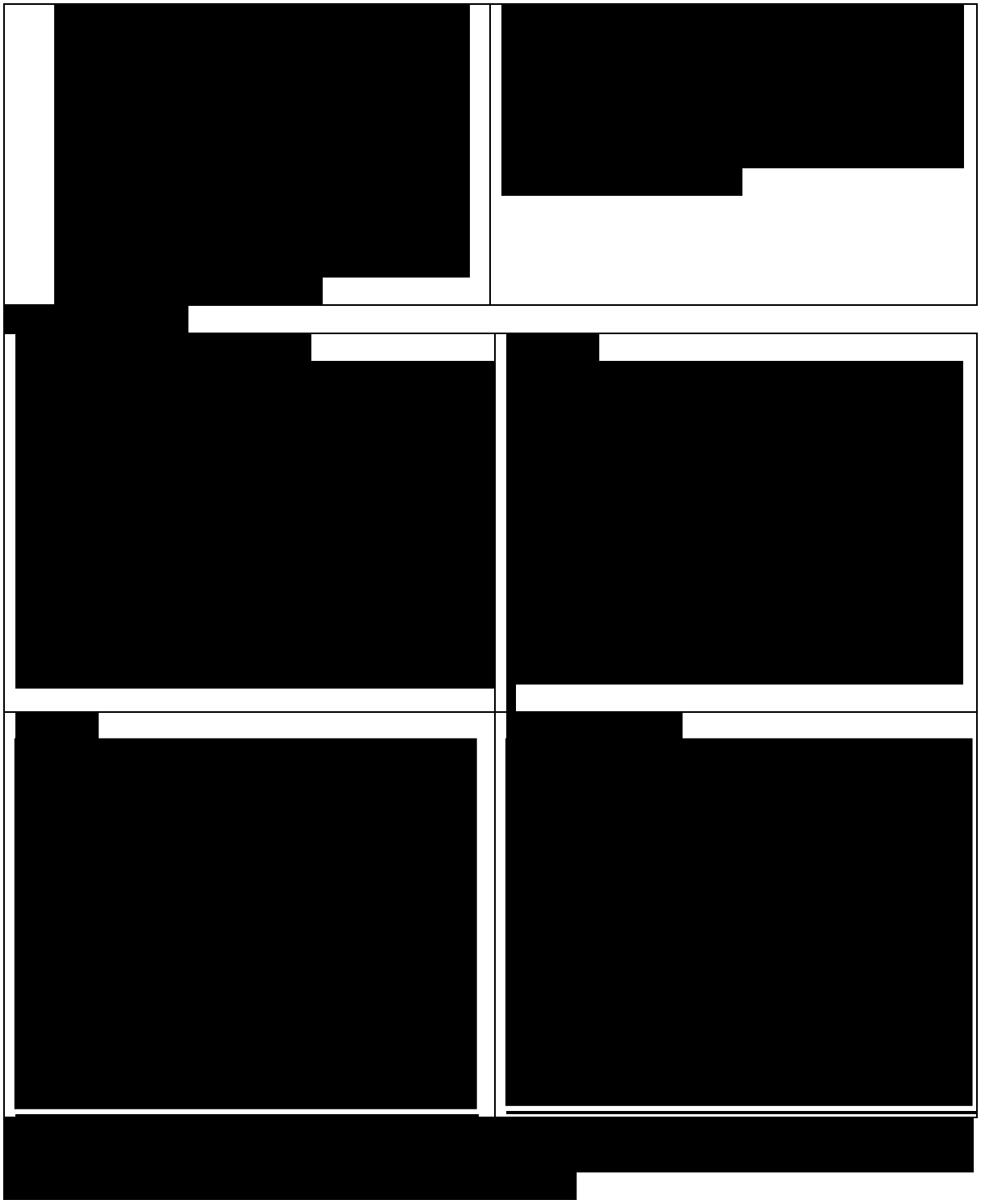


Abstract verified by:
Project lead: Dr Ravi Assomull, Consultant Cardiologist, London North West University Healthcare NHS Trust **********

Economic modelling: Imperial Health Care Partners

3.2. Verily Partnership

iRhythm recently announced a partnership with Verily, an Alphabet company. This partnership is evidence of the strength of our AI based arrhythmia diagnosis and the company's continued commitment to AF detection.

iRhythm and Verily have a shared mission to create a new standard of care for cardiac patients - making heart health data more actionable so patients can live longer, healthier lives. Verily is one of the world's most reputable technology companies, with proven machine learning and data management capabilities, as well as global reach. Verily has honed patient-centric disease management platforms and hardware capabilities. The company has focused on collecting, organizing and activating disparate health information across key healthcare arenas, including health systems, clinical research and medical devices.

Together, iRhythm and Verily will develop tech-enabled solutions in the cardiovascular space with the goal of improving screening of patients who are at risk for AFib, as well as diagnosing and managing the disorder.

iRhythm Announces Collaboration with Verily to Develop Health Management Solutions for Atrial Fibrillation Patients

SAN FRANCISCO, September 4, 2019 — iRhythm Technologies, Inc. (NASDAQ: IRTC) today announced a collaboration with Verily, an Alphabet company, focused on the development of solutions aimed at improving the screening, diagnosis and management of patients with atrial fibrillation (AFib). This collaboration brings together iRhythm's expertise in AI based arrhythmia diagnosis and Verily's advanced health data analytics technologies to address the millions of patients living with undiagnosed AFib.

iRhythm estimates that more than 10 million Americans are at high risk for a common heart rhythm disorder known as atrial fibrillation. AFib is associated with a five-fold increase in the risk of stroke as compared to those without AFib, with these strokes tending to be more severe and associated with higher mortality rates.[1] For approximately 20 percent of individuals who experience a stroke due to AFib, the occurrence of AFib was not diagnosed until the time of their stroke or shortly afterward.[2] Further, an estimated one-third of those who have AFib are not aware they have it.[3] Asymptomatic or "silent" AFib is associated with certain risk factors like high blood pressure, diabetes and sleep apnea – which increase an individual's likelihood for developing the disorder.

The iRhythm and Verily collaboration aims to address this significant, underserved population at risk for asymptomatic or silent AFib. Under the terms of the agreement, iRhythm and Verily plan to collaborate on solutions capable of providing earlier warnings, enabling the identification and management of patients that could otherwise go undiagnosed until they have a cardiac event, such as a stroke.

Clinical research is demonstrating a major unmet need in the market for this early warning approach. At the annual meeting of the American College of Cardiology in May, the first phase of the mSToPS study, published in JAMA, showed that patients who were diagnosed with AFib in iRhythm's Zio XT Service-monitored group had a significantly lower rate of hospitalizations and emergency room visits than the non-monitored control group.

"We are excited to partner with iRhythm, a pioneer in ambulatory cardiac monitoring, to find innovative ways to deliver more efficient care to patients with atrial fibrillation," said Dr. Jessica Mega, chief medical and scientific officer of Verily. "With the high prevalence of cardiovascular-related health issues, we have an opportunity to not only improve how we

diagnose, manage and monitor conditions like atrial fibrillation, but also develop patient-centric solutions that could ultimately prevent serious cardiac events."

"iRhythm and Verily have a shared mission to create a better standard of care for cardiac patients - making heart health data more actionable so patients can live longer, healthier lives," said Kevin King, president and CEO of iRhythm. "We are pleased to partner with one of the world's most reputable healthcare technology companies to better serve the millions of people living with AF today. Verily's patient-centric approach to disease management and advanced hardware capabilities will prove critical in providing patients and providers with the tools needed to increase the efficiency of heart healthcare."

Terms of the Agreement

Under the terms of the agreement, iRhythm will make an upfront payment to Verily of $5 million and potential milestone payments of up to $12.75 million upon the achievement of various development and regulatory milestones.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934 and the Private Securities Litigation Reform Act of 1995. These statements include statements regarding our expectations for our collaboration with Verily. Such statements are based on current assumptions that involve risks and uncertainties that could cause actual outcomes and results to differ materially. These risks and uncertainties, many of which are beyond our control, include risks described in the section entitled "Risk Factors" and elsewhere in the Company's public filings with the Securities and Exchange Commission. These forward-looking statements speak only as of the date hereof and should not be unduly relied upon. iRhythm disclaims any obligation to update these forward-looking statements.

4. Zio XT Service Regulatory Documents

4.1. CE certificate – *attached separately*

4.2. Clinical Reference Manual – *attached separately*

4.3. Declaration of Conformity – *attached separately*

5. Manuscript PDFs and EndNote library

Available here:
https://www.dropbox.com/sh/h3hyo1mzl5wfo9n/AABFWBiDAEnYRuqql2Q8pu1ja?dl=0

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Digital Health Technology (DHT) Pilot

Zio XT Service for detecting cardiac arrhythmias

Company evidence submission

Part 2: Economic evidence

Company name	iRhythm
Submission date	04 December 2019
Contains confidential information	Yes

November 2019 v1.0

Contents

1 Published and unpublished economic evidence

1.1 Identification and selection of economic studies

Complete the following information about the number of economic studies identified.

Number of economic studies identified as being relevant to the decision problem (as per Part 1 submission, Section 4).		16 + 4 efficacy studies
Of the relevant economic studies identified:	Number of published economic studies.	17
	Number of economic abstracts.	3
	Number of ongoing economic studies.	0

1.2 List of relevant economic studies

In table 1, provide brief details of any published or unpublished economic studies or abstracts identified as being relevant to the decision problem.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data provided.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix D.

The search identified 16 studies that reported only the cost or economic evaluations related to the management of cardiac arrhythmias or their complications, in particular atrial fibrillation and stroke, and/or the use of the Zio XT Service or other devices to detect arrhythmias. Four additional studies that also reported costs or resource use data were also included; these have been summarised in more detail in the Clinical efficacy submission.

Of these 20 studies;

- Ten were economic evaluations of devices to detect and monitor arrhythmias:
  - Three were developed for the UK (Diamantopoulos 2016; Kaura 2019; Rinciog 2019);
  - Three were based in Canada (Anon 2017; Rockx 2005; Yong 2016);
  - One each were based in Australia (Kinlay 1996), the Netherlands (Quiroz 2017), Sweden (Levin 2014), and the USA (Zimetbaum 1998);
  - One (Kinlay 1996) was also a clinical trial that was reported in the clinical efficacy submission.
- Ten were publications that reported costs or resource use in the UK:

    - Three assessed costs associated with the management of atrial fibrillation (Boggon 2012; Halcox 2017; Stewart 2004)
    - Two assessed costs of managing stroke due to atrial fibrillation (Ali 2015; Yiin 2014)
    - Five reported costs associated with devices to detect arrhythmias (Chandratheva 2017; Ghosh 2018; NICE 2017; NICE 2018; Reed 2019);
    - Four of these costs publications were also clinical trials that were reported in the clinical efficacy submission (Halcox 2017; Kaura 2019; Kinlay 1996; Reed 2019).

Devices with relevant economic data included:

- The Zio XT Service:
    - one budget impact model in the UK (Kaura 2019);
    - two cost analyses compared with Holter monitors or a 3-day e-patch in the UK (Chandratheva 2017; Ghosh 2018);
    - one NICE Medtech innovation briefing (NICE 2017);
- Reveal LINQ:
    - one NICE Medtech innovation briefing (NICE 2018);
- King of Hearts continuous loop recorder:
    - one cost-effectiveness evaluation in the USA (Zimetbaum 1998);
- AliveCor smartphone-based event recorder:
    - One clinical trial compared with usual care in the UK (Reed 2019);
- Handheld ECG monitor:
    - One cost-utility analysis compared with 24-hour Holter monitors in Sweden (Levin 2014);
- External loop recorders:
    - One cost-effectiveness analysis (Rockx 2005) and one cost-utility analysis (Yong 2016), both compared with Holter monitors in Canada;
    - One budget impact model compared with continuous ECG monitors in Canada (Anon 2017);
- Implantable cardiac devices:
    - Three cost-utility analyses compared with usual care in the UK (Diamantopoulos 2016; Rinciog 2019) and the Netherlands (Quiroz 2017);
- Trans-telephonic event monitors:
    - One cost-effectiveness analysis based on a clinical trial compared with Holter monitors in Australia (Kinlay 1996)

The relevant papers and their economic outcomes are outlined below in table 1. A more detailed table including all unit costs reported by the publications and other details is available in table 3 in appendix A.

Table 1 Summary of all relevant economic studies (published and unpublished)

Author, year, location	Patient population and setting	Intervention and comparator	Results	Sensitivity analysis and conclusion
Ali 2015 Costs standardised to GB pounds in 2011-2012, UK (P)	213 patients admitted to hospital with acute stroke	None	**Mean cost of ischaemic stroke:** With AF = £9,083 (SD = £7,381) With no AF = £5,729 (SD = £6,071), p<0.001 **Mean cost of haemorrhagic stroke:** With AF = £7,058 (SD = £6,494) With no AF = £8,790 (SD = £7,054), p=0.764 Presence of AF independently increased acute care costs of ischaemic stroke by £2,173 (95%CI £91 to 4,255), p<0.041	Overall mean cost of ischaemic stroke per patient was almost double in those with AF compared with those without AF. The presence of AF did not make a significant difference to the costs of haemorrhagic stroke. The costs in patients with AF were significantly higher than for patients in sinus rhythm for hospital admissions and bed-days, pathology tests, feeds, fluids, medications, ward consumables, therapist rehabilitation and specialist referrals and procedures. Sensitivity analyses were not conducted in this cost analysis study.
Boggon 2012 Data collected for 2001 to 2006, UK (P)	15,373 adults with AF and controls matched for age, gender, general practice and time	None	**Resource use for all patients with AF, n=15,373** **Number of drug substances prescribed in preceding 6 months** [n patients (%)]; 0 drug substances: 390 (2.5) 1–5 drug substances: 4117 (26.8) 6–10 drug substances: 6516 (42.4) 11–15 drug substances: 3116 (20.3)	Patients with AF had significantly more drug prescriptions than controls in the past 6 months and had significantly higher numbers of contacts, referrals, tests and hospitalisations per year than controls. Levels of resource use also increased with higher levels of NICE stroke risk strata. All-cause mortality rate was 107.6/1,000 person-years with AF compared with 35.0/1,000 person-years in the control

Author, year, location	Patient population and setting	Intervention and comparator	Results	Sensitivity analysis and conclusion
			16+ drug substances: 1234 (8.0) **Mean (standard deviation) number of contacts, referrals, tests and hospitalisations per year**: Surgery: 9.9 (10.2) Practice clinic: 1.9 (4.9) House visits: 1.1 (3.7) Administration/letters: 31.3 (19.9) Phone contacts: 2.6 (5.5) Specialist referrals: 0.8 (1.5) Laboratory tests (excluding INR): 36.9 (48.1) Hospitalisations: 1.0 (3.9) Hospitalisations - Due to circulatory system: 0.2 (1.0) Days in hospital: 6.3 (26.0) Days in hospital - Due to circulatory system: 1.7 (12.2)	group, a relative risk of 3.11 (95%CI 2.92 to 3.31). Sensitivity analyses were not conducted in this cost analysis study.
Stewart 2004 Data from 1995 extrapolated to estimate costs for 2000, UK (P)	All registered patients with AF in the UK	None	**Estimated cost (millions) for care of all 601,149 people with AF in 2000** **Cost of prescriptions for atrial fibrillation** in the UK by drug class and % prescribed Cardiac glycosides (60% prescribed) = £1.99m Aspirin (50% prescribed) = £1.76m	Total NHS costs in 1995 were £243.9 million, estimated to reach £459.0 million in 2000, or £1307.4 million if nursing home care and admissions, where AF was a secondary diagnosis, are included. 50% of costs were hospital admissions, 20% drugs, 13% GP visits, 12% for referrals and 6% for post-discharge visits.

Author, year, location	Patient population and setting	Intervention and comparator	Results	Sensitivity analysis and conclusion
			Warfarin (30% prescribed) = £5.4m Antiarrhythmics (25% prescribed) = £15.75m Total = £24.9m **Hospital care** Primary admissions = £271.6m Post-discharge OPD visits = £31.7m Hospitalisations with secondary diagnosis of AF = £726.6m Community care: GP consultations = £49.8m GP referred OPD visits = £36.4m Drug prescriptions and anticoagulant clinics = £69.5m Long-term nursing home care = £111.7m **Total direct cost of AF** (excluding secondary admissions and nursing home costs) = £459.0 million **Indirect costs in 1995** Cost of long-term long term associated residential care for men = £18.9 million	Sensitivity analyses were not conducted in this cost analysis study.

Author, year, location	Patient population and setting	Intervention and comparator	Results	Sensitivity analysis and conclusion
			Cost of long-term long term associated residential care for women = £27.5 million	
Yiin 2014 Costs adjusted to 2008-2009 GB pounds, extrapolated to estimate costs in 2030 and 2050, UK (P)	454 patients with AF-related events in Oxfordshire from 2002 to 2012	None	**Mean AF-related ischaemic stroke costs (presumably per patient)** Total care costs for ischemic stroke = £22,423 (SD = 41,802) Hospital care costs = £12,417 Long-term residential care costs = £10,007 Total costs in patient <80 years = £19,603 (35,676) Total costs in patient aged 80+ years = £24,345 (45,561) **Mean systemic embolism costs (presumably per patient):** Hospital/total costs: all patients = £13,720 (SD = 21,593) **Estimated total costs for UK in 2050:** AF-related ischaemic stroke = £1.7 billion AF-related systemic embolism = £221 million	Mean total care costs related to IS were higher in patients with AF who were over 80 years of age. Mean total costs of systemic emboli were slightly higher in the older age group but not significantly. By 2050 it is estimated that AF-related IS stroke will cost £1.7 billion and systemic emboli will cost £221 million. Sensitivity analyses were not conducted in this cost analysis study.
Ghosh 2018 Cost year unclear, UK	Patients with minor stroke or TIA at a UK hospital	Zio patch and 24-hour Holter used	Cost of the investigation plus follow-up: Holter = £367	The Zio XT Service was more costly than 24-hour Holter monitoring however it provided a more comprehensive follow up

Author, year, location	Patient population and setting	Intervention and comparator	Results	Sensitivity analysis and conclusion
(only available as conference abstract) (P)		concurrently in each patient	Zio XT = £440	and allowed timely investigation and management. There was a delay of a median 59 days before patients could access the Holter monitor (range 14 to 102 days) that did not occur with the Zio XT Service, which was fitted in the clinic. Nearly half of patients attending the follow-up clinic did not have Holter results due to administrative issues. Sensitivity analyses were not conducted in this study.
Chandratheva 2017 Cost in 2015 GB pounds, UK (P)	80 patients with TIA at a UK hospital	Zio patch, 3-day e-patch, 72-hour Holter, Apoplex monitoring	The Zio patch provided the cheapest form of monitoring, followed by 72-hour Holter. Time from clinic to device placement was lowest with the Zio patch and highest with 72-hour Holter. Time to reporting after device placement was not significantly different between Zio and Holter but was lower in the E-patch and Apoplex.	The Zio XT Service was cheaper than the 72-hour Holter monitor and incurred lowest delays before monitoring could start. Sensitivity analyses were not conducted in this study.
NICE MIB141 2018, Cost year unclear, UK (P)	Patients after cryptogenic stroke whose AF remains undiagnosed by	Reveal LINQ	**Overall costs** Reveal LINQ = £19,631 Usual care = £17,045	The costs of the LINQ are higher than for standard ECG monitoring or stress testing, but these costs may be offset if its use leads to a greater detection of AF and initiation of preventive therapy.

Author, year, location	Patient population and setting	Intervention and comparator	Results	Sensitivity analysis and conclusion
	standard stroke care		Economic evaluation based on cost-utility model from Diamantopoulos 2016: ICER = £17,175/QALY if patients newly-diagnosed with AF are treated with non-warfarin anticoagulants ICER = £13,296/QALY if patients newly-diagnosed with AF are treated with warfarin	Costs are also lower if the device can be fitted outside a catheter laboratory.
NICE MIB101 2017 Cost year unclear, UK (P)	People suspected of having cardiac arrhythmias	Zio XT Service	No overall costs or economic evaluation reported.	Purchase price is lower for the Zio XT Service than a Holter monitor but per patient costs are higher with the Zio XT Service. These costs may be offset if the Zio patch leads to more accurate diagnosis and better treatment of arrhythmias. (Please note: the price of Zio has since been reduced from £800 as reported in this publication).
Diamantopoulos 2016 Cost year unclear, GB pounds, UK (P)	Hypothetical cohort of patients with recent cryptogenic stroke or transient ischaemic attack	Reveal XT implantable cardiac monitor (ICM) versus usual care	A reduction of 40 strokes per 1,000 patients is seen with ICM versus usual care (SoC). **Total costs by CHADS2 score** CHADS2 score 2: SoC= £17,204 ICM=£20,023 CHADS2 score 3: SoC= £17,431 ICM=£19,940 CHADS2 score 4, 5 or 6: SoC= £13,444 ICM=£15,911	Sensitivity analysis: Replacing NOAC with warfarin showed an ICER of £13,296 per QALY. Deterministic analysis cost over lifetime: SoC = £17,045 ICM = £19,631 Difference = £2,587 Probabilistic analysis cost over lifetime: Soc = £17,951 (13874 to 23348) ICM = £20,525 (16640 to £25744) Difference = £2,574 (1529 to 3878)

Author, year, location	Patient population and setting	Intervention and comparator	Results	Sensitivity analysis and conclusion
			Deterministic analysis comparing ICM to SoC over patient's lifetime showed an incremental cost of £2,587. **Cost savings** were generated from reduction in stroke-related and post-stroke related costs ICM = £3,958 SoC = £4,387 The Reveal XT ICM strategy had a 63.4% probability of being cost effective at the £20,000 threshold and 81% at the £30,000 threshold. **Base-case analysis**: Reveal XT ICM was cost effective, ICER = £17,175/QALY gained. The ICER varied by CHADS 2 score, increasing to £23,355 for a score of 2, and decreasing to £13,621 for scores 4 to 6.	ICM monitoring was associated with fewer recurrent strokes than with SoC and increased QALYs (7.37 vs 7.22). Reduction in stroke related costs were reduced in the ICM model, but overall costs remained higher vs SoC (£19,631 vs £17,045).
Rinciog 2019, UK (P)	Patients from the REVEAL AF trial	ICM vs SoC	**QALYs gained** ICM = 6.5 SoC = 6.3 4.8 fewer strokes per 100 population.	**Probabilistic analysis:** ICM were cost effective in 77.4% of the simulations. **Base case deterministic analysis:** ICM provided a benefit over SoC of 0.1994

Author, year, location	Patient population and setting	Intervention and comparator	Results	Sensitivity analysis and conclusion
			Total Costs (Base case analysis) SOC = £11,936 ICM = £13,360 **Base case results** ICER = £7,140/QALY gained for ICM vs SoC, The number of ICMs needed to prevent one stroke was 21, and to prevent a major bleed is 37.	QALYs at an incremental cost of £1424 across a patient's lifetime. ICM monitoring had higher initial costs compared with SoC; it was also associated with slightly higher health state and bleed-related costs. By reducing the rates of IS events, use of ICMs generated cost-savings both from IS event costs as well as post-stroke health state costs.
Rockx 2005, Canada (P)	100 patients referred for ambulatory monitoring with syncope or presyncope.	1-month External loop recorder (ELR) vs 48-hour Holter monitor	**Cost of previous health care resource use** Holter = $467.91 ±426.09, ELR = $476.78 ±366.92 **Total costs per 100 patients** Holter = $17,518 ELR = $53,356 Cost per diagnosis with Holter: $745 Cost per diagnosis with ELR: $843 ICER for ELR vs Holter = $901.74 per extra successful diagnosis.	If patients received Holter monitoring followed by loop recorder, the overall cost ($481+/-267) was lower than if they received the devices the other way round ($551 +/-$83), but this strategy had a lower diagnostic yield (49% vs 63%), and an overall higher cost per diagnosis ($982 vs $871, p=0.08). Analyses showed that 90% of cost-effectiveness ratios were less than $1250.

Author, year, location	Patient population and setting	Intervention and comparator	Results	Sensitivity analysis and conclusion
Anon 2017, Canada (P)	Patients with symptoms of, or suspected arrythmia	Long term continuous event monitor (LCEM) and external loop recorder (ELR)	**Results for base case analysis (total costs and net budget impact)** Current state (constant proportions of ELR (56%) and LCEM (44%): 2016= $29.1M 2017= $31.42M 2018= $33.74M 2019= $36.05M 2020= $38.37M Increase in LCEM tests along the 2011-2014 trend: 2016= $29.23M 2017= $31.61 M 2018= $33.99M 2019= $36.36M 2020= $38.74M Net budget impact: 2016= $0.13M 2017= $0.19M 2018= $0.25M 2019= $0.31M 2020= $0.37M	Estimated total cost of funding long term ambulatory ECG testing ranged from $29.1 million in 2016 to $38.4 million in 2020. Net budget impact of increasing LCEM and decreasing ELR ranges from $0.13million in 2016 to $0.37 million in 2020. Analysis suggested that if trends of use continued, publicly funding both devices will result in additional costs ranging between $130,000 to $370,000 per year over the next 5 years. Sensitivity analyses show that the greatest cost savings occur in a scenario where only tests via ELR are publicly funded.
Levin 2014, Sweden (P)	249 patients with a recent ischaemic stroke or TIA	Zenicor-EKG handheld ECG vs SoC	**Total QALYs gained** No screening = 6435 Holter = 6442 Handheld ECG = 6458 **Total Costs:**	Continuous 24hr Holter monitoring was inferior to intermittent handheld ECG monitoring in terms of cost effectiveness due to its lower sensitivity and higher costs.

Author, year, location	Patient population and setting	Intervention and comparator	Results	Sensitivity analysis and conclusion
			No screening = € 4,020,000 Holter = € 4,255,000 Handheld ECG = € 3,976,000 (dominant) The implementation of the handheld ECG screening programme on 1000 patients resulted in 11 avoided strokes and the gain of 29 life-years or 23 QALYs and cost savings of €55,400 over a 20-year period	Costs over time were higher for the first year in the screening group due to upfront cost. After 7 years, the screening programme with handheld ECG would become cost saving. Cost savings were based on 85% of patients receiving anticoagulant treatment, if this is reduced to 50% screening was no longer cost saving but remained cost effective. Screening cost was estimated to be €108, but if raised to €220 the screening was no longer cost saving and the cost per QALY was €2600. When the time horizon is reduced to 5 years the cost per QALY became €6400.
Quiroz 2017 Cost year unclear, €, Netherlands (P)	Patients who have had a cryptogenic stroke	ICM vs SoC	ICER = € 24,715 per QALY gained for base case. CHADS2 score 4 to 6: ICER = € 22,011 CHADS2 score 2: ICER = € 29,795	Probabilistic sensitivity analysis suggested that ICM had a probability of 91% of being cost-effective at a threshold of € 80,000 per QALY gained.
Yong 2016, Canada (P)	Hypothetical population based on the EMBRACE trial cohort	30-day ECG monitoring with external loop recorder vs 24-hour Holter	**QALYs gained** 30d ELR = 0.013 14-day Holter = 0.008 7-day Holter = 0.004 **Additional life-years saved** 30d ELR = 0.017 14-day Holter = 0.011 7-day Holter = 0.005	Using 30d event loop recorder would prevent 16 more IS and 2 more intracranial haemorrhages during a lifetime for every 1000 patients screened. 30d event loop recorder monitoring was highly cost effective, and it was predicted to gain 17 life years and 13 QALYs at an additional cost of $28,000 in a cohort of 1000 patients.

Author, year, location	Patient population and setting	Intervention and comparator	Results	Sensitivity analysis and conclusion
			Total cost ($): 30d event loop recorder = $59,712 24-hour Holter = $59,798 Incremental= -$86 **Total cost ($) (discounted 5%):** 30d event loop recorder = $43,689 24-hour Holter = $43,661 Incremental= $28 **Total incremental cost (USD$)** 30d event loop recorder= $28 14-day Holter = -$101 7-day Holter = -$74 **Incremental cost per QALY gained vs 24-hour Holter** 30d event loop recorder = $2166 14-day Holter = Dominant 7-day Holter = Dominant	Cost effectiveness was affected by stroke recurrence risk, and the effectiveness and presence of anticoagulants.
Zimetbaum 1998, USA (P)	105 outpatients referred for continuous loop recorder placement	King of hearts loop recorder	**New diagnoses per patient made with loop recorder over time** Week 1 = 1.04 Week 2 = 0.15 Week 3+ = 0.01	The cost-effectiveness ratio increases over time from $98 per new diagnosis after 1 week to $5832 per new diagnosis after week 3.

Author, year, location	Patient population and setting	Intervention and comparator	Results	Sensitivity analysis and conclusion
			Monitoring costs of the loop recorder: Week 1 = $102 Week 2 = $96 Week 3 = $81 **Incremental cost effectiveness per new diagnosis with the loop recorder** Any diagnosis: Week 1 = $98 (81 to 121) Week 2 = $576 (382 to 1066) Week 3 = $5832 (1975 to no limit) Serious diagnosis: Week 1 = $340 (261 to 536) Week 2 = $1224 (686 to 3200) Week 3 = no limit.	
Kaura 2019, UK (P)	Adults with ischaemic stroke or TIA and no prior AF diagnosis in a clinical trial	Zio patch vs Holter monitor	1-year time horizon medial costs and social care cost: Comparison of Zio vs Current strategy: Incremental cost: -£154,716 Incremental strokes prevented: 10.8 Overall incremental cost using Zio: -£210,865 Incremental cost per stroke prevented: Dominant	The economic model (budget impact) demonstrated that implementation of the Zio XT Service would result in 10.8 strokes being avoided per year at King's College Hospital NHS Foundation Trust, compared to current Holter monitoring, and a yearly saving of £113,630, increasing to £162,491 over 5 years.

Author, year, location	Patient population and setting	Intervention and comparator	Results	Sensitivity analysis and conclusion
			5-year time horizon medial costs and social care cost: Comparison of Zio vs Current strategy: Incremental cost: -£410,449 Incremental strokes prevented: 10.8 Overall incremental cost using Zio: -£466,598 Incremental cost per stroke prevented: Dominant	
Kinlay 1996, Australia (P)	Patients with previously uninvestigated palpitations who were referred for Holter monitoring	Aerotel event monitor vs 48hr Holter monitoring	ICER per additional ECG recorded during symptoms = -$213 with event recorder vs 24-hr Holter ICER per additional clinically significant arrhythmia detected = -$373 for event recorder vs 24-hr Holter	A cost-effectiveness analysis from a societal perspective concluded that the ICER was -$213 per additional ECG recorded during symptoms and -$373 per additional clinically significant arrhythmia detected with the event recorder compared with the 24-hr Holter monitor. The event recorder dominated in all the scenario analyses conducted.
Halcox 2017, UK (P)	Individuals >65 years of age with a CHADS-VASc score >2 not in receipt of OAC without a known diagnosis of AF taking part in the clinical trial	Single lead ECG with AliveCor device vs routine clinical care	Overall, 19 cases of AF were detected; thus, the intervention cost was $10 780 (£8255) per AF diagnosis. The overall cost of the intervention was $204830 (£156 837). This consisted of device costs of $28698 (£21 974), patient training costs of $3750 (£2871), and defective	Patients in the AliveCor group were significantly more likely to receive a diagnosis than those receiving usual care (p=0.004). No sensitivity analysis reported.

Author, year, location	Patient population and setting	Intervention and comparator	Results	Sensitivity analysis and conclusion
			technology costs of $2194 (£1680)	
Reed 2019, UK (P)	Patients aged 16+ presenting with palpitations or presyncope	AliveCor smartphone case and app vs Standard care	Median overall healthcare costs were higher with AliveCor (£108 vs £0 with standard care) but the cost per symptomatic rhythm diagnosis was lower with AliveCor (£474 versus £1395 with standard care). There were more emergency department presentations after the index event for palpitations or presyncope in the AliveCor group (9.7% compared with 2.6% of the control group, p=0.031) but no significant differences in hospital admissions, outpatient visits, GP visits or ECGs performed due to palpitations or presyncope.	A symptomatic arrhythmia was detected in 8.9% of the patients using the AliveCor monitor compared with 0.9% of the control group, a relative risk of 10.3 (95%CI 1.3 to 78.5, p=0.006). The mean time to symptomatic arrhythmia detection was 9.9 days with AliveCor compared with 48 days with standard care, p=0.0004.

1.3 Details of relevant economic studies

Please give details of all relevant studies (all studies in table 1). Copy and paste a new table into the document for each study. Please use 1 table per study.

Ali 2015	
What are main differences in resource use and clinical outcomes between the technologies?	Technologies not assessed here; this is a cost analysis of Stroke in patients with AF.
How are the findings relevant to the decision problem?	Not directly relevant, study reports costs associated with AF and stroke.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Earlier diagnosis using a new technology could lead to stroke prevention and therefore a reduction in costs and resources.
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	This was a cost analysis. Overall cost of ischemic stroke was almost double in patients with AF compared to those without.
What are the limitations of this evidence?	Costs were limited to acute care episode and direct social care costs or indirect costs from loss of productivity to patients or caregivers were not included. This could mean the financial impact has been underestimated. This was a UK based study of one institution so is applicable to health systems of a similar structure in the UK but could be applied to other organisations. Stroke patients who were not hospitalised were not included.
How was the study funded?	No funding support

Boggon 2015	
What are main differences in resource use and clinical outcomes between the technologies?	Technologies not assessed here; this is a cost analysis of Stroke in patients with AF.
How are the findings relevant to the decision problem?	Not directly relevant, study reports costs associated with AF and stroke.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Earlier diagnosis using a new technology could lead to stroke prevention and therefore a reduction in costs and resources.
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	This is a cost analysis of resource use in stroke patients who do or do not have AF

What are the limitations of this evidence?	The study was observational and not randomised. Information on the AF diagnostic criteria was not presented. Most stroke cases could not be classified and therefore were recorded in the GPRD without a classification.
How was the study funded?	Study was supported by Bayer.

Stewart 2004	
What are main differences in resource use and clinical outcomes between the technologies?	Technologies not assessed here; this is a cost analysis of patients with AF.
How are the findings relevant to the decision problem?	Not directly relevant, study reports costs associated with AF
Does this evidence support any of the claimed benefits for the technology? If so, which?	This study does not directly support any of the claimed benefits, it is a cost analysis of all AF patients in the UK.
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	This is a cost analysis of direct costs associated with AF in the UK. 50% of costs were hospital admissions, 20% drugs, 13% GP visits, 12% for referrals ad 6% for post discharge visits.
What are the limitations of this evidence?	Data was extrapolated from the Scottish rates of hospitalisation and GP consultations and applied to the UK. Heart disease prevalence is higher in Scotland so the cost of AF may be marginally inflated in the UK. New intervention and surgical approaches to AF were not considered. Indirect costs (lack of productivity) were not calculated.
How was the study funded?	National health federation of Australia and the British Heart Foundation.

Yiin 2014	
What are main differences in resource use and clinical outcomes between the technologies?	Technologies not assessed here; this is a cost analysis of patients with AF.
How are the findings relevant to the decision problem?	Not directly relevant, study reports costs associated with AF and stroke and systemic emboli.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Earlier diagnosis using a new technology could lead to stroke prevention and therefore a reduction in costs and resources.
Will any information from this study be used in the economic model?	No

What cost analysis was done in the study? Please explain the results.	This is a cost analysis of stroke and systemic emboli in AF patients.
What are the limitations of this evidence?	Study findings cannot be generalised to other populations or healthcare systems. Detection of paroxysmal AF may have biased the comparison of OCSP and OXVASC. It is possible that ascertainment of more minor strokes was more effective in OXVASC than in OCSP. Not all apparently AF-associated systemic emboli or stroke would have been due to AF. Individual patient data on anticoagulation in the underlying study population was not available.
How was the study funded?	Wellcome trust, Wolfson foundation, Medical research council, Dunhill medical trust, UK stroke association, NIHR.

Ghosh 2018	
What are main differences in resource use and clinical outcomes between the technologies?	Zio patch was more expensive than Holter monitoring (£440 vs £367). Resource use not reported.
How are the findings relevant to the decision problem?	Study supports that Zio gives a more rapid diagnosis than standard technology and assesses the cost of this service.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Use of Zio leads to earlier diagnosis (average wait for Holter was 59 days) which could reduce the clinical sequalae of arrythmia as well as reduce costs associated with complications of a late diagnosis.
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	This is a cost analysis paper that compared the cost of Zio XT to Holter monitoring. Holter is cheaper operationally but Zio provides a more comprehensive follow up and quicker investigation.
What are the limitations of this evidence?	Not reported
How was the study funded?	Not reported

Chandratheva 2017	
What are main differences in resource use and clinical outcomes between the technologies?	72-hour Holter = £569 Zio Patch = £300 per patch 3-day E-patch = £600 per unit, £16 per electrode, £35 per report In-clinic monitoring using Apoplex = £650 per unit, £20 per report
How are the findings relevant to the decision problem?	Study reports that the Zio patch is cheaper than alternative methods of monitoring and that time to

	placement of a monitoring device is shortest with Zio.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Earlier diagnosis using a new technology could lead to stroke prevention and therefore a reduction in costs and resources.
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	This is a cost analysis of 4 monitoring devices for AF. The Zio patch provided the cheapest form of monitoring, followed by 72-hour Holter. Time from clinic to device placement was lowest with the Zio patch and highest with 72-hour Holter. Time to reporting after device placement was not significantly different between Zio and Holter but was lower in the E-patch and Apoplex.
What are the limitations of this evidence?	Not reported
How was the study funded?	Not reported

NICE MIB141 2018	
What are main differences in resource use and clinical outcomes between the technologies?	This is a NICE technology summary for a Reveal LINQ device and did not directly compare with another technology.
How are the findings relevant to the decision problem?	Not directly relevant, study reports a technology summary of the Reveal LINQ device
Does this evidence support any of the claimed benefits for the technology? If so, which?	This technology summary does not directly support any of the claimed benefits of the submission.
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	This is a technology summary; outright costs of the device are stated; cost for device is £1800 +VAT.
What are the limitations of this evidence?	Not reported
How was the study funded?	Not reported

NICE MIB101 2017	
What are main differences in resource use and clinical outcomes between the technologies?	This is a NICE technology summary for the Zio XT Service and did not directly compare with another technology.
How are the findings relevant to the decision problem?	This summarises the Zio XT Service and supports the claim that its use can lead to earlier diagnosis.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Summary states that the service may be applied during consultation, this reduces wait time and leads to earlier diagnosis.

	Summary also states that there is less chance of the Zio patch failing than a Holter monitor, which improves diagnostic yield and minimises disruption to patients' lives, and also reduces staff burden as less retesting is carried out. Earlier diagnosis is discussed, leading to less hospital visits and therefore a reduction in costs.
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	This is a technology summary, so cost analysis was not stated. Summary states that the purchase cost of the Zio patch is lower than the Holter monitor but the costs per patient are higher. These costs may be offset if the Zio patch leads to more accurate diagnosis and better treatment of arrhythmias.
What are the limitations of this evidence?	Not reported
How was the study funded?	Not reported

Diamantopoulos 2016	
What are main differences in resource use and clinical outcomes between the technologies?	ICM was more costly than SoC but resulted in less ischemic strokes and more QALYs. In less than 5% of scenarios SoC was both less expensive and more effective than ICM.
How are the findings relevant to the decision problem?	Not directly relevant, study reports economic model of the Reveal XT device.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Earlier diagnosis and prevention of stroke leads to less resource use and costs.
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	A cost effectiveness analysis of Reveal XT vs SoC: The ICER was £17175 per QALY gained, compared to SoC in the base case scenario. Costs related to stroke were reduced in the ICM model but remained higher overall than standard care (£19631 vs £17045). If warfarin was used instead of non-vitamin-k-oral-anticoagulants, the ICER was £13296 per QALY instead.
What are the limitations of this evidence?	Detection rates for ICM and SoC were derived from countries other than the UK so may not be generalisable. Data was derived from a clinical trial and patient selection and physician treatment practices may not reflect outcomes outside of a trial setting.
How was the study funded?	This study was funded by Medtronic, Switzerland.

Rinciog 2019

What are main differences in resource use and clinical outcomes between the technologies?	Total cost of Reveal is higher than standard care (Holter) but generated more QALYs than SoC and prevented more strokes.
How are the findings relevant to the decision problem?	Not directly relevant, study reports an economic model of the Reveal XT device.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Earlier diagnosis and prevention of stroke leads to less resource use and costs and staff use is reduced.
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	Cost utility analysis. The total cost of Reveal was higher than SoC (£13360 vs £11936). Reveal generated more QALYs than SoC (6.5 vs 6.3) and the ICER was £7140/QALY gained, which is below the £20000/QALY threshold suggesting Reveal is cost effective.
What are the limitations of this evidence?	Limitations are not reported in this study. However, the use of trial data causes a potential lack of generalisability to a non-trial setting. All evidence is UK based so may not be generalised to other regions.
How was the study funded?	Study funded by Medtronic plc.

Rockx 2005	
What are main differences in resource use and clinical outcomes between the technologies?	The loop recorder costs $533.56 compared to $177.64 for the Holter monitor, but cost of diagnosis in the two groups was similar (Holter= $745, loop=$843). The diagnostic accuracy of the loop recorder was 63.2% compared to 23.53% by Holter.
How are the findings relevant to the decision problem?	Not directly relevant, study reports an economic model of loop recorders vs Holter monitoring.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Higher diagnostic accuracy leads to shorter diagnosis times and less chance of progression. Therefore, less resource use and staff costs.
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	Cost utility analysis: The ICER of the loop recorder was $901.74 per extra successful diagnosis.
What are the limitations of this evidence?	Results may not be applicable to other patient groups due to selective entry criteria. The study was not conducted in the UK so is not easily generalised to the NHS and UK systems.
How was the study funded?	Supported by grant R98-66 from physician services Inc, Canada.

Anon 2017	
What are main differences in resource use and clinical	Clinical outcomes not discussed.

outcomes between the technologies?	Budget impact of implementing LCEM testing over ECLR at the same rate from 2016 to 2020 would have a net budget impact of $0.37 million by 2020.
How are the findings relevant to the decision problem?	Not directly relevant, study reports the budget impact of long term cardiac monitoring over a 5 year time horizon.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Not directly applicable as Zio not included but does support cost savings implemented when the health service changes their standard practice.
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	Budget impact model. Use of LTCM grew steadily over time since the introduction in 2006, and faster since 2011 when 14-day monitoring became publicly funded, causing a corresponding decline in ELCR. Analysis suggested that if the trends continued, publicly funding both devices will result in addition costs ranging between $130000 to $370000 per year over the next 5 years.
What are the limitations of this evidence?	Insights from past research could not be used as there was no evidence that directly compared the two devices previously. Projections of volumes of ECG testing were derived from historical data so may not reflect current practice. A constant unit price was assumed but a change in price would change the study outcome. Carried out in Canada so not directly applicable to UK.
How was the study funded?	Not reported

Levin 2014	
What are main differences in resource use and clinical outcomes between the technologies?	Use of handheld ECG was dominant for QALYs gained vs no screening and Holter ECG, and resulted in the most life years gained. The total cost effectiveness for screening was calculated to be dominant for the Handheld ECG over the other screening methods.
How are the findings relevant to the decision problem?	Not directly relevant, study reports an economic model of handheld ECG screening in Sweden.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Not directly applicable as Zio not included but does show a financial and diagnostic benefit in changing from standard care to a new device.
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	Cost utility analysis. Total costs: No screening: € 4,020,000; Holter: € 4,255,000; Handheld ECG: € 3,976,000 (dominant).

	The implementation of the handheld ECG screening programme on 1000 patients resulted in 11 avoided strokes and the gain of 29 life-years or 23 QALYs.
What are the limitations of this evidence?	Based on a single study of a Swedish cohort so not easily generalised to a wider population. Cost effectiveness was estimated for screening at 75 years old, but stroke events can happen at any age. No probabilistic sensitivity analyses were performed.
How was the study funded?	This study was funded by a grant from VINNOVA- Swedish Governmental Agency for Innovation Systems

Quiroz 2017	
What are main differences in resource use and clinical outcomes between the technologies?	Resource use and clinical outcomes not reported.
How are the findings relevant to the decision problem?	Not directly relevant, study reports an economic model of insertable cardiac monitors.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Not directly applicable as Zio not included, may be used in the model as an indirect comparison.
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	Cost utility analysis ICER = € 24,715 per QALY gained for base case. ICM had a probability of 91% of being cost-effective at a threshold of € 80,000 per QALY gained.
What are the limitations of this evidence?	This is an abstract only and so limited information is available. Carried out in the Netherlands so not generalisable to a wider population.
How was the study funded?	Not reported

Yong 2016	
What are main differences in resource use and clinical outcomes between the technologies?	The 30-day event recorder was slightly more costly than a 24-hour Holter. Using the 30-day event recorder would prevent 16 more IS and 2 more intracranial haemorrhages during a lifetime for every 1000 patients screened
How are the findings relevant to the decision problem?	Not directly relevant, study reports an economic model of the 30 day event recorder.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Not directly applicable as Zio not included, may be used in the model as an indirect comparison.

Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	Cost utility analysis. Incremental cost per QALY gained vs 24-hour Holter 30d event loop recorder = $2166. 30d event loop recorder monitoring was highly cost effective (ICER per QALY $2000), and it was predicted to gain 17 life years and 13 QALYs at an additional cost of $28000 in a cohort of 1000 patients.
What are the limitations of this evidence?	Results are predicted from a model rather than actual events. Risk of recurrent IS associated with paroxysmal AF in patients with cryptogenic stroke is uncertain. Minimum duration of clinically significant AF varies and changing the clinically significant level affects the risk of stroke.
How was the study funded?	Grants from the Canadian stroke network and the Ontario centres of Excellence

Zimetbaum 1998	
What are main differences in resource use and clinical outcomes between the technologies?	King of Hearts assessed only.
How are the findings relevant to the decision problem?	Not directly relevant, study reports an economic model of the King of Hearts continuous loop event recorder.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Not directly applicable as Zio not included. Cost comparisons to the savings using Zio could be made if a similar population was assessed.
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	Cost effectiveness analysis. If a patient received a diagnosis and it was considered "meaningful", the cost effectiveness ratio for week 1 of event monitoring was $98 (CI $82 to $121) per diagnosis. This increased to $576 (CI $383 to $1066) during week 2, and to $5832 (CI $1975 to infinity) during week 3 and beyond.
What are the limitations of this evidence?	Based in the USA so not directly applicable to the UK. Other limitations not stated by the paper.
How was the study funded?	Grants from the G. Harold and Leila Y. Mathers Charitable Foundation, and the National Aeronautics Space Administration.

Kaura 2019

What are main differences in resource use and clinical outcomes between the technologies?	Using Zio instead of the current strategy (Holter) and a 5 year time horizon gave an incremental cost of -£106342 and prevented 10.8 strokes compared with standard care at King's College Hospital NHS Foundation Trust. When social care costs are considered, this number increases to -£410449.
How are the findings relevant to the decision problem?	The study reports costs associated with the use of the Zio XT Service and reports a reduction in the cost of diagnosis and an increase in the number of strokes prevented.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Earlier diagnosis and less need to attend follow up means lower costs and staff use at hospitals.
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	Budget impact analysis. Implementation of the Zio XT Service would result in 10.8 strokes being avoided per year, compared to current Holter monitoring, and a yearly saving of £113630, increasing to £162491 over 5 years.
What are the limitations of this evidence?	Dropout rate was 20% due to Holter ECG service provision; compliance with Holter devices is low even in clinical trials. Study did not directly compare extended monitoring systems but instead compared a short monitoring system with a long one. Detected PAF may include the incidence of PAF in the background population as aged matched healthy controls were not assessed.
How was the study funded?	Research grant from Bristol-Myers-Squibb-Pfizer alliance

Kinlay 1996	
What are main differences in resource use and clinical outcomes between the technologies?	Using the event recorder resulted in a decrease in cost when compared to the Holter monitor. AF or flutter was detected in 6% of patients with the event recorder and no patients with 24-hour Holter. Clinically significant arrhythmias were detected in 19% of patients with the event recorder and no patients with the 24-hour Holter monitor.
How are the findings relevant to the decision problem?	Not directly relevant, study reports costs associated with using an event recorder in comparison to Holter monitoring.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Not directly related to Zio but increasing diagnostic accuracy with a new device leads to a reduction in cost and staff time.

Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	Cost effectiveness analysis. ICER per additional ECG recorded during symptoms = -$213 with event recorder vs 24-hr Holter. ICER per additional clinically significant arrhythmia detected = -$373 for event recorder vs 24-hr Holter.
What are the limitations of this evidence?	Paper does not report limitations of the study. Research was completed in Australia and so is not easily generalisable to a UK population.
How was the study funded?	Not reported

Halcox 2017	
What are main differences in resource use and clinical outcomes between the technologies?	Compared to routine care, patients using the device were significantly more likely to receive a diagnosis (p=0.004).
How are the findings relevant to the decision problem?	Not directly relevant, study reports costs associated with the AliveCor device.
Does this evidence support any of the claimed benefits for the technology? If so, which?	More accurate diagnosis with new technology is cost saving as it leads to less follow up tests and appointments, saving time and money.
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	This was a cost analysis of the AliveCor Kardia device vs standard care. The overall cost of the intervention was $204 830 (£156 837). This consisted of device costs of $28 698 (£21 974), patient training costs of $3750 (£2871), and defective technology costs of $2194 (£1680)
What are the limitations of this evidence?	Participants without internet access were excluded from the study which may have removed a high-risk group of patients. A full assessment of the devices diagnostic performance was not completed. The study was not blinded.
How was the study funded?	A joint grant from the Welsh Government Health Technology and Telehealth fund and AliveCor Inc.

Reed 2019	
What are main differences in resource use and clinical outcomes between the technologies?	Time to arrhythmia detection was significantly shorter with the AliveCor app than with standard care (p=0.0004). Serious outcomes were more common in the device group at 90 days, but death was not significantly different. Median overall costs were higher with the device, but the cost per diagnosis was lower.

How are the findings relevant to the decision problem?	Not directly relevant, study reports costs associated with the AliveCor device.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Not directly related to Zio but decreasing time to diagnosis relives burden on staff and leads to cost savings.
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	This was not a model but included the cost of technologies being assessed. Median overall healthcare utilisation costs: AliveCor = £108 (IQR 99.0–246.50, range 99–2697) Standard care = £0 (IQR 0–120.0, range 0–4161); p = 0.0001 Cost per symptomatic rhythm diagnosis: AliveCor = £474 Standard care = £1395
What are the limitations of this evidence?	A large proportion of recruitment occurred in office hours so may not have recruited as many people as they could have. Other study limitations are not discussed.
How was the study funded?	Chest, Heart and Stroke Scotland, The British Heart Foundation.

2 Economic model

This section refers to the de novo economic model that you have submitted.

2.1 Description

Patients

Describe which patient groups are included in the model

There are two models dealing with two distinct patient populations, in line with the Cardiology and Stroke clinical care pathways described in Part 1 of this submission:

1. Patients with symptomatic palpitations or syncope referred to cardiology outpatients for evaluation ("Cardiology Model")

2. Patients who have experienced an ischaemic stroke or transient ischaemic attack (TIA) without current evidence of atrial fibrillation (AF), referred for the identification of intermittent AF episodes

A third care pathway was described in part 1 of the submission, that considered an alternative direct-access route to evaluating symptomatic populations. This was not separately modelled within the current submission because:

a) The input population was identical to that included in the cardiology model, along with the estimates of diagnostic yield associated with the different technologies. The outcomes would therefore not be expected to be substantially different to those of the cardiology model
b) Because direct access services are poorly captured within HES data and subsequent management and re-referral patterns within primary care are not explicitly documented within GP Read/Snomed coding systems, it proved impossible to source reliable estimates of patient flows.

Whilst it may be expected that similar gains to those seen in the other models would be realisable in a direct access or community-driven approach, reliable modelling of this option will require a better understanding of patient flows than are currently available.

In the future we intend to model the Zio XT Service within primary and community care settings, particularly those utilising community Pharmacist-led anticoagulation services. In this pathway, following receipt of the Zio XT technical report the prescribing clinician can refer the patient directly to the pharmacist for counselling and treatment. This process supports the appropriate place of care within a developing integrated care system as well as improves GP efficiency while enabling the patient to receive a specialist treatment care plan within the community setting. An example of such a service is the Liverpool CCG Anticoagulation Community service.

Technology and comparator(s)

State the technology and comparators used in the model. Provide a justification if the comparator used in the model is different to that in the scope.

The technology evaluated is the Zio XT Service, which includes up to 14 days use of a Zio monitor by the patient, analysis of the resulting record by iRhythm and the creation of a detailed report by iRhythm which is returned to the referring clinician. The comparator is a blended combination of 24 hour Holter monitoring with the use of a 7-day event triggered monitor (Cardiac Event Recorder; CER). In both cases, the monitor is fitted and removed by NHS staff, as is the analysis and reporting of the results. These two comparator technologies have been identified by our clinical advisors as the most likely to be used within an NHS context. The relative proportions of use for each comparator have similarly been guided by our clinical advisors. The use of implantable loop recorders (ILR) is an option for monitoring that is sometimes used. However, because of its high cost, our advisors agree that it would never be a first-line option in the defined patient groups. We have built in the use of ILRs as a downstream option in patients in whom the other technologies (both Zio XT Service and the comparators) yield inconclusive results in the presence of a high clinical submission of cardiac arrhythmia.

2.2 Model structure, assumptions and parameter values

Provide a diagram of the model structure you have chosen in Appendix B. Justify the chosen structure of the model by referring to the clinical care pathway(s) outlined in part 1, section 3 (Clinical context) of your submission.

Both of the models (see appendix B) use a decision tree structure to evaluate NHS diagnostic process costs over a twelve-month period. Although there will inevitably be between-patients variation in the time from referral to diagnosis, our clinical advisors felt that the large majority of patients would have completed the diagnostic process within 1 year. This assumption is also consistent with the requirement by NICE to primarily consider in-year savings for the DHT Pilot. Beyond the point of diagnosis, the ongoing treatment pathway beyond 1 year will be identical regardless of the technology under consideration, and will therefore not differ between arms.

The two structures are based on the Cardiology and Stroke patient pathways outlined in part 1, section 3. Given the simple structure of the clinical pathways and the relatively limited potential for recursion between states within the 12 month time horizon, it was felt that a decision tree was both sufficient and appropriate to address this research question, with a Markov health state transition approach being unlikely to add significantly greater understanding to the process impact of the Zio XT Service.

Where the original clinical pathways proved to be insufficiently granular to drive the model, we have used clinical advisors to refine and expand the structures.

A third exploratory model extending the Stroke Model is also presented, which evaluates the inferred cost consequences of earlier, more sensitive diagnosis of AF on the risk of patients sustaining a recurrent stroke event in the first year after the index event.

All modelling has been carried out in TreeAge Pro v2019 R2.1.

In table 2, list the main assumptions in the model, justify why each has been used and the source of the assumption.

Table 2 Model assumptions

Assumption	Justification	Source
In symptomatic patients, positive test results (clinically significant arrhythmia captured) or negative test results (no arrythmia in the presence of symptoms) will result in no further monitoring being carried out	Both these outcomes are diagnostically explicit and therefore do not require further exploration	Clinician advice
In symptomatic patients, inconclusive results may incur the option of repeating the test	In the absence of a definitive diagnosis in the presence of infrequent symptoms, repeat testing may refine the result, especially for short duration Holter monitoring	Clinician advice Analysis of HES data documenting repeat testing for individual patients
In stroke patients either negative or inconclusive results may lead to repeat testing	The objective of monitoring these patients is to identify runs of atrial fibrillation which may or may not be symptomatic. A negative test	Clinician advice

	result over a short duration may therefore not exclude the diagnosis	CRYSTAL-AF study [Diamantopoulos 2016]
Where monitoring is repeated, a different technology may be used (eg CER after Holter24). The use of an implantable device is an option where there is a significant concern	The availability of devices is a major determinant of what is used. Holter monitors are the most readily available and tend to be used first in most patients. The cost of implantable devices restricts their use to a very small number of patients in whom there remains uncertainty in the presence of significant clinical concern.	Clinician advice Analysis of HES data on relative use of external and internal devices
In patients undergoing repeat testing, a mean of 1.44 additional procedures is assumed	73% of patients have only a single test within a 12-month period. The figure of 1.44 is the mean number of additional tests carried out in the group who do require a repeat	Analysis of HES data documenting repeat testing for individual patients
The costs of any diagnostic and therapeutic procedures carried out subsequent to rhythm monitoring is not included in the model	These procedures will be identical regardless of the technology used to make the diagnosis and therefore do not represent an incremental cost in the context of the current appraisal	Clinician advice

In table 3, describe the clinical parameters, patient and carer outcomes and system outcomes used in the model.

Table 3 Clinical parameter, patient and carer outcomes and system outcomes

Parameter/outcomes	Source	Relevant results	Range or distribution +/-20% applied to all parameters	How are these values used in the model?
Parameters applied across both models				
cHolter (cost per patient for each use of a Holter 24 hour monitor)	Base NHS process cost for applying and removing monitor + analysis and reporting of results based on PLICS data [Appendix D: #5 PLICS]. Supplementary data relating to hardware, maintenance and replacement costs derived from FOI request data from 53 NHS trusts [Appendix D: #2 FOI]	PLICS analysis: £158 per use FOI analysis: £27.12 TOTAL: £185.12 per use	£148.10 - £222.14	Cost applied to each use of a Holter 24 hour monitor across both models
cCER (cost per patient for each use of a 7-day event-triggered monitor)	As for previous parameter: PLICS data relates to all monitoring technology and is not available broken down by individual device.	PLICS analysis: £158 per use FOI analysis: £27.12 TOTAL: £185.12 per use	£148.10 - £222.14	Cost applied to each use of a 7 day event-triggered monitor across both models
cZIOservice (cost per patient for each use of the Zio XT Service)	Information provided by iRhythm	£310 per service use	£248 - £372	Cost applied to each use of the Zio XT Service across both models
cOPDAssessment + cOPDFU (cost of outpatient attendance in cardiology clinic)	NHS Reference Costs 2017-18	£142	£113.60 - £170.40	Costs applied to any outpatient attendance consequent on the diagnostic process. Not applied within the primary context of the monitoring technologies, as this is already factored in to the parameters detailed above

cImplantable (cost of providing and 1 year monitoring of ILR)	Aggregate of device cost [NICE MIB 141], outpatient insertion cost [National Reference Costs 2017/18] and monitoring cost for 1 year [NICE MIB 141]	£3,221	£2576.80 - £3865.20	Cost applied when patient progresses to ILR after inconclusive diagnostic work-up with other technologies
pNoRepeat (Probability of a patient with inconclusive monitoring result not progressing to repeat monitoring	Analysis of HES data for England [Appendix D: #1 HES]. No distinction possible between technology used or reason for monitoring	73%	58.3% - 100%	Applied throughout both models for both CER and Holter 24 Upper limit restricted to keep probability ≤ 1
nRepeat (mean number of additional monitoring episodes in patients having repeat testing	Analysis of HES data for England [Appendix D: #1 HES]. No distinction possible between technology used or reason for monitoring	1.44	1.15 – 2.16	Applied throughout both models for both CER and Holter 24
Parameters applied to Cardiology model alone				
pPositiveZio (probability of a Zio test yielding a positive result – arrhythmia identified at the time symptoms are experienced)	Data from iRhythm [Appendix D: #3 Zio Palpitations]. Retrospective UK analysis of results from 5,058 patients with symptomatic palpitations assessed using Zio XT Service	63.5%	50.8% - 70.1%	Used as estimate of positive diagnostic yield in all arms of the two symptomatic models where Zio XT Service is used. Upper limit restricted to ensure positive + negative probabilities do not sum to greater than 1
pPositiveCER (probability of a CER test yielding a positive result – arrhythmia identified at the time symptoms are experienced)	Data from Tsang et al [2014]. Retrospective US claims database analysis of 24,023 patients assessed using CER	23.0%	18.4% - 27.6%	Used as estimate of positive diagnostic yield in all arms of the two symptomatic models where CER is used
pPositiveHolter (probability of a Holter test yielding a positive result – arrhythmia identified at the time symptoms are experienced)	Data from Tsang et al [2014]. Retrospective US claims database analysis of 57,143 patients assessed using Holter monitor	24.2%	19.4% - 36.3%	Used as estimate of positive diagnostic yield in all arms of the two symptomatic models where Holter 24 is used

pNegativeZio (probability of a Zio test yielding a negative result – no arrhythmia identified despite symptoms being experienced)	Data from iRhythm [Appendix D: #3 Zio Palpitations]. Retrospective UK analysis of results from 5,058 patients with symptomatic palpitations assessed using Zio XT Service	29.9%	23.9% - 44.9%	Used as estimate of negative diagnostic yield in all arms of the two symptomatic models where Zio XT Service is used
pNegativeCER (probability of a CER test yielding a negative result – no arrhythmia identified despite symptoms being experienced)	Tsang et al [2014] did not give data for negative results. Estimate was arrived at by applying the ratio of positive:negative seen in a small CER study (Balmelli et al) [2003] to the positive results figure for CER in Tsang et al [2014]	18.5%	14.8% - 27.8%	Used as estimate of negative diagnostic yield in all arms of the two symptomatic models where CER is used
pNegativeHolter (probability of a Holter test yielding a negative result – no arrhythmia identified despite symptoms being experienced)	Tsang et al [2014] did not give data for negative results. Estimate was arrived at by applying the ratio of positive:negative seen in the Zio analysis [Appendix D: #3 Zio Palpitations] to the positive results figure for Holter in Tsang et al [2014]	11.4%	9.1% - 17.1%	Used as estimate of negative diagnostic yield in all arms of the two symptomatic models where Holter monitor is used
pCER (proportion of patients with primary monitoring using CER rather than Holter)	Clinical opinion	15%	12% - 18%	Applied at outset of model to determine the proportion of comparator patients assigned to CER or Holter arms.
pHolterSwitchZio (proportion of patients who would have had a Holter monitor switched to Zio XT Service	Clinical opinion	80%	64% - 96%	According to the clinical pathways, all CER patients will be switched to Zio. Our clinical advisors suggest that most Holter patients will also be switched. This parameter captures this
pImplantable (probability that a patient with an inconclusive result will have an ILR implanted	Clinical opinion	2%	1.6% - 2.4%	Applied to all treatment arms where repeat testing is inconclusive and further evaluation is indicated

Parameters applied in Stroke model alone				
pIPmonit (proportion of stroke patients undergoing monitoring as in-patient	Clinical opinion	50%	40% - 60%	Applied to both arms of model to determine proportion undergoing monitoring as outpatient
pNewAFStroke (proportion of patients first diagnosed with AF at time of index admission)	SSNAP report [2019]	5.6%	4.5% - 8.4%	Applied to all patients undergoing in-patient monitoring
pStroke (proportion of all patients in model with non-haemorrhagic stroke)	66% of patients with new stroke or TIA have stroke [Giles 2007]. 87.3% of strokes are non-haemorrhagic [SSNAP [2019] 0.66 x 0.873 = 0.576	57.6%	46.1% - 86.4%	Applied to all patients in both arms to determine split between stroke and TIA
pPrimaryHolter (% of patients with Stroke/TIA who are monitored with Holter24 (rather than ER)	Clinical opinion	50%	40% - 60%	Applied to all patients in both arms to determine split between Holter and CER
pZioTIA (% of patients with TIA who are monitored with ZIO)	Clinical opinion	75%	60% - 90%	Applied to patients in Zio TIA arm to determine split between Zio and Holter/CER
pPositiveCER (Proportion of stroke/TIA patients with new AF identified by CER)	7-day results from EMBRACE study [Gladstone 2014]	7.4%	5.9% - 11.1%	Used as estimate of positive diagnostic yield in all arms where CER is used
pPositiveHolter	Results from Kaura 2019 (EPACS study)	2.1%	1.7% - 2.5%	Used as estimate of positive diagnostic yield in all arms where Holter is used
pPositiveZIO	Results from Kaura 2019 (EPACS study)	16.1%	12.9% - 19.3%	Used as estimate of positive diagnostic yield in all arms where Zio is used

2.3 Assumptions used to extrapolate clinical outcomes

If any outcomes listed in table 3 are extrapolated beyond the study follow-up periods, explain the assumptions that underpin this extrapolation.

The primary models evaluate only process costs and therefore there are no clinical extrapolations used. An exploratory scenario analysis has been carried out on the Stroke Model to evaluate the potential impact of increased sensitivity and decreased time to diagnosis associated with the use of Zio versus either Holter or CER. This analysis uses literature-based results to estimate:

- 1 year risk of stroke with or without AF
- 1 year risk of stroke with AF when anticoagulated
- Delay from decision to monitor to point when results are available for each technology
- 1 year direct medical costs associated with stroke

The analysis assumes that all patients diagnosed with AF will be started on anticoagulation. The annual risk of stroke is estimated based on the proportion of time off or on anticoagulation, based on the mean delay to monitoring results being available. Patients monitored with Holter or CER undergo one repeat test in the absence of a positive result. Patients monitored with Zio undergo a single test only.
No costs of monitoring are included in this model, as this element has already been captured in the process model.

The table below lists the variables used in the model, together with the sources.

Parameter/outcomes	Source	Relevant results	Range or distribution	How are these values used in the model?
pTrueAF (True prevalence of AF in post stroke/TIA patients without AF at index event)	3 year ILR results from CRYSTAL-AF study	30%	24% - 36%	Applied to each AF-diagnosed arm to assess proportion of patients identified by each technology
pPositiveCER (Proportion of stroke/TIA patients with new AF identified by CER)	7-day results from EMBRACE study [Gladstone 2014]	7.4%	5.9% - 8.9%	Used as estimate of positive diagnostic yield in CER arm
pPositiveHolter	Results from EPACS study	2.1%	1.7% - 2.5%	Used as estimate of positive diagnostic yield in Holter arm
pPositiveZio	Results from EPACS study	16.1%	12.9% - 19.3%	Used as estimate of positive diagnostic yield in Zio arm
cStroke (First year direct medical cost of managing stroke)	Analysis of SSNAP data by Xu et al [2019]	£13,452	£10,762 - £16,142	Cost applied when patient in any arm has stroke
pStrokeAFuntreated (proportion of patients with AF not on anticoagulation experiencing a stroke in 1 year)	Results of EAFT study [1993]	12.3%	9.8% - 14.8%	Used for AF related stroke rates in patients not on anticoagulation
pStrokeAFtreated (proportion of patients with AF on anticoagulation experiencing a stroke in 1 year)	Results of EAFT study [1993]	3.9%	3.1% - 4.7%	Used for AF related stroke rates in patients on anticoagulation
ORStrokeAF (Odds ratio for additional risk of stroke associated with presence of AF)	Results from Burn et al [1994]	1.24	0.99 – 1.49	Used in calculation of non-AF related stroke rates

pStrokeNoAF (proportion of patients experiencing a recurrent stroke in year 1 in the absence of AF)	Calculated as: pStrokeAFuntreated/ ORSrokeAF	9.9%	7.9% - 11.9%	Applied to patients in whom AF is not diagnosed
tHolter (mean delay between the decision to carry out monitoring with Holter and the availability of results in the patient record)	Results of a HES analysis based on patients with a prior stroke/TIA analysis + results of FOI requests Mean delay to fit device = 36 days [HES] Time for monitoring and return: 1 day monitoring + 1 day to return device = 2 days [Assumption] Mean time for results to be available following test completion = 32 days [FOI] Total = 70 days	70 days	56 - 84	Used to estimate time to diagnosis in patient monitored with Holter

tCER (mean delay between the decision to carry out monitoring with CER and the availability of results in the patient record)	Results of a HES analysis based on patients with a prior stroke/TIA analysis + results of FOI requests Mean delay to fit device = 71 days [HES] Time for monitoring and return: 7 days monitoring + 1 day to return device = 8 days [Assumption] Mean time for results to be available following test completion = 9 days [FOI] Total = 88 days	88 days	70 - 106	Used to estimate time to diagnosis in patient monitored with CER
tZio (mean delay between the decision to carry out monitoring with Zio and the availability of results in the patient record)	Data from iRhythm Mean delay to fit device = 0 days (device fitted in clinic) Time for monitoring and return: 14 days monitoring + 1 day to return device = 16 days [Assumption] Mean time for results to be available following test completion = 4 days [iRhythm service level agreement] Total = 19 days	19 days	15 - 23	Used to estimate time to diagnosis in patient monitored with Zio XT Service

2.4 Other parameters in the model

Describe any other parameters in the model. Examples are provided in the table 4. You can adapt the parameters as needed.

Table 4 Other parameters

Parameter	Description	Justification	Source
Time horizon	12 months	The majority of patients will be diagnosed within 1 year. Management thereafter is identical regardless of the technology used	Clinical opinion
Discount rate	None applied	Not relevant given 1 year time horizon	n/a
Perspective (NHS/PSS)	NHS	Costs incurred in the primary analysis relate purely to NHS trust expenditure	n/a
Model cycle length	n/a	Not relevant to decision tree structure	n/a
Sources of unit costs	NHS Reference Costs 2017-18 + PLICS	Costs are incurred within trusts and usually fall into block contracts, so tariff prices are not relevant here	refs

3 Resource identification, measurement and valuation

3.1 Price of technology

Provide the unit list price(s) for the technology, including all related charges such as licence fees and subscription charges (excluding VAT). Please explain if these charges vary by factors such as number of users. If these prices were not used in the economic model, provide a justification for the difference.

Unit list price is £310 per patient using the service. This includes all elements including hardware, processing and reporting fees. The price is not subject to volume variation.

3.2 NHS and unit costs

Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs, the national tariff and unit costs (from PSSRU and HSCIC). Please provide relevant codes and values (e.g. OPCS codes and ICD codes) for the operations, procedures and interventions included in the model.

Outpatient use of cardiac monitors

NHS Reference costs 2017-18
OPROC worksheet
Currency code EY51Z: Electrocardiogram Monitoring or Stress Testing
Service Code 300; General Medicine. National average unit cost = £210
Service Code 320; Cardiology. National average unit cost = £141
Service Code 328; Stroke Medicine. National average unit cost = £328
Service Code 329; Transient Ischaemic Attached. National average unit cost = £172

Range across the relevant specialities = £141 = £328

Given the limitations of the variation in the sources described above, we undertook a costing exercise specifically for outpatient rhythm monitoring procedures based on PLICS and supplemented by information derived from Freedom of Information requests made to NHS trusts. This research is attached as Equipment costs relating to ECG ambulatory monitoring tests - Results of a Freedom of Information Request.
Direct NHS attributable costs based on PLICS amounted to £158 per procedure.
Additional costs attributable to hardware acquisition, maintenance and replacement amounted to a median additional cost of £27.12 per procedure.
This adds up to a total cost of £185.12 per monitoring procedure.

NHS Tariff 2019-20
APC & OPROC worksheet
Currency code EY51Z: Electrocardiogram Monitoring or Stress Testing
Outpatient tariff = £122
Note: Our information from our clinical advisors is that cardiac monitoring is generally carried out as part of a block contract and therefore individual procedures are not charged for using tariff prices.

Unit Costs of Health & Social Care (PSSRU)
Procedure costs not documented.

Attendance at cardiology outpatients

NHS Reference costs 2017-18
OPROC worksheet
Currency codes: WF01B: Non-Admitted Face-to-Face Attendance, First and WF01A Non-Admitted Face-to-Face Attendance, Follow-up.
National average unit cost: WF01B = £163; WF01A = £128
Note: As patients in our models are likely to have a mix of First and Follow-up appointments, we applied a weighted mean cost of £142 per attendance of any type.

3.3 Resource use

Describe any relevant resource data for the NHS in England reported in published and unpublished studies. Provide sources and rationale if relevant. If a literature search was done to identify evidence for resource use then please provide details in appendix C.

Ambulatory ECG monitoring: £185.12

- Unit cost per activity: £158. NHS process cost for applying and removing monitor + analysis and reporting of results. Based on Patient-Level information and Costing Systems (PLICS) 2016/17. Published as PLICS Public View Prototype. Based on PLICS data submitted by NHS Trusts to NHS Improvement for HRG EY51Z OPROC https://analytics.improvement.nhs.uk/t/Public/views/PLICSPublicViewPrototype2016-17data/CostofNHSservices?iframeSizedToWindow=true&:embed=y&:showAppBanner=false&:display_count=no&:showVizHome=no

- Unit cost per activity: £27.12. Sunken costs relating to equipment-related costs (not included in the PLICS unit cost above) validated by a Freedom of Information request [Appendix D: #2 (FOI)]

Outpatient follow-up appointment: £142

- Unit cost per activity: £142. National Schedule of Reference Costs, 2017-18. Outpatient Attendances. Service code 320. Cardiology. Consultant-led.

Implantable loop recorder monitoring: £3,221

- Unit cost per implantation - outpatient: £308. National Schedule of Reference Costs, 2017-18. Outpatient Procedures (OPROC). Service code 320. Cardiology. HRG EY12B Implantation of Electrocardiography Loop Recorder
- Unit cost per device: £1,800. NICE MIB 141. Reveal LINQ insertable cardiac monitor to detect atrial fibrillation after cryptogenic stroke. Feb2018
- Daily cost of continuous monitoring (per patient) @£3.05: £1,113. NICE MIB 141. Reveal LINQ insertable cardiac monitor to detect atrial fibrillation after cryptogenic stroke. Feb2018

First year direct medical cost of managing stroke: £13,452

- Unit cost (year 1) of healthcare attributable to stroke: £13,452. Xu *et al*. The economic burden of stroke care in England, Wales and Northern Ireland: Using a national stroke register to estimate and report patient-level health economic outcomes in stroke. Eur Stroke J 2018;3(1):82–91

Describe the resources needed to implement the technology in the NHS. Provide sources and rationale.

The Zio XT Service is a stand-alone service. The price includes the Zio XT biosensor device, analysis and reporting. The only additional resource required is nurse time (no more than Band 3 required) to fit the monitor, approximately <10mins in an outpatient clinic room. The Zio biosensor can be fitted at the first appointment therefore there is no requirement for an additional appointment to fit the monitor, unlike the current comparators.

Describe the change in resources associated with the change in patient outcomes after implementing the technology. Provide sources and rationale.

An exploratory scenario analysis has been carried out on the Stroke Model to evaluate the potential impact on patient outcomes of increased sensitivity and decreased time to diagnosis associated with the use of Zio versus either Holter or CER. The modelled reduction in stroke events is associated with a reduction in healthcare resource use and cost @£13,452 per stroke (year 1 costs). This scenario is described in Section 2.3.

Describe the change in resources associated with the change in system outcomes after implementing the technology. Please provide sources and rationale.

Changes in resources associated with the change in system outcomes after implementing the technology include:

- Reduced cardiology outpatient appointments. The modelled scenarios assume a higher conclusive rule-out diagnosis (p-negative rate) with Zio compared with the comparators. The model assumes patients with a p-negative diagnosis are discharged to the referring clinician without need for further outpatient attendance.

- Reduced repeat tests. The modelled scenarios assume a higher conclusive rule in diagnosis (p-positive) or rule-out diagnosis (p-negative rate) with Zio compared with the comparators, therefore a reduced rate of 'inconclusive' test results (and a reduced requirement for repeat tests. The current rate of repeat ECG tests was obtained from analysis of HES data [Appendix D: #1 (HES)], where 27% of patients had one or more further Electrocardiogram Monitoring & Stress Testing events subsequent to the index Electrocardiogram Monitoring & Stress Testing event within a 12-month period.

- Reduced resources associated with the Holter and event recorder monitoring: staff time (associated with fitting and removal, reading and reporting), estate costs (associated with fitting and removal) and equipment costs. With the Zio XT Service:
    - The biosensor is fitted at the first appointment (removing the need for patients to return for a separate Holter fitting appointment or to return the monitor.
    - All reading and reporting of the ECG tapes are outsourced, reducing the cardiac physiology staff resource associated with this function.
    - There is no requirement for capital outlay for monitors, analysers or software or for annual/monthly service costs for equipment. No costs associated with equipment loss or repair. When the Zio XT Service is fully implemented, trusts will need to maintain only a very small proportion of Holter stock, with an associated reduction in associated costs (estimated 80% reduction).

- Reduced requirement for implantable loop recorder monitoring. Zio is expected to reduce the number of implantable loop recorders that are implanted following an inconclusive test. The modelled scenarios currently estimate that the proportion of patients having a repeat test (due to inconclusive results from the first test) who progress to an implantable loop recorder is 2%. Zio is associated with a significantly reduced requirement for repeat testing, so the number of patients who progress to an implantable loop recorder is also reduced.

In table 5, summarise how the model calculates the results of these changes in resource use. Please adapt the table as necessary.

Table 5 Resource use costs

	Technology costs	Comparator 1 costs	Difference in resource use costs (technology vs comparator 1)
Cost of resource use to implement technology	The model assumes an initial cardiology outpatient appointment for both technologies (i.e., no incremental cost), at which time the Zio monitor will be fitted	The Holter and CER technologies require a separate fitting attendance, the cost of which is integrated into the PLICS assessment of total cost of comparator	The PLICS estimate of cost to implement the comparator technologies is the sum of resource costs used in that activity to fit the monitor, read and report on the results. This will include the department costs, staff time, supplies and services etc. Published PLICS (and National Reference costs) do not provide a breakdown of this cost, so it is not possible to measure the difference in resource cost to the implement technologies.
Cost of resource use associated with patient outcomes	Stroke costs are based on year 1 direct management costs only. The mean cost per patient on the Zio route is modelled as £1,261	For the comparator arm the mean cost is £1,384, on the assumption of a 50:50 mix between Holter and CER	-£123

Cost of resource use associated with system outcomes	After fitting, all subsequent analysis and reporting costs are bundled into the cost of the Zio XT Service. This cannot be separately costed Repeat testing costs are considered likely to be negligible – in the event of an inconclusive test it is likely that other diagnostic procedures will be used. The costs associated with ILR use in this situation is included in the model Outpatient attendance (other than the initial assessment appointment) is a key cost for patients in both arms. This is less likely in the presence of a clear negative test and consequently this cost element tends to be lower in the Zio arm	The PLICS analysis identifies a total cost of £158 per use, excluding the hardware and maintenance costs Repeat testing occurs in 27% of patients. Each re-test incurs an identical cost to the original cost (£158 + £27.12) See comments on left	It is not meaningful to estimate incremental costs at this deconstructed level, as the actual expenditure is intimately related to the care pathway followed. The results of the Cardiology and Stroke models capture these process outcome elements alone and consequently provide the best estimate of overall costs.
Total costs	In order to interpret this comparison meaningfully it is essential to consider the expenditure in the context of the pathway followed. This is the basis of our cost modelling, and consequently the results presented in section 4 provide the best estimate of resource use		

3.4 Adverse events

If costs of adverse events were included in the analysis, explain how and why the risk of each adverse event was calculated.

The only documented adverse events with monitoring technologies relate to allergic reactions to electrode adhesives. As all technologies are equally susceptible to this problem, this element was not separately costed in the analysis.

In table 6, summarise the costs associated with each adverse event included in the model. Include all adverse events and complication costs, both during and after long-term use of the technology. Please explain whether costs are provided per patient or per event.

Table 6 Adverse event costs

Not applicable

3.5 Miscellaneous costs, savings, resources and capacity changes

Describe any additional costs, resource or capacity considerations that have not been included elsewhere (for example, PSS savings, patient and carer costs, and changes to capacity of the service). If none, please state.

None included in the model but see below.

Are there any other opportunities for resource savings, including impact on capacity and demand, or redirection of resources that have not been possible to quantify?

Arrhythmia monitoring services are subject to excess demand, as evidenced by the long documented lag-times from referral to monitor fitting and from monitor fitting to follow-up appointment for the current pathway [Appendix D: #4 Wait and #6 Delay]. In addition, anecdotally, there is often a delay to a patient having access to monitoring due to monitoring equipment not being available on the day of the appointment to fit the monitor, and/or results of the monitoring not being available to the consultant at the follow-up appointment. Although the economic impact of these delays on the system costs is difficult to quantify, we might reasonably expect that use of the Zio XT Service will reduce these delays, particularly as the Zio biosensor is fitted at the first outpatient appointment, eliminating time waited for a fitting appointment. Additionally, the results of the Zio monitor are available to the prescribing clinician within 4 days of the Zio biosensor being returned by the patient, compared with an average of 32 days for Holter monitoring [Appendix D: #6

Delay]. Hospital Episode Statistics has also shown that the current average waiting time from an appointment for a Holter monitor fitting and the follow-up appointment in outpatients to discuss the results is 142-149, depending on the type of monitoring. Although this waiting time is very dependent on outpatient capacity, a future integrated pathway scenario enabled by the Zio Service could expect to see GP or pharmacist-initiated treatment without the need for a follow-up in secondary care.

Anecdotal evidence from trusts suggests that there is a high rate of failure to attend appointments to fit and remove monitoring devices (one trust measured this DNA figure to be 24%). Given the lack of requirement for these appointments for the use of Zio, this may also be expected to yield an increase in capacity and reduction in wasted appointments. However, it has not been possible to identify any quantitative estimates of the impact of these opportunity gains on costs or trust income, so this element has not been included in the model.

As described above, an exploratory scenario analysis has been carried out on the Stroke Model to evaluate the potential impact on patient outcomes of increased sensitivity and decreased time to diagnosis associated with the use of Zio versus either Holter or CER. This scenario analysis modelled the overall risk of a general population of stroke patients. It did not look at specific populations who may be more at risk of stroke than others and in whom consideration of health inequalities may be important, such as the elderly and ethnic minorities. For example, people of African or Caribbean origin are twice as likely to have a stroke, and at a younger age, than other people in the UK [Stroke Association].

3.6 Total costs

In the following tables, summarise the total costs:

- Summarise total costs for the technology in table 7.
- Summarise total costs for the comparator in table 8. This can only be completed if the comparator is another technology.

Table 7 Total costs for the technology in the model

Description	Cost	Source
Cost per use over lifetime of technology including license fees	£310	List price from iRhythm
Consumables per year (if applicable) and over lifetime of technology	0	Included in list price
Maintenance cost per year and over lifetime of technology	0	Single-use monitor
Training cost over lifetime of technology	0	Not required
Other costs per year and over lifetime of technology	0	None
Total cost per treatment/patient over lifetime of technology	£310	Text

Table 8 Total costs for the comparator in the model

Description	Cost	Source
Cost per use over lifetime of technology or treatment	£158	Analysis of PLICS data [Appendix D: #5 PLICS]
Amortised cost per use associated with hardware acquisition, maintenance, replacement + consumables	£27.12	FOI request to NHS trusts [Appendix D: #2 FOI]
Maintenance cost per year and over lifetime of technology or treatment	Aggregated within figure above	n/a
Training cost over lifetime of technology or treatment	None required	n/a
Other costs per year and over lifetime of technology or treatment	Aggregated within figure above	n/a
Total cost per use over lifetime of technology or treatment	£185.12	Text

4 Results

4.1 Base-case results

In table 9, report the results of the base-case analysis. Specify whether costs are provided per treatment or per year. Adapt the table as necessary to suit the cost model. If appropriate, describe costs by health state.

Table 9 Base-case results

Cardiology model

	Mean discounted cost per patient using the technology (£)	**Mean discounted cost per patient using the comparator (Holter 24 + CER + Implantable) (£)**	**Difference in mean discounted cost per patient (£): technology vs comparator**
Technology cost	£264.09*	£42.85	£221.24
Aggregated Staff cost Administration cost Monitoring costs Consumables Follow-up	£167.24	£473.74	-£306.50
Adverse events	0	0	0
Total	£431.33	£516.59	-£84.76

** Note that a proportion of patients in the Zio XT Service arm of the model continue to receive monitoring with Holter 24, so the mean technology cost is less than the list price for the Zio XT Service*

Stroke model

	Mean discounted cost per patient using the technology (£)	**Mean discounted cost per patient using the comparator (Holter 24 + CER + Implantable) (£)**	**Difference in mean discounted cost per patient (£): technology vs comparator**
Technology cost	£294.75*	£209.64	£85.11
Aggregated Staff cost Administration cost Monitoring costs Consumables Follow-up	£87.94	£228.33	-£140.39
Adverse events	0	0	0
Total	£382.69	£437.97	-£55.28

** Note that a proportion of patients in the Zio XT Service arm of the model continue to receive monitoring with other devices, so the mean technology cost is less than the list price for the Zio XT Service*

Scenario analysis methods
If relevant, explain how scenario analyses were identified and done. Cross-reference your response to the decision problem in part 1, section 1 of the submission.

A single scenario analysis has been carried out, extrapolating the results of the Stroke model to incorporate consequential gains in terms of reduced cost of avoidable strokes. This has been fully described in section 2.3.

Describe the differences between the base case and each scenario analysis.

The three base case models evaluate process cost savings alone associated with the use of the Zio XT Service. In the case of the stroke model, there is a well-documented link between undiagnosed/untreated AF and recurrent stroke risk. At this time, there are no explicit data relating to Zio that documents this outcome. However, given the long-established and robust evidence base associated with AF-related stroke and anticoagulation, this exploratory scenario was carried out to evaluate the magnitude of this cost saving, based on extrapolation from diagnostic yield to stroke risk.

4.2 Scenario analyses results

In table 10 describe the results of any scenario analyses that were done. Adapt the table as necessary.

Table 10 Scenario analyses results

	Mean discounted cost per patient using the technology (£)	**Mean discounted cost per patient using the comparator* (£)**	**Difference in cost per patient (£)***
Stroke downstream model (total costs)	£1,256.15	£1,364.18	-£108.03
Combined stroke + stroke downstream model (total costs)	£1,638.84	£1,802.15	-£163.31

Negative values indicate a cost saving

*Assumes a 50:50 split between Holter and CER monitoring in comparator arm, as used in Stroke model.

4.3 Sensitivity analysis methods

Describe what kinds of sensitivity analyses were done. If no sensitivity analyses have been done, please explain why.

Deterministic sensitivity analysis was carried out based on all input parameters used in the model. Results were expressed as tornado diagrams. Full tabulation of results are presented in appendix B.

Summarise the variables used in the sensitivity analyses and provide a justification for them. This may be easier to present in a table (adapt as necessary).

There was no *a priori* reason to select a subset of variables to test in a sensitivity analysis. Given that the number of parameters in each model is relatively small, we therefore elected to include all variables in the analysis in order to avoid missing any associations. Estimates of variability were available for very few of the parameters used in the model. In order to avoid biasing the results, we therefore elected to apply a range of +/- 20% to all parameters. Details of the parameters evaluated are provided in tabular form in table 3 and section 2.3.

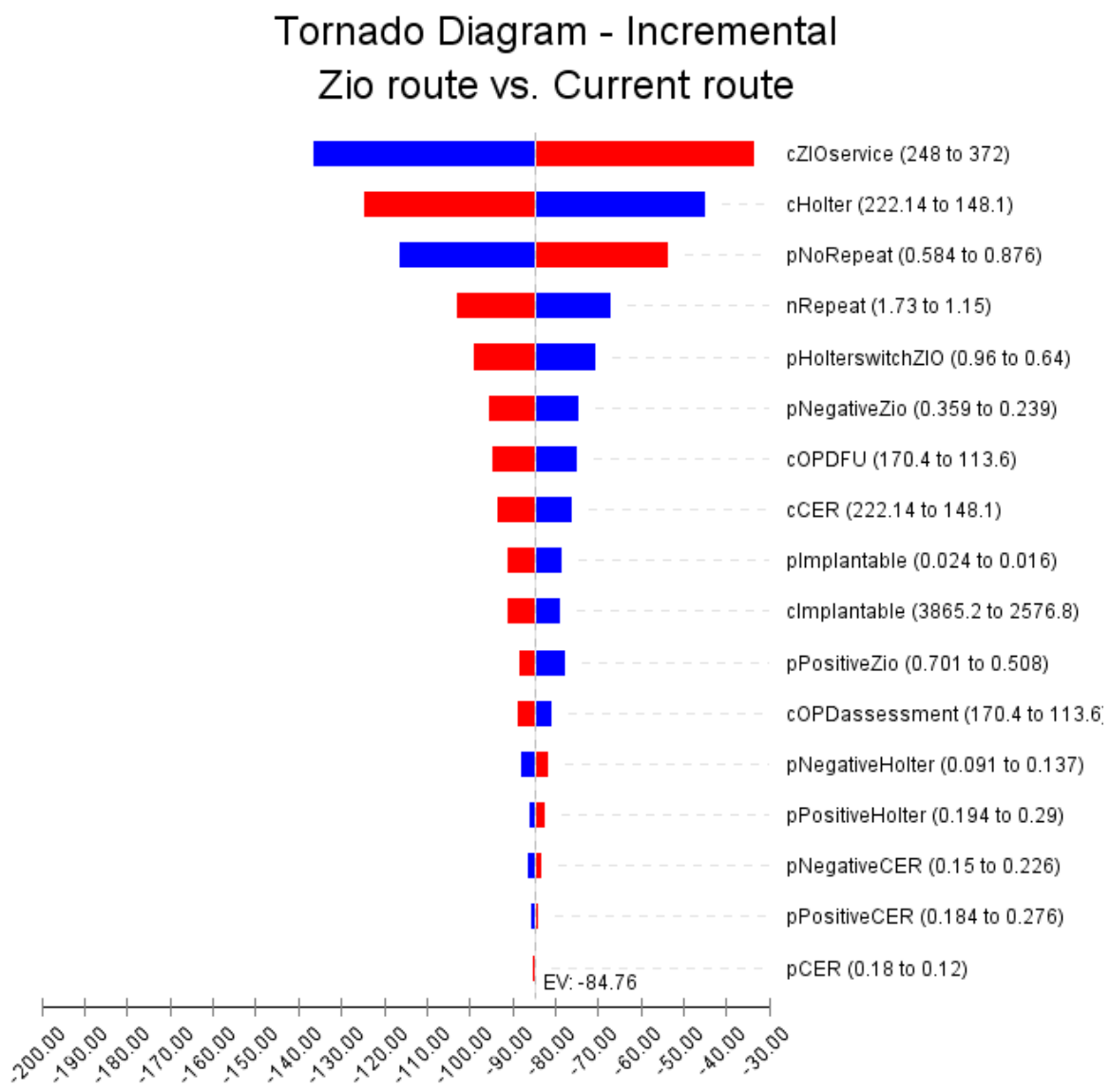
If any parameters or variables listed in table 3 were omitted from the sensitivity analysis, please explain why.

None omitted.

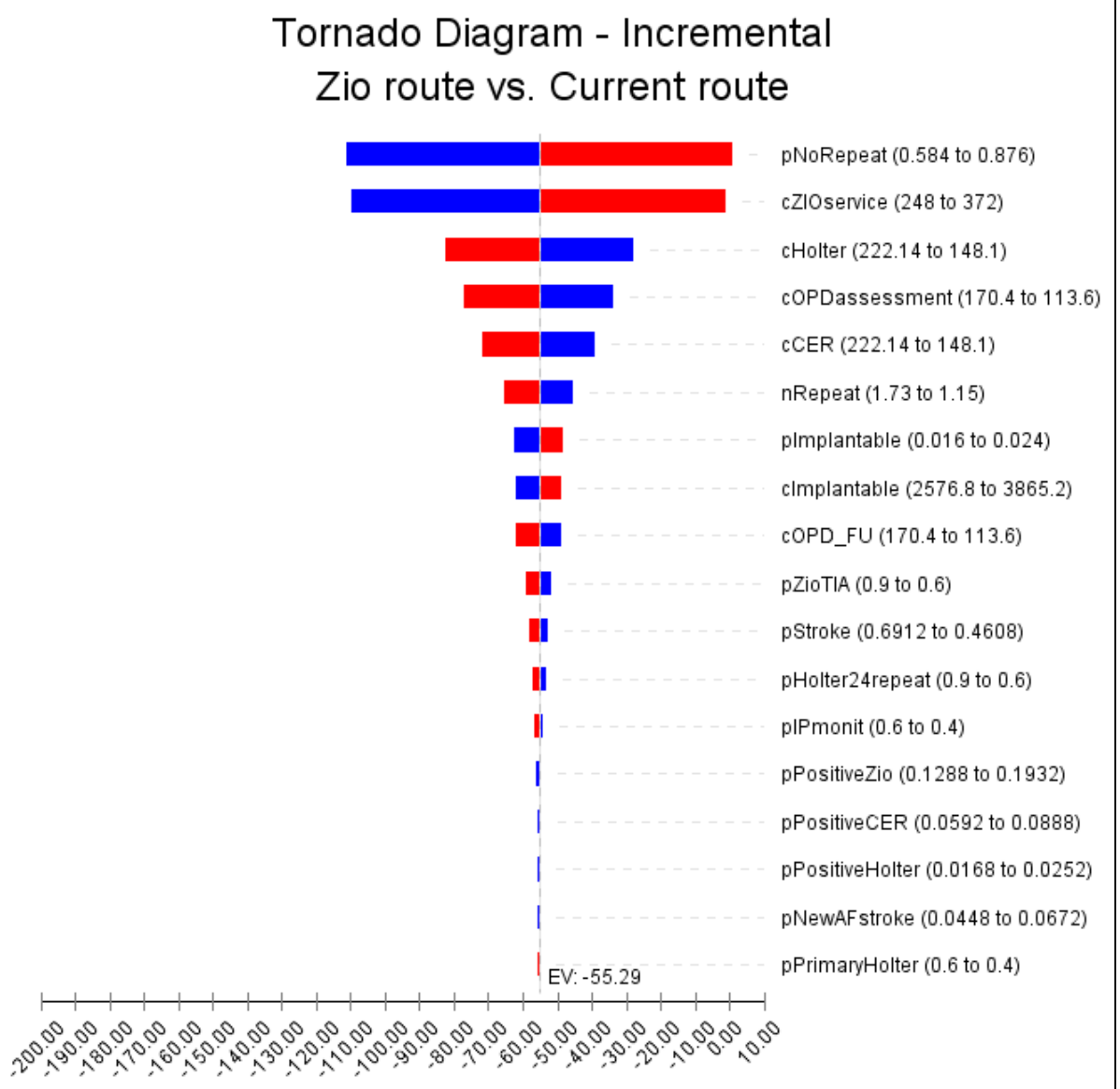
4.4 Sensitivity analyses results

Present the results of any sensitivity analyses using tornado plots when appropriate.

Cardiology model



Stroke Model



What were the main findings of each of the sensitivity analyses?

Cardiology model

All parameters were tested in a deterministic sensitivity analysis across a range of +/- 20%. The results showed savings in all cases.
The results were most sensitive to the following parameters:

- Costs of devices (Zio XT Service, Holter and CER). It was relatively insensitive to the cost of an implantable device as, although the unit cost is high, very few patients are actually fitted with this type of monitor
- Probability of not having a repeat test and the mean number of repeat tests in those having a repeat

The results were somewhat sensitive to:

- The proportion of patients in the Zio arm who were still tested with Holter. Notably, the more patients who were monitored with Holter, the lower the savings
- The cost of an outpatient attendance

The model was relatively insensitive to all other parameters

Stroke model

The results of the sensitivity analysis were qualitatively similar to the cardiology model.
The model was most sensitive to:

- The probability of not having a repeat test
- The cost of devices (Zio XT Service, Holter and CER)
- The cost of an outpatient attendance

The model was relatively insensitive to all other parameters

What are the main sources of uncertainty about the model's conclusions?

The costs associated with Holter and CER are subject to some degree of uncertainty. An assessment of NHS reference costs revealed a range of estimates, according to the specialty considered. These ranged from £141 - £328 for the service element (see section 3.2). In addition to this, the hardware acquisition and maintenance, together with consumables costs adds an extra £27.12. A plausible range for total costs is therefore £168 - £365 per use. Our central estimate of £185, which was based on a PLICS analysis, therefore falls at the low end of the range. It is likely, therefore, that our estimate of savings associated with Zio is conservative.

The second major potential source of uncertainty is the proportion of patients having a repeat test and the number of tests that are then undertaken. We are reasonably confident that our central estimates are not excessive, as they are based on an analysis of individual patient level HES Outpatient Procedure data covering the whole of NHS

England. However, the level of outpatient procedure coding at Trust level is not optimal and it is possible that those trusts that fail to record this data have different patient pathways from those that do record it. It is reassuring, however, that across the range tested for these parameters in the cardiology model, all results were cost saving, while for the Stroke model, at the highest end of the range cost neutrality was demonstrated. Another cost element that is a source of uncertainty is the cost of a cardiology outpatient attendance. This will tend to vary between trusts and will also depend on whether the clinic is consultant-led, nurse-led or is a multidisciplinary approach. We used data from NHS Reference costs to support our central estimate, but unfortunately the outpatient data from HES are insufficiently granular to weight the estimate by follow-up type for monitoring procedures. Having said that, it is noteworthy that none of the values tested in the sensitivity analyses yielded a result that suggested a reversal of the savings trend.

The final uncertainty relates to the model exploring the downstream benefits in terms of stroke outcomes:

Firstly we must recognise that there are no studies available for either Zio or the comparator technologies that quantify stroke outcomes. The analysis is therefore predicated on an extrapolation of AF diagnostic rates to the expected number of strokes over the subsequent 12 months. However, this evidence base is extremely robust and has formed the basis for anticoagulant treatment guidelines and GP quality outcomes assessment in the UK for many years. We therefore feel reasonably confident that our estimates of this effect are not unreasonably speculative.

A second factor also needs to be considered, in that the evidence base related to the relative stroke risk in anticoagulated vs untreated populations is necessarily many years old. Given the clear-cut evidence of benefit it is no longer ethical to carry out placebo controlled trials in this field. One uncontrollable factor is that the general risk management approach for secondary stroke prevention has changed substantially over the past few decades, so the baseline estimates of stroke risk are likely to be different from those in the published papers. However, there is no reason to believe that the relative benefit of anticoagulation will have changed, and as we are essentially only looking at this component of the management plan, the incremental differences based on the arrythmia monitoring strategy is unlikely to have been significantly impacted.

4.5 Miscellaneous results

Include any other relevant results here.

None

4.6 Validation

Describe the methods used to validate, cross-validate (for example with external evidence sources) and quality assure the model and resource use for the technology and comparator(s) pathways. Provide sources and cross-reference to evidence when appropriate.

The models have been shared with expert clinicians over the course of their development, to ensure that both care pathways and transition probabilities are a fair reflection of current NHS practice.

The completed models have been independently reviewed by the Health Economics department at Imperial College Health Partners, to ensure that the approach and modelling assumptions are reasonable and methodologically robust.

Give details of any clinical experts who were involved in validating the model, including names and contact details. Highlight any personal information as confidential.

[redacted]

5 Summary and interpretation of economic evidence

Describe the main findings from the economic evidence and cost model. Explain the potential cost savings and the reasons for them.

The two main models, together with the clinical outcomes scenario all demonstrate a consistent saving is accrued by the use of the Zio XT Service in the patient groups considered. These estimates are robust to a range of sensitivity analysis and suggest that a saving in process costs of around £55-£85 per patient referred for monitoring should be deliverable, compared to current standard care.

These savings are fundamentally attributable to the enhanced diagnostic yield associated with the Zio XT Service and the more rapid availability of results, which has the following impacts:

- Reduced requirement for repeat testing
- Reduced requirement for referral on for cardiology outpatient review
- Reduced risk of a recurrent event in the stroke population

In addition to the in-service savings, the reduced demand on conventional monitoring services may carry a further opportunity saving, freeing up expert professional time for more complex patients who may currently face delays in accessing specialist diagnostic services. Although our clinical advisors have all highlighted this as a potential benefit, we have been unable to source sufficient robust data to model this element, so our projected cost savings reported above do not include this component.

Briefly discuss the relevance of the evidence base to the scope.

The scope asked for the financial impact of three care pathways to be examined:

1. Adults referred for ambulatory ECG monitoring, who experience asymptomatic arrhythmia events
2. Adults referred for ambulatory ECG monitoring in primary care
3. Adults referred for ambulatory ECG monitoring in secondary care

We were able to identify sufficient evidence for scenario 1. This patient group is primarily represented by patients who have suffered a stroke or TIA, which was the subject of a specific controlled trial carried out within the UK [Kaura 2019]
We were unable to identify sufficiently reliable data to model a primary care direct referral pathway and were consequently unable to address this element of the scope
For the third scenario, we were able to draw on clinician advice to characterise the care pathway and used UK data relating to the use of Zio in this context to provide high quality information on diagnostic yield. Although direct comparative data for Zio versus the comparator technology were not available, there was a sufficient evidence base to provide good estimates of the corresponding figures for the comparators.

The two primary models presented are based entirely on process costs, as these were best supported by the available evidence base. We have further explored the potential impact of the new technology on clinical outcome costs within the stroke model –

specifically the effect on the probability and cost of an incident stroke in the first year following the index event.
There were no high quality primary clinical data available to populate this model for any of the technologies under consideration. In consequence, the basis of this model is an extrapolation from diagnostic yield data, using this to infer stroke risk. Whilst clearly this must be considered as an exploratory analysis only, it is not an unreasonable extrapolation, given the well-established and accepted evidential chain that quantitatively links the presence of atrial fibrillation to an increased stroke risk, and the use of anticoagulation in these patients to a reduction in this risk.

Although not explicitly defined as a comparator in the scope, the consideration of implantable loop recorders within our cost impact modelling was considered. Our clinical advice was that, owing to its interventional nature and high cost, this technology would not be considered to be a first-line comparator for either Zio, Holter or CER monitors. We therefore incorporated implantable devices in a 2nd/3rd line position within our care pathway models.

Briefly discuss if the results are consistent with the published literature. If they are not, explain why and justify why the results in the submission be favoured over those in the published literature.

The use of the Zio XT Service has been evaluated in three economic analyses. Although these offer supportive evidence that is consistent with our findings, none of these explicitly and completely address the detail of the current scope.

Chandratheva et al carried out a cost evaluation of four devices for the identification of AF in 80 patients who had experienced a TIA (Zio, 72 hour Holter, e-Patch – an extended 3 day Holter monitor and Apoplex – an in-clinic monitoring device [Chandratheva 2017]. The authors found that Zio was the lowest cost option of the devices tested. However, given that the study has only been published as an abstract and the comparator devices were not those evaluated in this submission, it can only be considered as supportive.

Ghosh et al compared the costs associated with the use of both Zio and Holter 24 hour monitoring in 30 patients with a minor stroke or TIA [Ghosh 2018]. All patients were monitored with both technologies. They found that the cost of the investigation plus follow up was £367 and £440 for a Holter and Zio respectively. Although the Zio system is more expensive in operational costs, it provided a more comprehensive follow up, and allowed timely investigation and management. Nearly half the patients attending the follow up clinic did not have Holter results because of administrative issues. The comparator and care pathway were relevant to the scope of the current submission but the data have only been published as an abstract, so it is not possible to assess whether the resource use captured was equivalent to those evaluated in our stroke model. Equally, the diagnostic yields quoted (1/30 and 0/30) were very low compared to other studies so, in the absence of a full publication, it is difficult to ascertain whether the population in this study were comparable to the group that we had modelled.

Finally, Kaura et al carried out an economic assessment derived from the results of the EPACS study, that compared Zio or Holter 24-hour monitoring in 116 patients with a minor stroke or TIA [Kaura 2019]. Although the 90 day follow-up period in the study precluded the collection of meaningful clinical follow-up data, the authors carried out a speculative exploration of the cost benefit of the Zio system. The authors concluded that Zio dominated Holter 24, in that there was a projected reduction in cost (£57,481 in year 1), with a reduction in stroke risk (10.8 fewer strokes), if the results of the study were to be extrapolated to the entire NHS trust. This is an important study, with the diagnostic yield data forming the basis of our Stroke Model. However, it needs to be borne in mind that the economic model is based on extrapolation from a number of literature-based assumptions, using a similar methodology to our own "Stroke Downstream" model. The results are consistent with our own in this regard, but the published paper did not separate out the process elements of the costing, so it is difficult to equate directly with our own Stroke Model.

In summary, the results of our analyses are qualitatively consistent with the existing published literature, although differences in study design and a limited amount of information for two of the three studies make a direct quantitative comparison difficult to carry out.

Describe if the cost analysis is relevant to all patient groups and NHS settings in England that could potentially use the technology as identified in the scope.

In line with the scope, the analysis is relevant to two distinct groups:

- Patients referred to cardiology for assessment of symptomatic palpitations and/or syncope
- Patients with a prior stroke or TIA being screened for undiagnosed intermittent AF

As discussed in the introduction to this submission, we have been unable to source sufficiently robust data to model a care pathway using either direct access or primary care delivered monitoring services. Whilst there is no *a priori* reason to suppose that the qualitative results for the use of Zio would be any different in this care context, further data collection and service evaluation will be required to clarify this option.

Briefly summarise the strengths and limitations of the cost analysis, and how these might affect the results.

The strengths of this analysis lie in:

- The availability of extensive use data from both the UK and elsewhere to support the enhanced diagnostic yield associated with the Zio XT Service
- A good evidence base to allow accurate estimation of the diagnostic performance of comparator technologies
- Robust evidence from NHS sources (HES, PLICS, NHS Reference Costs) to allow confidence in many of the model input parameters

Weaknesses may be identified in:

- A relative lack of large head-to-head comparisons of the Zio XT Service with comparator technologies
- A lack of long term clinical outcome studies for any of the technologies considered
- A reliance on clinician input for many of the transition probabilities related to the actions likely to be taken in response to a range of test scenarios

Each of these weaknesses has the potential to bias the results of our analysis, although the sensitivity analyses carried out show that this bias may flow in either direction. Overall, the magnitude of demonstrated savings is sufficiently large that only very major changes in input parameters are likely to change the qualitative conclusions of the analysis.

Detail any further analyses that could be done to improve the reliability of the results.

We would like to see work undertaken to better clarify patient flow patterns and resource use analysis across the primary/secondary care interface, in order to both validate and extend the generalisability of the results.

6 Resource impact analysis

The Resource Impact Team at NICE estimate the costs or savings (budget impact) associated with technologies so the NHS can plan for and implement guidance. In order to produce a resource impact report and template the Team requests the following information.

6.1 Population and uptake estimates

In table 11 provide estimates of the number of people who would be eligible to use your technology in years 1 to 5 and the expected uptake in each 5 years.

The number of patients currently undergoing cardiac rhythm monitoring is uncertain, as recording of outpatient procedures is not mandatory under PbR regulations. Hospital Episode Statistics for 2017-18 documents 271,007 outpatient attendances for rhythm monitoring (Procedure codes U19.1, U19.2, U19.3, U19.5, U19.6), so this can reasonably be regarded as a minimum estimate for current service use.

There are currently no English NHS trusts that routinely use the Zio XT Service, although some are using it in special circumstances, so we can effectively say that baseline usage of the system is zero.

All Adults (18 years or older) with suspected cardiac arrhythmia referred for ambulatory ECG monitoring are eligible for the Zio XT Service. NHS clinical experts have indicated that the Zio XT Service would be used in place of current monitoring modalities in people with symptomatic episodes more than 24 hours apart. Clinical experts have estimated that this would comprise at least 80% of patients (estimated 216,000 per year) currently undergoing ambulatory cardiac monitoring.

The future uptake and assumptions below are based on the arbitrary assumption that over the next five years, uptake of the Zio XT Service will rise to 45% of the estimated 216,000 at a fairly constant year-on-year rate. Uptake at this level assumes appropriate funding will be in place to enable and accelerate access to this service.

Table 11 Population and uptake estimates

	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of people eligible to use technology[1]	216,000	216,000	216,000	216,000	216,000
Cryptogenic stroke / TIA population (assumes 18% of eligible population[2])	38,880	38,880	38,880	38,880	38,880
Cardiology population (assumes 82% of eligible population[3])	177,120	177,120	177,120	177,120	177,120
1. Based on 80% of current number of patients per year 2. Based on Health Episode Statistics 2018/19; admissions for cerebral infarction 71,764 (clinical opinion assumes 30% are cryptogenic); admissions and outpatient attendances for transient ischaemic attack 28,578. Total estimated eligible cryptogenic stroke & TIA population = 50,107. As proportion of total patient population (270,000) = 18% 3. Assumes remaining 82% of patients are cardiology (after removing 18% for stroke/TIA)					
Uptake of technology	8% uptake	16% uptake	24% uptake	32% uptake	45% uptake
Cryptogenic stroke population (assumes 18% of eligible population)	3,110	6,221	9,331	12,442	17,496
Cardiology population (assumes 82% of eligible population)	14,170	28,339	42,509	56,678	79,704
Total uptake (stroke and cardiology population)	17,280	34,560	51,840	69,120	97,200

6.2 Sales

In table 12 provide estimates of the number of this technology you expect to sell in years 1 to 5 in the UK.

Table 12 Sales estimates

	Year 1	Year 2	Year 3	Year 4	Year 5
Sales of technology	17,280	34,560	51,840	69,120	97,200

6.3 Acquisition costs with and without VAT

In table 13 provide an estimate of the aggregate purchase costs of the technology and associated set-up and implementation costs across the NHS in each of the five years with and without VAT.

Table 13 Aggregate total costs

	Year 1	Year 2	Year 3	Year 4	Year 5
Purchase cost of technology excluding VAT	£5.36M	£10.71M	£16.07M	£21.43M	£30.13M
Purchase cost of technology including VAT	N/A	N/A	N/A	N/A	N/A
Other set-up and implementation costs	Nil	Nil	Nil	Nil	Nil
Total costs excluding VAT	£5.36M	£10.71M	£16.07M	£21.43M	£30.13M
Total costs including VAT	N/A	N/A	N/A	N/A	N/A

If the purchase cost used in table 13 does not use the list price and other charges advised in section 4.1, advise what unit prices are used and explain the differences.

N/A

7 References

Please include all references below using NICE's standard referencing style.

Ali, A.N., Howe, J., Abdel-Hafiz, A. (2015). "Cost of acute stroke care for patients with atrial fibrillation compared with those in sinus rhythm." Pharmacoeconomics 33(5): 511-520.

Anonymous (2017). "Long-Term Continuous Ambulatory ECG Monitors and External Cardiac Loop Recorders for Cardiac Arrhythmia: A Health Technology Assessment." Ont Health Technol Assess Ser 17(1): 1-56.

Balmelli N, Naegeli B, Bertel O. Diagnostic yield of automatic and patient-triggered ambulatory cardiac event recording in the evaluation of patients with palpitations, dizziness or syncope. Clin Cardiol 2003;173-6

Boggon, R., Lip, G.Y.H., Gallagher, A.M., et al. (2012). "Resource utilization and outcomes in patients with atrial fibrillation: a case control study." Appl Health Econ Health Policy 10(4): 249-259.

Burn J, Dennis M, Bamford J et al. Long term risk of recurrent stroke after a first ever stroke. Stroke 1994;24:333-7

Chandratheva, A., Pleming, J., Dados, A., et al. (2017). "New versus conventional non invasive cardiac monitoring for atrial fibrillation detection in TIA Clinic." European Stroke Journal **2**(1): 117.

Diamantopoulos, A., Sawyer, L.M., Lip, G.Y.H., et al. (2016). "Cost-effectiveness of an insertable cardiac monitor to detect atrial fibrillation in patients with cryptogenic stroke." Int J Stroke 11(3): 302-312.

EAFT (European Atrial Fibrillation Trial). Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. Lancet 1993;342:1255-62

Ghosh, M., Lochrie, N., Mahmood, S., et al. (2018). "Improving detection of atrial fibrillation after transient ischaemic attack and stroke." European Stroke Journal **3**(1): 228.

Giles M, Rothwell P. Substantial underestimation of the need for outpatient services for TIA and minor stroke. Age Aging 2007;36:676-80

Gladstone D, Spring M, Panzov V et al. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med 2014;370:2467-77

Halcox, J., Wareham, K., Cardew, A., et al. (2017) "Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation: the REHEARSE-AF Study". Circulation 136, 1784-1794 10.1161/CIRCULATIONAHA.117.030583.

Kaura, A., Sztriha, LO., Chan, F.K., et al. (2019). "Early prolonged ambulatory cardiac monitoring in stroke (EPACS): an open-label randomised controlled trial." Eur J Med Res **24**(1): 25.

Kinlay, S., Leitch, J.W., Neil, A., et al. (1996) "Cardiac event recorders yield more diagnoses and are more cost-effective than 48-hour Holter monitoring in patients with

palpitations. A controlled clinical trial". Annals of Internal Medicine 124, 16-20 10.7326/0003-4819-124-1_part_1-199601010-00003.

Levin, L.A., Husberg, M., Sobocinski, P.D., et al. (2014). "A cost-effectiveness analysis of screening for silent atrial fibrillation after ischaemic stroke." Europace 17(2): 207-214.

National Institute for Health and Care Excellence. (2017). Zio XT Service for detecting cardiac arrhythmias. Medtech innovation briefing [MIB101]. Available from: https://www.nice.org.uk/advice/mib101

National Institute for Health and Care Excellence. (2018). Reveal LINQ insertable cardiac monitor to detect atrial fibrillation after cryptogenic stroke. Medtech innovation briefing [MIB141]. Available from: https://www.nice.org.uk/advice/mib141

Quiroz, M., Wolff, C., Eggington, S. (2017). "Insertable cardiac monitor versus standard of care for detection of atrial fibrillation in patients following cryptogenic stroke: A Dutch cost-effectiveness analysis." Value in Health 20(9): A588.

Reed, M.J., Grubb, N.R., Lang, C.C., et al. (2019). "Multi-centre Randomised Controlled Trial of a Smartphone-based Event Recorder Alongside Standard Care Versus Standard Care for Patients Presenting to the Emergency Department with Palpitations and Pre-syncope: The IPED (Investigation of Palpitations in the ED) study." EClinicalMedicine 8:37-46.

Rinciog, C.I., Sawyer, L.M., Diamantopoulos, A., et al. (2019). "Cost-effectiveness of an insertable cardiac monitor in a high-risk population in the UK." Open Heart 6(1).

Rockx, M., Hoch, J.S., Klein, G.J., et al. (2005) "Is ambulatory monitoring for "community-acquired" syncope economically attractive? A cost-effectiveness analysis of a randomized trial of external loop recorders versus Holter monitoring". American Heart Journal 150, 1065 10.1016/j.ahj.2005.08.003.

Sanna T, Diener H-C, Passman R et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014;370:2478-86

SSNAP. Sentinel Stroke National Audit Programme (SSNAP). SSNAP Portfolio for April – June 2019 admissions and discharges. Available from: https://www.strokeaudit.org/results/Clinical-audit.aspx

Stewart, S., Murphy, N., Walker, A., et al. (2004). "Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK." Heart 90(3): 286-292.

Tsang J-P, Mohan S. Benefits of monitoring patients with mobile cardiac telemetry (MCT) compared with the Event or Holter Monitors. Medical Devices: Evidence and Research 2014;7:1-5

Xu X-M, Vestesson E, Paley L et al. The economic burden of stroke care in England Wales and Northern Ireland: using a national stroke register to estimate and report patient-level health economic outcomes in stroke. Eur Stroke J 2017;3:82-91

Yiin, G.S., Howard, D.P.J., Paul, N.L.M., et al. (2014). "Age-specific incidence, outcome, cost, and projected future burden of atrial fibrillation-related embolic vascular events: a population-based study." Circulation 130(15): 1236-1244.

8 Appendices

Appendix A1: Structured abstracts

Structured abstracts for unpublished studies

Study title and authors A. Chandratheva, J. Pleming, A. Dados and R. Simister (2017). NEW VERSUS CONVENTIONAL NON-INVASIVE CARDIAC MONITORING FOR ATRIAL FIBRILLATION DETECTION IN TIA CLINIC. Presented at the European Stroke Organisation conference 2017
Introduction New non-invasive cardiac monitoring devices are available for atrial fibrillation (AF) detection.
Objectives We aimed to compare these to current Holter monitoring.
Methods Setting: University College London hospitals, daily TIA clinic. Consecutive TIA patients from September 2015. After initial brain and vascular imaging, aetiology remained unknown or suggestive of cardio embolism had: 72-hour Holter monitor reviewed by cardiac technician, 14- day Zio Patch, 3-day E-patch both reported by computerized algorithm and reviewed by cardiac technician. In clinic monitoring using Apoplex AF monitor reported by computerized algorithm.
Results Of 80 patients, 48(60%) male, mean age 61.4 years (SD14.4), 9(11.3%) >80yrs. Twenty had 72 hour Holter (£569), 20 Zio Patch (£300/ patch), 20, 3 day E-patch (£600/unit, £16/electrode, £35/report), 20 had in-clinic monitoring using Apoplex (£650/unit, £20/report). Average time to device placement from clinic (days): Holter 54, Zio Patch 0.2, E-patch 1, Apoplex 1. Time to reporting from device placement (days): Holter 13.4, Zio Patch 15.6, E-patch 9.5, Apoplex 1.2. Time to reporting from clinic date in days was significantly shorter for both Zio Patch 15.0 (SD 4.6) and E-Patch 11 (SD8.9) vs Holter 64.3(SD26.9), p<0.01. Artefact; Zio Patch 1.5%, E-patch 12.8% not routinely reported by Holter or Apoplex. AF was detected in four patients, ZIO:1(5%), E-patch:2(10%), Apoplex:1(5%), Holter 0. Other significant arrhythmias were recorded by all devices except Apoplex, 9 brief VT (Holter:1, Zio:8) and 15 SVT (Holter:4, Zio:11), no significant pauses detected.
Conclusion New patch devices provide an immediate, cost-effective and well tolerated means of cardiac monitoring with little artefact compared to standard Holter monitoring and significantly shorter delays to reporting.

Study title and authors M. Ghosh, N. Lochrie, S. Mahmood, E. Lawrence and Y.Y.K. Kee. (2018). IMPROVING DETECTION OF ATRIAL FIBRILLATION AFTER TRANSIENT ISCHAEMIC ATTACK AND STROKE. Presented at the European Stroke Organisation conference 2018
Introduction Atrial fibrillation (AF) is a known risk factor for embolic stroke. Improved detection of AF reduces the risk of future strokes. Studies have shown that AF detection rates are highest close to the event, underlining the need for prompt diagnosis. Newer Adhesive Ambulatory ECG patch devices (AAECG) may offer alternatives to traditional cardiac telemetry.
Objectives This pragmatic study aimed to compare AAECG (Zio XT device) against traditional 24 hr ambulatory monitoring.
Methods Patients with minor stroke or TIA were recruited from the TIA Clinic at Croydon University Hospital. Patients had the AAECG applied in clinic and a 24-hour Holter ordered. Patients were subsequently followed up in clinic to review results.

Results 30 patients were recruited. AF was detected in 1 patient using the AAECG and none on the Holter. Patients waited a median of 59 days for the Holter (range 14-102days). Investigations were completed for 29 patients from the AAECG compared to 18 from Holter. All AAECG reports were available in clinic compared to 6 from the Holter. Cost of the investigation plus follow up was £367 and £440 for a Holter and an AAECG respectively.
Conclusion Although the Zio system is more expensive in operational costs, it provided a more comprehensive follow up, and allowed timely investigation and management. Nearly half the patients attending the follow up clinic did not have Holter results because of administrative issues. The use of AAECG will allow services to offer “one-stop” TIA clinics leading to improved patient care and experience.

Study title and authors M. Quiroz, C. Wolff, and S. Eggington (2017). INSERTABLE CARDIAC MONITOR VERSUS STANDARD OF CARE FOR DETECTION OF ATRIAL FIBRILLATION IN PATIENTS FOLLOWING CRYPTOGENIC STROKE: A DUTCH COST-EFFECTIVENESS ANALYSIS.
Introduction Documentation of atrial fibrillation (AF) is required to initiate oral anticoagulation therapy for recurrent stroke prevention. The cause of ischemic stroke remains uncertain despite a complete diagnostic evaluation in 20-40% of cases (cryptogenic stroke), and conventional standard of care (SoC) often fails to diagnose AF. An insertable cardiac monitor (ICM) is a diagnostic device which has been shown to improve detection of AF in this patient population.
Objectives We evaluated the cost-effectiveness of ICM versus SoC, in patients with a cryptogenic stroke, from a Dutch payer perspective.
Methods A lifetime Markov model was developed to assign patients to health states according to the presence and detection of AF, the occurrence of cerebrovascular and bleeding events, and death. Utilities and costs were applied to each state according to occurrence of stroke, AF diagnosis and drug therapy use. The model used 3-month cycle length for state transitions and a lifetime horizon. Costs and QALYs were discounted at 4% and 1.5% per year, respectively. Probabilistic sensitivity analysis was undertaken to explore the effect of parameter uncertainty.
Results In the base-case analysis, the model predicted an incremental cost-effectiveness ratio (ICER) of €24,715 per QALY gained. Amongst the CHADS2 sub-group analyses, the ICER ranged from €22,011 (CHADS2 score 4 to 6) to €29,795 CHADS2 score 2). Probabilistic sensitivity analysis suggested that ICM had a probability of 91% of being cost-effective at a threshold of €80,000 per QALY gained.
Conclusion The results suggest that ICM is a cost-effective intervention in patients following cryptogenic stroke, leading to improved health outcomes at acceptable additional cost via improved detection of AF and subsequent strokes avoided. The ICER was within the cost-effectiveness threshold used in the Netherlands and the probabilistic analysis showed a high probability of cost-effectiveness, indicating that the model is robust to variability in the input parameters.

Appendix A2: Unit Costs and Results

Summary table of unit costs and results not reported in the main section.

Data source	Author, year and location	Patient population and setting	Intervention and comparator	Unit costs and Resource use	Outcomes and results
Prospective data collection from patients	Ali 2015, UK	213 acute stroke patents, admitted to hospital	None	Mean cost of ischaemic stroke with AF = £9,083 (SD = £7,381) Mean cost of ischaemic stroke with no AF = £5,729 (SD = £6,071), p<0.001 Mean cost of haemorrhagic stroke with AF = £7,058 (SD = £6,494) Mean cost of haemorrhagic stroke with no AF = £8,790 (SD = £7,054), p=0.764 Presence of AF independently increased acute care costs of stroke by £2,173 (95%CI £91 to 4,255), p<0.041 Mean (SD) unadjusted costs, per patient, of acute care for ischaemic stroke with atrial fibrillation; Hospital admission = £348 (204) Radiology and cardiology = £347 (288) Pathology = £83 (66) Feed = £11 (31) Fluids = £42 (64) Blood products = £3 (28) Medications = £207 (287) Ward consumables = £40 (188) Bed days = £7,839 (6,915) Therapist rehabilitation = £134 (175) Specialist referrals and procedures = £37 (80)	Overall mean cost of ischaemic stroke per patient was £9,084 in those with AF compared with £5,729 in those with no AF. The difference in costs of haemorrhagic stroke was not significantly different in those with or without AF, £7,058 vs. £8,790, p = 0.764. The presence of AF independently increased acute care costs of ischaemic stroke by £2,173 (95%CI £91 to £4,255, p=0.041), with a history of congestive cardiac failure and NIHSS stroke score the only other independent predictors of costs. The increase in costs with AF was significantly higher than for patients in sinus rhythm for hospital admissions and bed-days, pathology tests, feeds, fluids, medications, ward consumables, therapist rehabilitation and specialist referrals and procedures

				Total direct inpatient costs = £9,083 (7,381) Health service unit costs Emergency ambulance: £230 GP visit: £36 Emergency department attendance: £114 Haematology: £3 Biochemistry: £1 Immunology: £8 Microbiology/virology: £8 Histopathology: £31 CT head: £84 MRI head: £150 MR angiogram: £163 CT 2 areas: £102 CT 3 areas: £141 X-ray one area: £26 Carotid ultrasound: £64 Abdominal ultrasound: £64 ECG: £36 ECHO: £62 24- and 48-h Holter monitor: £112 Transoesophageal ECHO: £281 Upper GI endoscopy: £436 Lower GI endoscopy: £572 Insertion gastrostomy tube: £810 ERCP: £998 Carotid stent insertion: £2350 Carotid endarterectomy: £3923 Unit of blood: £125 Unit of platelets: £280 1 L crystalloids + IV line: £6 0.5 L crystalloids + IV line: £4	

				1 L colloids + IV line: £11 0.5 L colloids + IV line: £7 Peripheral cannula: £2 Urinary catheter: £5 Nasogastric tube: £7 Stroke unit: £363/ bed-day Rehabilitation facility: £228/ bed-day General medical ward: £235/ bed-day Physiotherapy: £23.25 Occupational therapy: £23.25 Speech and language therapy: £23.25 Dietician: £23 Psychology: £45 Healthcare assistant: £16.5	
General practice research database (GPRD).	Boggon 2012, UK	15373 adults aged over 18 with AF	None	Resource utilisation for all AF patients in study, n=15,373 Number of drug substances prescribed in preceding 6 months [n patients (%)]; 0 drug substances: 390 (2.5) 1–5 drug substances: 4117 (26.8) 6–10 drug substances: 6516 (42.4) 11–15 drug substances: 3116 (20.3) 16+ drug substances: 1234 (8.0) Mean (standard deviation) number of contacts, referrals, tests and hospitalizations per year, all AF: Surgery: 9.9 (10.2) Practice clinic: 1.9 (4.9) House visits: 1.1 (3.7) Administration/letters: 31.3 (19.9) Phone contacts: 2.6 (5.5) Specialist referrals: 0.8 (1.5) Laboratory tests (excluding INR): 36.9 (48.1)	Patients with AF had significantly more drug prescriptions than controls in the past 6 months and had significantly higher numbers of contacts, referrals, tests and hospitalisations per year than controls. All-cause mortality rate was 107.6/1,000 person-years with AF compared with 35.0/1,000 person-years in the control group, a relative risk of 3.11 (95%CI 2.92 to 3.31).

				Hospitalizations: 1.0 (3.9) Hospitalizations - Due to circulatory system: 0.2 (1.0) Days in hospital: 6.3 (26.0) Days in hospital - Due to circulatory system: 1.7 (12.2) AF patients with low NICE stroke risk score, n=1273 Number of drug substances prescribed in preceding 6 months [n patients (%)]; 0 drug substances: 224 (17.6) 1–5 drug substances: 783 (61.5) 6–10 drug substances: 213 (16.7) 11–15 drug substances: 35 (2.7) 16+ drug substances: 18 (1.4) Mean (standard deviation) number of contacts, referrals, tests and hospitalizations per year: Surgery: 6.3 (7.6) Practice clinic: 1.0 (3.3) House visits: 0.1 (1.0) Administration/letters: 16.9 (15.4) Phone contacts: 1.6 (4.6) Specialist referrals: 0.6 (1.2) Laboratory tests (excluding INR): 15.2 (35.6) Hospitalizations: 0.4 (1.4) Hospitalizations - Due to circulatory system: 0.2 (0.7) Days in hospital: 0.8 (7.9) Days in hospital - Due to circulatory system: 0.3 (2.2)	

				AF patients with moderate NICE stroke risk score, n=4135 Number of drug substances prescribed in preceding 6 months [n patients (%)] 0 drug substances: 83 (2.0) 1–5 drug substances: 1503 (36.3) 6–10 drug substances: 1747 (42.2) 11–15 drug substances: 603 (14.6) 16+ drug substances: 199 (4.8) Mean (standard deviation) number of contacts, referrals, tests and hospitalizations per year: Surgery: 9.3 (9.2) Practice clinic: 1.7 (4.2) House visits: 0.6 (2.6) Administration/letters: 27.8 (17.6) Phone contacts: 2.1 (4.6) Specialist referrals: 0.7 (1.4) Laboratory tests (excluding INR): 32.4 (43.8) Hospitalizations: 0.9 (5.3) Hospitalizations - Due to circulatory system: 0.2 (0.8) Days in hospital: 3.7 (18.2) Days in hospital - Due to circulatory system: 0.6 (6.0) AF patients with high NICE stroke risk score, n=9965 Number of drug substances prescribed in preceding 6 months [n patients (%)]; 0 drug substances: 83 (0.8) 1–5 drug substances: 1831 (18.4) 6–10 drug substances: 4556 (45.7)	

				11–15 drug substances: 2478 (24.9) 16+ drug substances: 1017 (10.2) Mean (standard deviation) number of contacts, referrals, tests and hospitalizations per year: Surgery: 10.6 (10.7) Practice clinic: 2.0 (5.3) House visits: 1.4 (4.2) Administration/letters: 34.6 (20.2) Phone contacts: 3.0 (5.9) Specialist referrals: 0.8 (1.6) Laboratory tests (excluding INR): 41.6 (50.2) Hospitalizations: 1.1 (3.3) Hospitalizations - Due to circulatory system: 0.3 (1.2) Days in hospital: 8.0 (29.8) Days in hospital - Due to circulatory system: 2.3 (14.6)	
GPRD, Information and statistics division of NHS Scotland, Intercontinental Medical Statistics Ltd, published literature.	Stewart 2004, UK	All registered patients with AF in the UK	None	Projected unit costs for 2000: estimated 601,149 people with AF General practitioner consultations Clinic visit: £22 Domiciliary visit: £59 General practitioner referred OPD consultations Cardiology review: £120 Anticoagulation visits Clinic visit: £19 International normalised ratio check: £7 Hospital costs (per diem) Geriatric unit: £127 General medical unit: £220 Intensive care unit: £1385	Total NHS costs in 1995 were £243.9 million and this was estimated to increase to £459.0 million in 2000, or £1307.4 million if nursing home care and admissions where AF was a secondary diagnosis are included. Of this total, 50% of the costs were for hospital admissions, 20% for drug treatments, 13% for GP visits, 12% for GP OPD referrals and 6% for post-discharge OPD visits.

				Post-discharge OPD consultations Cardiology review: £120 General medical review: £84 Post-discharge nursing home care Residential care (per week): £332 Estimated cost (millions) for care of all 601,149 people with AF in 2000 Cost of prescriptions for atrial fibrillation in the UK by drug class and % prescribed: Cardiac glycosides (60% prescribed): £1.99m Aspirin (50% prescribed): £1.76m Warfarin (30% prescribed): £5.4m Antiarrhythmics (25% prescribed): £15.75m Total: £24.9m Hospital care: Primary admissions: £271.6m Post-discharge OPD visits: £31.7m Hospitalisations with secondary diagnosis of AF: £726.6m Community care: GP consultations: £49.8m GP referred OPD visits: £36.4m Drug prescriptions and anticoagulant clinics: £69.5m Long-term nursing home care: £111.7m Total direct cost of AF (excluding secondary admissions and nursing home costs): £459.0 million Indirect costs in 1995:	

				Cost of long-term long term associated residential care for men: £18.9 million Cost of long-term long term associated residential care for women: £27.5 million	
Hospital records, ONS predictions	Yiin 2014, UK	454 patients with AF-related events from 2002 to 2012	None	Mean AF-related ischaemic stroke costs (190 incidents in the first 5 years): Hospital costs = £12,417 (SD = 14,759) Long-term costs = £10,007 (SD = 35,034) Total care costs for ischemic stroke = £22,423 (SD = 41,802) Total costs in patient <80 years = £19,603 (35,676) Total costs in patient aged 80+ years = £24,345 (45,561) Mean systemic emboli costs (32 incidents in the first 5 years): Hospital/total costs: all patients = £13,720 (SD = 21,593) Total costs in patient <80 years = £13,969 (19,905) Total costs in patient aged 80+ years = £13,606 (22,769) Ischaemic stroke costs in patients with known AF (126 incidents in the first 5 years): Hospital costs: mean = £12,042 (SD = 14,920) Long-term costs: mean = £11,303 (SD = 37,778)	Mean total care costs of AF-related ischaemic stroke at 2008-09 costs were £22,423, of which £12,417 was due to hospital care and £10,007 was due to long-term institutionalisation. Mean costs were higher in patients aged 80 years and older compared with younger patients. Mean hospital and total costs of systemic emboli were £13,720 and were slightly higher in the older age-group. By 2050, the estimated care costs, at 2008 prices, of AF-related incident ischaemic stroke would be £1.7 billion, and £221 million for systemic emboli. AF places a costly burden on the NHS in the UK and costs associated with the disease are set to increase over time.

				Total care costs: mean = £23,345 (SD = 44,456) Total costs in patient <80 years = £21,593 (40,822) Total costs in patient aged 80+ years = £24,659 (47,237) Systemic emboli in patients with known AF (31 incidents in the first 5 years): Hospital/total costs: mean = £13,634 (SD = 21,944) Total costs in patient <80 years = £13,702 (21,094) Total costs in patient aged 80+ years = £13,606 (22,769) Estimated total costs for UK in 2050 (at 2008 costs) AF-related ischaemic stroke = £1.7 billion AF-related systemic emboli = £221 million	
Not reported	Ghosh 2018, UK	Patients with minor stroke or TIA at a UK hospital	Zio patch and 24-hour Holter	Cost of the investigation plus follow-up: Holter = £367 Zio XT = £440	Zio monitoring is more costly than 24-hour Holter monitoring but did prevent a time delay that was seen with the Holter monitor (median 59 days till monitoring). Zio is more expensive in operational costs but provides a more comprehensive follow up and timely investigation and management compared to Holter; nearly half of Holter monitor patients did not get a result.
Not reported	Chandratheva 2017, UK	80 patients with TIA at a UK hospital	Zio patch, 3-day e-patch, 72-hour Holter	72-hour Holter = £569 Zio Patch = £300 per patch 3-day E-patch = £600 per unit, £16 per electrode, £35 per report	The costs of each device were cheapest for the Zio patch (£300, compared with £569 for the 72-hour Holter, £651 for the 30day E-patch and £670 for 9in-clinic monitoring.)

				In-clinic monitoring using Apoplex = £650 per unit, £20 per report	The Zio patch provided the cheapest form of monitoring, followed by 72-hour Holter. Time from clinic to device placement was lowest with the Zio patch and highest with 72-hour Holter. Time to reporting after device placement was not significantly different between Zio and Holter but was lower in the E-patch and Apoplex. Patch devices provide an immediate and cost-effective alternative to standard 72-hour Holter monitoring.
Not reported	NICE MIB141, 2018, UK	Not reported	Reveal LINQ	Cost of reveal LINQ with mycarelink patient monitor: £1800 (ex VAT) Follow up costs; 2 per year over 3 years: £474 Estimated daily cost over 3 years of continuous monitoring: £3.05 Cost of implant + consumables: £96 Cost of explant +consumables: £889 Electrocardiogram monitoring or stress testing: £122 outpatient tariff, £369 day case Cost for implanting loop recorder with critical care score 3+: £3982 Cost for implanting loop recorder with critical care score 0 to 2: £3878	The costs of the LINQ are higher than for standard ECG monitoring or stress testing, but these costs may be offset if its use leads to a greater detection of AF and initiation of preventive therapy. Costs are also lower if the device can be fitted outside a catheter laboratory. Initial costs of this device are higher compared to standard care but can be offset by an increased detection rate and preventative therapy.
Not reported	NICE MIB101, 2017, UK	Not reported	Zio XT Service	£800 per unit, data analysis and report for Zio XT Service. 24 hr Holter+ result interpretation: £95.42 without overheads (staff, heating, computer use) 24 hr Holter + result interpretation: £118.60 with overheads	The outright cost of a Zio patch is lower than a Holter monitor, but per patient costs are higher. Per patient costs using Zio are higher than with 24hr Holter. These costs may be offset if the Zio patch leads to more accurate

				24hr Holter + no results: £39.17 without overheads 24hr Holter+ no results: £48.69 with overheads Reusable Holter monitor: £1632.14	diagnosis and better treatment of arrhythmias.
CRYSTAL-AF trial data	Diamantopoulos 2016, UK	Hypothetical cohort of CS or TIA patients	None	Deterministic analysis comparing ICM to SoC over patient's lifetime showed an incremental cost of £2587. Cost savings were generated from reduction in stroke-related and post-stroke related costs (ICM: £3958, SoC: £4387). Total costs over patient lifetime: Deterministic analysis: SoC: £17045 ICM: £19631 Difference: £2587 Probabilistic analysis: Soc: £17951 (13874 to 23348) ICM: £20525 (16640 to £25744) Difference: £2574 (1529 to 3878) Total costs by CHADS2 score CHADS2 score 2: SoC= £17204, ICM=£20023 CHADS2 score 3: SoC= £17431, ICM=£19940 CHADS2 score 4, 5 or 6: SoC= 13444, ICM=£15911	ICER (£/QALY) SoC vs ICM by CHADS2 score: CHADS2 score 2: £23355 CHADS2 score 3: £17950 CHADS2 score 4, 5 or 6: £13621 Reduction of 40 strokes/1,000 patients with ICM vs SoC. The probabilities that the ICM strategy would be cost-effective under thresholds of £20,000 and £30,000 per QALY were 63.4% and 81%, respectively. The comparison of the ICM and SoC strategies showed an estimated ICER of £17,175 per QALY gained, making the ICM cost-effective. The ICER increased when we considered patients with a CHADS2 score of 2, compared to the base-case analysis (£23,355 vs. £17,175). CHADS2 scores 4–6 decreased the ICER to £13,621 per QALY gained.

					Monitoring with an ICM was associated with fewer recurrent strokes in the patient's lifetime and increased QALYs compared to SoC (7.37 vs 7.22). Due to the reduction in recurrent strokes, costs related to stroke were reduced in the ICM model but remained higher overall than standard care (£19631 vs £17045). The ICER was £17175 per QALY gained, compared to SoC in the base case scenario. This figure is below the established QALY willingness to pay threshold and so is deemed cost effective. If warfarin was used instead of non-vitamin-k-oral-anticoagulants, the ICER was £13296 per QALY instead Sensitivity analysis: Replaced NOAC with warfarin showed an ICER of £13296 per QALY. Deterministic analysis cost over lifetime: SoC: £17045 ICM: £19631 Difference: £2587 Probabilistic analysis cost over lifetime: Soc: £17951 (13874 to 23348) ICM: £20525 (16640 to £25744) Difference: £2574 (1529 to 3878) ICM monitoring was associated with fewer recurrent strokes than with SoC and increased QALYs (7.37 vs 7.22). Reduction

					in stroke related costs were reduced in the ICM model, but overall costs remained higher vs SoC (£19631 vs £17045).
REVEAL-AF clinical trial data	Rinciog 2019, UK	Patients from the REVEAL AF trial	ICM vs SoC	ICM monitoring had higher initial costs compared with SoC; it was also associated with slightly higher health state and bleed-related costs. By reducing the rates of IS events, use of ICMs generated cost-savings both from IS event costs as well as post-stroke health state costs (total stroke-related costs for ICM were £3783 versus £4270 for SoC). **Total Costs** Base case analysis: SOC= £11936, ICM=£13360 CHADS2 score 2: SOC=£10654, ICM: £12332 CHADS2 score 3: SOC=£12130, ICM=£13591 CHADS2 score 4 5 or 6: SOC: £11629, ICM=£13070 Time horizon 3 years: SOC=£2257, ICM=£4142 Time horizon 5 years: SOC = £3966, ICM=£5669 Time horizon 10 years: SOC= £7969, ICM=£9363 Time horizon 25 years: SOC= £11923, ICM=£13345 Subgroup analyses also available for treatment differences in supplementary data sheet**	**Base case results** ICER = £7,140/QALY gained for ICM vs SoC, 4.8 fewer strokes per 100 population. The total cost of ICM was higher than SoC (£13360 vs £11936). ICM generated more QALYs than SoC (6.5 vs 6.3) and the ICER was £7140/QALY gained, which is below the £20000/QALY threshold suggesting ICM is cost effective. Total stroke related costs were £3783 for ICM vs £4270 for SoC as more strokes were prevented with ICM than SoC. The number of ICMs needed to prevent one stroke was 21, and to prevent a major bleed is 37. In the probabilistic sensitivity analyses, ICM were cost effective in 77.4% of the simulations. The base case deterministic analyses found that ICM provided a benefit over SoC of 0.1994 QALYs at an incremental cost of £1424 across a patient's lifetime. Total stroke related costs were £3783 for ICM vs £4270 for SoC as more strokes were prevented with ICM than SoC.

					The number of ICMs needed to prevent one stroke was 21, and to prevent a major bleed is 37.
Data from a clinical trial (Sivakumaran, 2003).	Rockx 2005, Canada	100 patients referred for ambulatory monitoring with syncope or presyncope.	External loop recorder vs Holter monitor	Comparison of costs of pre enrolment testing, US$ ECG: Holter= 20.57 ± 28.89, Loop= 21 ± 3.10 (p=0.29) Tilt: Holter 15.62 ± 39.57, Loop= 13.94 ± 37.71 (p=0.59) Previous Holter: Holter=60.20 ± 85.99, loop=88.46 ± 91.22 (p=0.057) Echocardiography: Holter=80.46 ±110.02, loop=60.47 ± 101.68 (p=0.83) CXR: Holter=0 ±0, loop= 2.13 ±6.38 Blood work: Holter=5.45 ±4.80, loop=5.48 ±4.80 EEG: Holter= 22.74 ±32.48, loop=12.53 ±26.69 CT or MRI head: Holter=108.09 ± 209.60, loop=110.82 ±198.75 Carotid doppler: Holter=16.13 ±55.85, loop= 12.60 ±49.82 Stress test: Holter=4.28 ±21.40, loop=6.68 ±26.44 Family physician initial cost: Holter=28.26 ±21.99, loop=33.09 ±20.09 Family physician follow up: Holter= 53.63 ±177.02, loop=50.79 ±112.51 Consultant: Holter=94.78 ±131.45, loop=161.61 ±298.36 Emergency room visit: Holter=93.96 ±146.46, loop=101.71 ±100.96 Total: Holter= 467.91 ±426.09, loop=476.78 ±366.92	The loop recorder costs $533.56 compared to $177.64 for the Holter monitor, but cost of diagnosis in the two groups was similar (Holter= $745, loop=$843). ICER for Loop vs Holter = $901.74 per extra successful diagnosis. After enrolment, 63% of patients in the loop recorder group had symptom recurrence compared to 24% in the Holter group (p=<0.0001). If patients received Holter monitoring followed by loop recorder, the overall cost ($481+/-267) was lower than if they received the devices the other way round ($551 +/-$83), but had a lower diagnostic yield (49% vs 63%), and an overall higher cost of diagnosis ($982 vs $871, p=0.08). Analyses showed that 90% of cost effectiveness ratios were less than $1250.

Systematic review of economic studies, Ontario Health Insurance Plan for claims relating to LCEM or ECLR use.	Anon 2017, Canada	Patients with symptoms of, or suspected arrythmia	Long term continuous monitor and external loop recorder	Unit costs of long-term ambulatory ECG tests: LCEM 3-13 days: Technical component-recording: $71.65 Technical component- screening: $98.10 Professional component: $95.85 Total=$265.60 LCEM >14 Days: Technical component-recording: $112.65 Technical component- screening: $164 Professional component: $122.25 Total=$398.90 ECLR: Technical component: $168.45 Professional portion: $122.25 Total: $290.70	Results for base case analysis (total costs and net budget impact) Current state (constant proportions of ECLR (56%) and LCEM (44%): 2016= $29.1M 2017= $31.42M 2018= $33.74M 2019= $36.05M 2020= $38.37M Increase in LCEM tests along the 2011-2014 trend: 2016= $29.23M 2017= $31.61 M 2018= $33.99M 2019= $36.36M 2020= $38.74M Net budget impact: 2016= $0.13M 2017= $0.19M 2018= $0.25M 2019= $0.31M 2020= $0.37M It was estimated that the total cost of funding long-term ambulatory ECG testing in Ontario in the current state would range from $29.1 million in 2016 to $38.4 million in 2020. The net budget impact of increasing the use of LTCM and decreasing the use of ELCR would range from $0.13million in 2016 to $0.37 million in 2020.

					The budget impact analysis showed that the use of LTCM grew steadily over time since the introduction in 2006, and faster since 2011 when 14-day monitoring became publicly funded, causing a corresponding decline in ELCR. Analysis suggested that if the trends continued, publicly funding both devices will result in addition costs ranging between $130000 to $370000 per year over the next 5 years. In the base case it was estimated that the total cost of funding long-term ambulatory ECG testing in Ontario in the current state would range from $29.1 million in 2016 to $38.4 million in 2020. The net budget impact of increasing use of long-term continuous monitors and decreasing use of external loop recorders, as compared with the current state, would range from $0.13 million in 2016 to $0.37 million in 2020. Sensitivity analyses show that the greatest cost savings occur in a scenario where only tests via ELCR are publicly funded.
Efficacy data from published trial (Sobicinski et al., 2012).	Levin 2014, Sweden	249 patients with a recent IS or TIA	Zenicor-EKG handheld ECG vs SoC	Total Costs: No screening: € 4,020,000 Holter: € 4,255,000 Handheld ECG: € 3,976,000 (dominant)	The implementation of the handheld ECG screening programme on 1000 patients resulted in 11 avoided strokes and the gain of 29 life-years or 23 QALYs. ICER per QALY gained or per LYG: Handheld ECG dominant Sensitivity analyses: Increasing cost of the screening procedure from €108 to €220: ICER = €2600

					Reduce time horizon to 5 years: ICER = €6400. Continuous 24hr Holter monitoring was inferior to intermittent handheld ECG monitoring in terms of cost effectiveness due to its lower sensitivity and higher costs. Base case analysis compared the intermittent handheld ECG screening with no screening in patients with recent stroke. Implementing a screening programme on 1000 patients resulted in 11 avoided strokes and the gain of 29 life years, or 23 QALYs and cost savings of €55400 over a 20-year period. Continuous 24HM was dominated by Handheld ECG due to its lower sensitivity and higher cost (€4255000/1000 patients). 24HM was then excluded from analyses and handheld ECG was compared to no screening. Total costs were lower for the handheld ECG patients (-€53600) making the screening program dominant to no screening. Costs over time were higher for the first year in the screening group due to upfront cost. After 7 years, the screening programme with handheld ECG would become cost saving. Cost savings were based on 85% of patients receiving anticoagulant treatment, if this is

					reduced to 50% screening was no longer cost saving but remained cost effective. Screening cost was estimated to be €108, but if raised to €220 the screening was no longer cost saving and the cost per QALY was €2600. When the time horizon is reduced to 5 years the cost per QALY became €6400.
Cost data from published clinical trial (Grond et al., 2013).	Quiroz 2017, Netherlands and USA	Patients who have had a cryptogenic stroke	ICM vs SoC	Not reported	ICER = € 24,715 per QALY gained for base case. CHADS2 score 4 to 6: ICER = € 22,011 CHADS2 score 2: ICER = € 29,795 Probabilistic sensitivity analysis suggested that ICM had a probability of 91% of being cost-effective at a threshold of € 80,000 per QALY gained.
Registry data.	Yong 2016, Canada	Hypothetical population based on the EMBRACE trial cohort	30-day ECG monitoring with external loop recorder vs 24-hour Holter	Total cost ($): 30d event loop recorder = $59,712 24-hour Holter = $59,798 Incremental= -$86 Total cost ($) (discounted 5%): 30d event loop recorder = $43,689 24-hour Holter = $43,661 Incremental= $28 Total incremental cost (USD$) 30d event loop recorder= $28 14-day Holter = -$101 7-day Holter = -$74	Incremental cost per QALY gained vs 24-hour Holter 30d event loop recorder = $2166 14-day Holter = Dominant 7-day Holter = Dominant Using 30d event loop recorder would prevent 16 more IS and 2 more intracranial haemorrhages during a lifetime for every 1000 patients screened. 30d event loop recorder monitoring was highly cost effective (ICER per QALY $2000), and it was predicted to gain 17 life years and 13 QALYs at an additional cost of $28000 in a cohort of 1000 patients. Both 7 day and 14-day ECG were cost saving and clinically effective at preventing IS when compared to 24-hour Holter, but 30-day

					monitoring was the most clinically effective. The use of 30-day ECG monitoring detected 129 extra cases of AF and lead to 104 patients receiving anticoagulant therapy. By using the 30d ECG, per 1000 people 16 IS could be prevented and 2 intracranial haemorrhages. Prolonged ECG monitoring (7, 14 and 30 days) prevented more IS and decreased mortality, as well as improving QALYs. If combined with anticoagulant treatment known to reduce stroke risk by 50% then 30-day ECG (cost $447) becomes highly cost effective at $2000 per QALY gained, in patients whose annual stroke recurrence risk was 4.5%. Cost effectiveness was affected by stroke recurrence risk, and the effectiveness and presence of anticoagulants. In the group of 1000 people, 30-day ECG predicted a life gain of 17 years, a QALY gain of 13 and an additional cost of $28000.
Not reported	Zimetbaum 1998, USA	105 outpatients referred for continuous loop recorder placement	King of hearts loop recorder	Monitoring costs of the continuous loop recorder: Week 1 = $102 Week 2 = $96 Week 3 = $81	Incremental cost effectiveness per new diagnosis with the continuous loop recorder Any diagnosis: Week 1 = $98 (81 to 121) Week 2 = $576 (382 to 1066) Week 3 = $5832 (1975 to no limit) Serious diagnosis: Week 1 = $340(261 to 536) Week 2 = $1224 (686 to 3200) Week 3 = no limit.

					The loop recorder recorded 1.04 diagnoses per patient in the first week, 0.15 in the second and 0.01 diagnoses per patient in week 3 and beyond. The cost effectiveness ratio increases over time from week 1 to week 2 from $98 per new diagnosis to $576 and then increased further in week 3 to $5832. For week 1 of monitoring the cost was estimated to be $102, including physician and technical fees. In week 2 it decreased to $96 and further decreased to $81 per week for week 3 and beyond. If a patient received a diagnosis and it was considered "meaningful", the cost effectiveness ratio for week 1 of event monitoring was $98 (CI $82 to $121) per diagnosis. This increased to $576 (CI $383 to $1066) during week 2, and to $5832 (CI $1975 to infinity) during week 3 and beyond.
EMBRACE trial data	Kaura 2019, UK	Adults with ischaemic stroke or TIA and no prior AF diagnosis in a clinical trial	Zio patch vs Holter monitor	1-year medical cost of stroke: £13452 1-year total cost of stroke: £22429 Cost of conventional testing: £133.43 Cost of Zio: £295 Cost of implantable monitor: £3583	1 YEAR TIME HORIZON MEDICAL COSTS: Comparison of Zio vs Current strategy: Incremental cost: -£57,481 Incremental strokes prevented: 10.8 Overall incremental cost using Zio: -£113,630 Incremental cost per stroke prevented: Dominant 5 YEAR TIME HORIZON MEDICAL COSTS: Comparison of Zio vs Current strategy: Incremental cost: -£106,342 Incremental strokes prevented: 10.8 Overall incremental cost using Zio: -£162,491

					Incremental cost per stroke prevented: Dominant 1 YEAR TIME HORIZON MEDICAL COSTS AND SOCIAL CARE COST: Comparison of Zio vs Current strategy: Incremental cost: -£154,716 Incremental strokes prevented: 10.8 Overall incremental cost using Zio: -£210,865 Incremental cost per stroke prevented: Dominant 5 YEAR TIME HORIZON MEDICAL COSTS AND SOCIAL CARE COST: Comparison of Zio vs Current strategy: Incremental cost: -£410,449 Incremental strokes prevented: 10.8 Overall incremental cost using Zio: -£466,598 Incremental cost per stroke prevented: Dominant The rate of detection of PAF at 90 days was 16.3% in the Zio group, compared to 2.1% in the Holter group (odds ratio 8.9, p=0.026). The economic model (budget impact) demonstrated that implementation of the Zio XT Service would result in 10.8 strokes being avoided per year, compared to current Holter monitoring, and a yearly saving of £113630, increasing to £162491 over 5 years.
Medicare fee schedule and	Kinlay 1996, Australia	Patients with previously uninvestigated	Aerotel event monitor vs	Total costs for 21.5 weeks Event recorder = $1258 24-hr Holter = $4245	ICER per additional ECG recorded during symptoms = -$213 with event recorder vs 24-hr Holter

clinical trial data.		palpitations who were referred for Holter monitoring	48hr Holter monitoring		ICER per additional clinically significant arrhythmia detected = -$373 for event recorder vs 24-hr Holter ECG recordings during symptoms: Event recorder = 29 24-hr Holter = 15 Clinically significant arrhythmia recorded: Event recorder = 8 24-hr Holter = 0 AF or flutter was detected in 6% of patients with the event recorder a nonpatients with 24-hour Holter. Clinically significant arrhythmias were detected in 19% of patients with the event recorder and no patients with the 24-hour Holter monitor. A cost-effectiveness analysis from a societal perspective concluded that the ICER was -$213 per additional ECG recorded during symptoms and -$373 per additional clinically significant arrhythmia detected with the event recorder compared with the 24-hr Holter monitor. The event recorder dominated in all the scenario analyses conducted.
RCT data	Halcox 2017, UK	Individuals >65 years of age with a CHADS-VASc score >2 not in receipt of OAC without a known	Single lead ECG with AliveCor device vs routine clinical care	60440 ECGs = $116823 (£89451) Pathway coordination of ECG: $37 793 (£28 938)	Overall, 19 cases of AF were detected; thus, the intervention cost was $10 780 (£8255) per AF diagnosis. The overall cost of the intervention was $204830 (£156 837). This consisted of device costs of $28698 (£21 974), patient training costs of $3750 (£2871), and defective technology costs of $2194 (£1680)

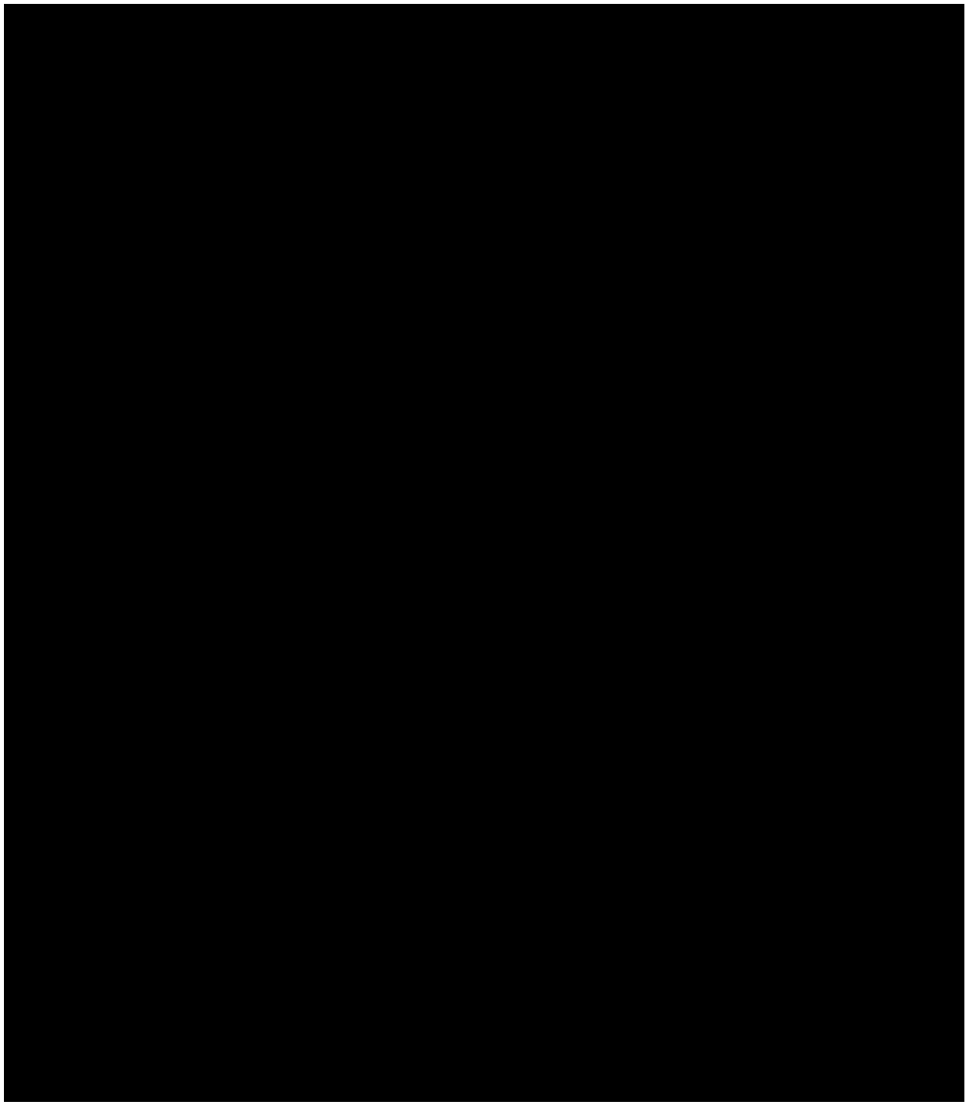
		diagnosis of AF taking part in the clinical trial			Patients in the AliveCor group were significantly more likely to receive a diagnosis than those receiving usual care (p=0.004). No sensitivity analysis reported.
Efficacy data based on the embedded crossover RCT	Reed 2019, UK	Patients aged 16+ presenting with palpitations or presyncope	AliveCor smartphone case and app vs Standard care	Median overall healthcare utilisation costs: AliveCor = £108 (IQR 99.0–246.50, range 99–2697) Standard care = £0 (IQR 0–120.0, range 0–4161); p = 0.0001 Cost per symptomatic rhythm diagnosis: AliveCor = £474 Standard care = £1395 Hospital admissions due to palpitations or presyncope: AliveCor = 2 Standard care = 1 p>0.999 Emergency department presentations after index event due to palpitations/ presyncope: AliveCor = 9.7% Standard care = 2.6% p=0.031	Median overall healthcare costs were higher with AliveCor (£108 vs £0 with standard care) but the cost per symptomatic rhythm diagnosis was lower with AliveCor (£474 versus £1395 with standard care). There were more emergency department presentations after the index event for palpitations or presyncope in the AliveCor group (9.7% compared with 2.6% of the control group, p=0.031) but no significant differences in hospital admissions, outpatient visits, GP visits or ECGs performed due to palpitations or presyncope. A symptomatic arrhythmia was detected in 8.9% of the patients using the AliveCor monitor compared with 0.9% of the control group, a relative risk of 10.3 (95%CI 1.3 to 78.5, p=0.006). The mean time to symptomatic arrhythmia detection was 9.9 days with AliveCor compared with 48 days with standard care, p=0.0004. Serious outcomes (all-cause death, myocardial infarction, life-threatening arrhythmias, insertion of pacemaker or

					internal cardiac defibrillator) were more common in the AliveCor group at 90 days, 8.9% compared with 1.7% with standard care, p=0.02, but deaths were not significantly different. Eighty of 92 (87.0%) participants found the AliveCor monitor easy to use. There were more emergency department presentations after the index event for palpitations or presyncope in the AliveCor group (9.7% compared with 2.6% of the control group, p=0.031) but no significant differences in hospital admissions, outpatient visits, GP visits or ECGs performed due to palpitations or presyncope. Median overall healthcare costs were higher with AliveCor (£108 vs £0 with standard care) but the cost per symptomatic rhythm diagnosis was lower with AliveCor (£474 versus £1395 with standard care).

Appendix B: Model structure

Please provide a diagram of the structure of your economic model.

[redacted]



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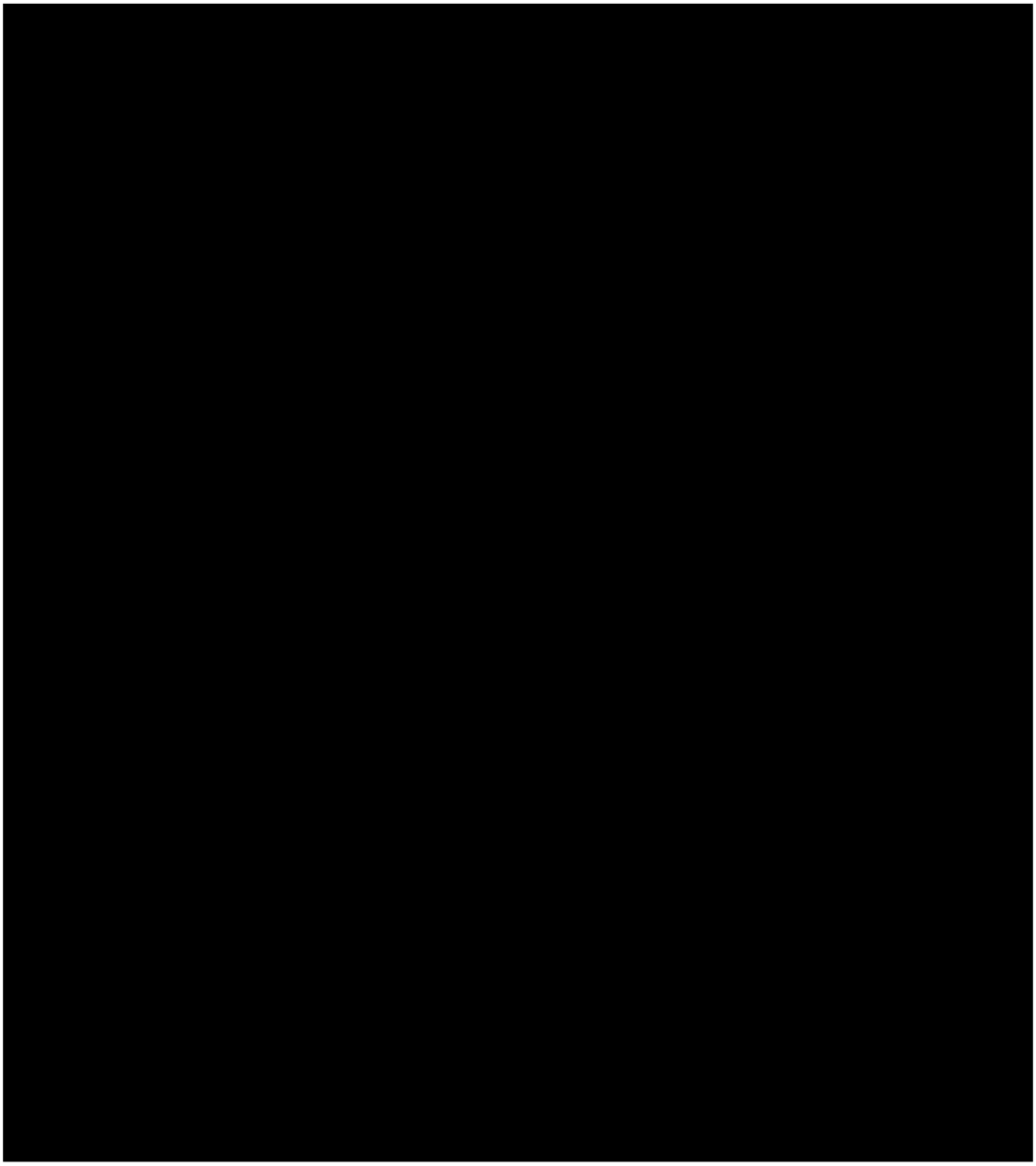


[redacted]

Results of univariate sensitivity analyses

1. Cardiology model

				Incremental reward (Base case = £84.76)		
Variable Name	**Low value**	**Base value**	**High value**	**Low**	**High**	**Spread**
cZIOservice	£248.00	£310.00	£372.00	£33.30	£136.22	102.92
cHolter	£148.10	£185.12	£222.14	£44.98	£124.55	79.58
pNoRepeat	0.584	0.730	0.876	£53.43	£116.09	62.66
nRepeat	1.150	1.440	1.730	£66.82	£102.71	35.88
pHolterswitchZIO	0.640	0.800	0.960	£70.49	£99.04	28.55
pNegativeZio	0.239	0.299	0.359	£74.34	£95.19	20.84
cOPDFU	£113.60	£142.00	£170.40	£75.01	£94.52	19.52
cCER	£148.10	£185.12	£222.14	£76.01	£93.52	17.51
pImplantable	0.016	0.020	0.024	£78.44	£91.09	12.66
cImplantable	£2,576.80	£3,221.00	£3,865.20	£78.70	£90.83	12.12
pPositiveZio	0.508	0.635	0.701	£77.67	£88.45	10.77
cOPDassessment	£113.60	£142.00	£170.40	£80.72	£88.81	8.09
pNegativeHolter	0.091	0.114	0.137	£81.46	£87.78	6.32
pPositiveHolter	0.194	0.242	0.290	£82.17	£86.08	3.91
pNegativeCER	0.150	0.188	0.226	£83.24	£86.12	2.88
pPositiveCER	0.184	0.230	0.276	£83.87	£85.40	1.53
pCER	0.120	0.150	0.180	£84.61	£84.92	0.31

2. Stroke model

				Incremental reward (Base case = £55.29)		
Variable Name	**Low value**	**Base value**	**High value**	**Low**	**High**	**Spread**
pNoRepeat	0.584	0.730	0.876	-£0.76	£111.33	112.10
cZIOservice	£248.00	£310.00	£372.00	£0.85	£109.72	108.86
cHolter	£148.10	£185.12	£222.14	£27.92	£82.65	54.72
cOPDassessment	£113.60	£142.00	£170.40	£33.54	£77.03	43.49
cCER	£148.10	£185.12	£222.14	£38.82	£71.75	32.94
nRepeat	1.150	1.440	1.730	£45.18	£65.39	20.21
pImplantable	0.016	0.020	0.024	£48.12	£62.45	14.34
cImplantable	£2,576.80	£3,221.00	£3,865.20	£48.73	£61.84	13.11
cOPD_FU	£113.60	£142.00	£170.40	£48.82	£61.75	12.93
pZioTIA	0.600	0.750	0.900	£51.75	£58.82	7.07
pStroke	0.461	0.576	0.691	£52.57	£57.99	5.43
pHolter24repeat	0.600	0.750	0.900	£53.43	£57.14	3.71
pIPmonit	0.400	0.500	0.600	£54.17	£56.40	2.22
pPositiveZio	0.129	0.161	0.193	£54.42	£56.15	1.74
pPositiveCER	0.059	0.074	0.089	£54.72	£55.85	1.13
pPositiveHolter	0.017	0.021	0.025	£54.99	£55.58	0.59
pNewAFstroke	0.045	0.056	0.067	£55.03	£55.54	0.51
pPrimaryHolter	0.400	0.500	0.600	£55.18	£55.39	0.21

Appendix C: Search strategy for resource use

Literature search not performed.

Appendix D: Data on File

The following data sources have been submitted as separate documents.

1. Electrocardiogram Monitoring & Stress Testing Hospital Episode Statistics Data Insights (HES)
2. Equipment costs relating to ECG ambulatory monitoring tests: Results of a Freedom of Information Request (FOI)
3. [redacted]ICHP Waiting Time Data (Wait) [Will be submitted by 6 December]
4. PLICS Reference Cost for ECG Monitoring (PLICS)
5. ECG Reporting Delays: Results of a Freedom of Information Request (Delay)

Appendix E: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☐ If no, please proceed to declaration (below)

Yes ☒ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information provided in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

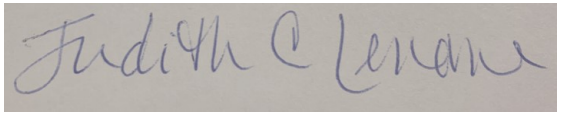
Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
# 104	☒ Commercial in confidence ☐ Academic in confidence	Zio XT Service Evaluation Tools contain data on the clinical results of every patient monitored by the Zio Service globally as well as within the UK and at individual NHS accounts. While completely anonymised and shared with explicit permission from our customers, iRhythm only distributes this data on a selective basis for business reasons.	Indefinite
Details	[redacted]		
#64	☐ Commercial in confidence ☒ Academic in confidence	Our clinical validators are willing to be contacted by NICE for purposes of this evaluation but for privacy reasons have asked that their names and contact information not be published.	Indefinite
Details	[redacted]		
# 100 - 102	☐ Commercial in confidence ☒ Academic in confidence	We worked alongside a number of NHS clinicians to develop the pathways utilised in our models. Our clinical partners have indicated interest in publishing these ACM pathways at a later date.	Indefinite
Details	[redacted]		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	4 December 2019
Print:	Judith C Lenane	**Role / organisation:**	Chief Clinical Officer & Executive Vice President, iRhythm Technologies

Contact email: [redacted]

NICE National Institute for Health and Care Excellence

Digital health technology (DHT): Collated expert questionnaires

Technology name & indication: Zio Service for detecting cardiac arrhythmias

Experts & declarations of interest (DOI)

Expert #1	Anthony Shannon, Highly Specialist Cardiac Physiologist, Liverpool Heart and Chest Hospital
	DOI: NONE
Expert #2	Gregory Lip, Price-Evans Chair of Cardiovascular Medicine, University of Liverpool,
	DOI: YES - Consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally.
Expert #3	Dr Matthew J Reed, Consultant and NRS Fellow in Emergency Medicine, NHS Lothian,
	DOI: YES - The Emergency Medicine Research Group Edinburgh (EMERGE) received £1000 funding from iRhythm Technologies, Inc. as sponsorship for the EMERGE10 conference on 22nd and 23rd of November, 2018. I am the group Director. 22nd and 23rd of November, 2018 iRhythm Technologies, Inc. provided the Zio XT monitors and ECG analysis service free of charge for the PATCH-ED study. iRhythm Technologies, Inc. and the funder had no involvement in the design, conduct, analysis or reporting of the study. I was study CI. 17 November 2015 to 16 June 2017. I was a Task Force member for the diagnosis and management of syncope guidelines of the European Society of Cardiology (ESC) published in March 2018. 2016 to March 2018. I am professor of the Royal College of Emergency Medicine. 2019 to ongoing. I am supported by an NHS Research Scotland Career Researcher Clinician award. 2012 to ongoing.
Expert #4	James Teo, Consultant Stroke Neurologist & Clinical Director of Data Science, Kings College Hospital NHS Foundation Trust,
	DOI: YES - Financial Interest Research Grant support from Innovate UK; PI (£500k out of total £10mill grant). Feb 2019 to ongoing. Speaker Honorarium from Goldman Sachs (<£2000). April 2019. Financial Support for open-access publishing fee for EPACS clinical trial (<£2000). June 2019.

	Research Grant support from Bristol-Meyers-Squibb (£40k); CI on clinical trial; EPACS (Trial Register ISRCTN50253271). January 2016 to June 2019 Conference Travel Grant support from Bayer to European Stroke Conference 2017 (<£1500). May 2017. Meal (Dinner) expense while at European Stroke Conference from iRhythm Technologies (<£100). May 2017. Speaker Honorarium from Bristol-Meyers-Squibb (<£2000). January 2016 to August 2018. Speaker Honorarium from Goldman Sachs (<£2000). April 2016 Personal ISA in tracker funds which may include pharmaceutical companies (<£5000). February 2008 to ongoing. Royalties from medical books, Wiley-Blackwells Publishing (<£500/yr). 2001 to ongoing.
Expert #5	Jacqueline Colwill, Cardiac Physiologist and Cardiology Service lead, South Tyneside and Sunderland NHS Foundation Trust,
	DOI: NONE
Expert #6	Joseph Mills, Consultant Cardiologist, Liverpool Heart & Chest NHS FT
	DOI: YES - Attendance at iRhythm Advisory Board (Honorarium received). January 2019.
Expert #7	Mark A Tanner, Consultant Cardiologist and Honorary Clinical Senior Lecturer, Western Sussex Hospitals NHS Trust and Imperial College London
	DOI: YES I had a brief informal discussion with irhythm representatives at European Society of Cardiology and Heart Rhythm UK regarding my clinical experiences of the Zio but have received no fees or honoraria. Aug 2019 to October 2019.
Expert #8	Mr Wajid Hussain, Consultant Cardiac Electrophysiologist, Royal Brompton and Harefield NHS Trust / Clinical Director of Digital Health at the RCP
	DOI: NONE

How NICE uses this information: the advice and views given in these questionnaires are used by the NICE medical technologies advisory committee (MTAC) to assist them in making their draft guidance recommendations on a technology. It may be passed to third parties associated with NICE work in accordance with the Data Protection Act 2018 and data sharing guidance issued by the Information Commissioner's Office. Expert advice and views represent an individual's opinion and not that of their employer, professional society or a consensus view (unless indicated). Consent has been sought from each expert to publish their views on the NICE website.

For more information about how NICE processes data please see our privacy notice.

1. **Please describe your level of experience with the technology, for example: Are you familiar with the technology? Have you used it? Have you used it? If so please give details, for example describe setting, length of time and version if applicable, Are you currently using it? Have you been involved in any research or development on this technology?**

Expert #1	Yes. I am familiar with the ZIO XT patch having attended round table meetings with iRhythm and presentations around the fitting of the devices and analysis of the device. I personally have not attached it to patients yet. We are currently not using ZIO at Liverpool Heart and Chest but are looking to commence within the next couple of months. I have not been involved in the research or development of this product.
Expert #2	Yes, has been demonstrated to me (have not used on patients yet) – also trial period in my hospital, Liverpool Heart & Chest Hospital. No actual research or development conducted per se
Expert #3	I am familiar with the Zio XT monitor having used it for several years in a research setting. I am currently not using it in clinical practice due to a lack of local funding. I have been involved in a study using the technology (Reed MJ, Grubb NJ, Lang CC, Gray AJ, Simpson K, MaCraild AJ, Weir CJ. Diagnostic yield of an ambulatory patch monitor in patients with unexplained syncope after initial evaluation in the Emergency Department: The PATCH-ED study. Emerg Med J 2018; 35:477–485. PMID: 29921622). Patients 16 years or over presenting within 6 hours of unexplained syncope were fitted in the Emergency Department with the Zio XT ambulatory patch ECG recorder. Primary endpoint was symptomatic significant arrhythmia at 90-day follow-up (https://www.ncbi.nlm.nih.gov/pubmed/29921622, https://clinicaltrials.gov/ct2/show/NCT02683174)
Expert #4	I have used the technology for NHS patients with a stroke or transient ischaemic attack (TIA). I have conducted a randomised clinical trial (EPACS; http://www.isrctn.com/ISRCTN50253271), which has been published https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6659210/. The study was conducted in a secondary care setting for inpatients and outpatients, and showed a positive outcome in terms of detecting more atrial fibrillation (16.3%) than a standard Holter ECG (2.1%). Based on health economic analysis, this was more cost-effective in terms of medical and social care costs across the whole pathway, but most of the cost for using the technology is borne by the secondary care provider. We are not currently using it as the NHS provider service does not have spare funding to spend on novel technologies or ways of delivering services.
Expert #5	I was introduced to Zio technology when I was looking to expand the provision of long term cardiac monitoring in Cardiology Outpatients. I implemented Zio recorders 3 years ago, initially as a pilot which is now embedded into routine practice to complement

	our existing resources for ECG monitoring. Zio technology allows a longer than current standard time to record heart rate and rhythm in the hope to capture a significant cardiac arrhythmia and support patient pathways for Stroke/TIA's/Falls and Syncope
Expert #6	I have used and am using the Zio XT in a Private practice setting (Spire Cheshire hospital). I am very familiar with its use, clinical indications, supporting data and reporting pathway. It is my default ECG monitor device at The Spire Cheshire and I have just completed a business case for its full introduction at Liverpool Heart & Chest to make it available to NHS patients. I have not been involved in any device development or research
Expert #7	I have been using this technology on a weekly basis since January 2017. It has become my preferred choice in the first line investigation of outpatients for possible arrhythmia. My experience is currently limited to the private sector as the technology is not currently available in my NHS practice.
Expert #8	I often use Ziopatch and other wearable technologies in both my private and NHS practice. Its my standard approach for the moment for monitoring greater than 3 days. I have not been involved in any research involving it.

2. Are there any issues with the usability or practical aspects of the using technology?

Expert #1	No issues at the time of writing.
Expert #2	Not that I am aware of
Expert #3	No. Reponses to the patient patch monitor satisfaction questionnaire in our study were received from 47 of the 86 who participated in our study. Forty-three patients (91% of respondents) agreed or strongly agreed that the patch monitor was easy to use, and 34 (72%) agreed or strongly agreed that the patch monitor was comfortable to wear. Thirty-nine patients (82%) agreed or strongly agreed that they were able to carry out normal activities, and 38 patients (80%) would use the patch monitor if required in the future. Nineteen participants (40%) submitted free-text comments that indicated the patch irritated the skin (six participants, 13%) and the patch lost adherence to the skin (seven participants, 15%).
Expert #4	Usability is superior to standard holter ECG systems as it can be easily deployed by stroke nurses and junior doctors at first contact in inpatient or outpatient settings. It is well-tolerated by patients and a far greater majority of patients complete the extended ECG recording than for standard holter-based ECG's. The main limitation is the current version of the technology available in the UK

	requires the recording to stop before any analysis or interpretation can occur (I understand there are newer models in N/America which can transmit the data via mobile phone networks).
Expert #5	No issues highlighted in routine practice
Expert #6	None whatsoever
Expert #7	Generally very positive experience but occasional reports of mild irritation from electrode patch and device adhesion issues over time
Expert #8	Its more usuable and better tolerated than current long term holter monitoring. The reports take a long time to come back.

3. Are you aware of any safety concerns or regulatory issues surrounding this technology?

Expert #1	There are currently no issues or concerns around this technology.
Expert #2	Not that I am aware of
Expert #3	No. We have had no safety issues.
Expert #4	I have no safety concerns and have not found any problems with skin reaction to the adhesive in the patch. A regulatory issue which has to be considered is the compliance of any cloud-based data processing in light of GDPR.
Expert #5	No safety concerns noted
Expert #6	No
Expert #7	No
Expert #8	No

Potential benefits

4. Does this technology have the potential to improve clinical outcomes? Could it lead, for example, to better monitoring of conditions or better adherence to treatment?

Expert #1	It has the potential to greatly improve the diagnostic yield of information we can gain from the device, therefore enabling earlier treatment of patients.
Expert #2	Ease of use; Outpatient use
Expert #3	Using a Zio XT Patch ambulatory ECG monitor strategy in Emergency Department patients with unexplained syncope/ transient loss of consciousness (TLoC) results in identification of a symptomatic significant arrhythmia (i.e. a clinically important cardiac abnormal rhythm) in 10% of patients (compared with 2% of historical unmatched comparators) and a diagnosis in 3 in 4 patients (Reed MJ, et al. Emerg Med J 2018; 35: 477–485 doi:10.1136/emermed-2018-207570). Whilst my research group are only investigating unexplained syncope/ transient loss of consciousness, I also believe that the Zio XT Patch ambulatory ECG monitor may be useful to quantify AF burden (both symptomatic but especially asymptomatic) in patients with paroxysmal AF or TIA/CVA in order to better stratify risk of further TIA/CVA events and help anticoagulation decisions.
Expert #4	Yes, there is a higher detection of rate of arrhythmia's due to the prolonged nature of the recording compared to Holters. This higher detection rate was found in our EPACS study (with a 14% absolute increase in detection rate in a very high risk population compared to UK standard – patients who have already had 1 suspicious stroke). Other N/American studies found 3.9% detection in community care moderately increased risk populations (mStops study https://jamanetwork.com/journals/jama/fullarticle/2687353)
Expert #5	Yes, I believe it could lead to quicker detection of significant cardiac arrhythmias as currently there is few resources available for 14 day monitoring, Zio recorders will support patient pathways for falls/syncope, palpitations, paroxysmal AF and Stroke/TIA
Expert #6	Yes – more sophisticated analysis algorithms over a more prolonged period of high quality ECG monitoring which is far more "patient friendly" and with rapid analysis and report availability – all lead to increased yield of arrhythmia, earlier diagnosis/treatment, better patient experience and reduced costs as repeat testing will be reduced
Expert #7	Potential detection of important arrhythmia such as Atrial Fibrillation might be enhanced through the longer recording period (up to 14 days) compared to conventional Holter monitors. Tolerability of device hence compliance may also be improved.
Expert #8	Yes, it can help with intermittent symptoms and allow a diagnosis when symptoms are too infrequent for 24hr holter which is the standard in both primary and secondary care

5. What do you consider to be the potential benefits to patients from using this technology? Are there any patient or carer benefits which are not likely to be captured in the clinical evidence?

Expert #1	Patients can send the ZIO patch back via Postbox and do not have to take time off work to attend hospital again. Again there is a higher chance of capturing primary arrhythmias leading to earlier diagnosis.
Expert #2	Ease of use; Outpatient use
Expert #3	Using a Zio XT Patch ambulatory ECG monitor strategy in Emergency Department patients has the potential to improve patient satisfaction with the way their unexplained syncope/ transient loss of consciousness (TLoC) is managed, changing first-line monitoring from low diagnostic yield Holter to higher yield patches and allowing earlier diagnosis and treatment of clinically important arrhythmias in turn reducing morbidity, anxiety (which is significant in patients with unexplained syncope) and increasing quality of life. There is likely to also be a reduced need for invasive treatment i.e. less requirement for implantable devices, less discomfort, less infection risk.Technology may reduce admission from the ED/Medical admissions/ward after presentation with unexplained syncope/TLoC as the intervention can be easily applied in the ED/ward rather than admit for observation and monitoring thereby saving bed days.
Expert #4	For the patient and carer, the convenience factor of the system without ECG's with holter-based wiring is a huge convenience. The return of the device by post is also very convenient especially for immobile patients who may require transport to reach hospital.The convenience of being water-proof is also a factor for showers (which increases the recording time).
Expert #5	1. Speed up or rule out diagnosis 2. Patient ease of use, 3. The recorder is showerproof, this is a huge factor for patient keeping the recorder on for a length of time. 4. The recorder comes with a pre-paid postage box to return device preventing an unnecessary visit to return the recorder.
Expert #6	No leads or hardware to inhibit normal day to day activities. Single use so can be used as "one-stop" monitor and avoid need for re-attending hospital for device fitting / removal.
Expert #7	The improved diagnosis of arrhythmia may allow earlier instigation of effective treatments/provide earlier reassurance where no pathology found. In addition, feedback from patients is very positive regarding comfort and ease of use of the device. The device can be easily fitted (eg by healthcare assistant) at the time of outpatient visit; patient can then return the device in pre-paid envelope without the need for a further trip to the hospital to return the device. The device is unobtrusive and appears to be better tolerated than traditional monitors (requiring several cables, need for removal for showering, sports etc.)
Expert #8	Quicker diagnosis, higher detection rate, better tolerated.

6. What do you consider to be the potential benefits to the health or social care system from using this technology?

Expert #1	Potentially less face-to-face follow ups with consultants. If greater diagnostic yield and earlier treatment, then likely increased long term cost savings in terms of treating heart failure / stroke patients due to onset of new Atrial Fibrillation.
Expert #2	Ease of use; Outpatient use
Expert #3	Using a Zio XT Patch ambulatory ECG monitor strategy in Emergency Department patients with unexplained syncope/TLoC has the potential to reduce hospital admissions and by changing first-line monitoring from multiple low diagnostic yield Holter to higher yield patches, reducing costs of investigation.
Expert #4	Efficiency gains for services as reduced transportation and clinic appointments for patients in TIA clinics. This was found in a small-scale study ID-AF presented by the Croydon Stroke service https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/improving-detection-of-af-in-patients-after-tia-id-af/
Expert #5	1.Speed up or rule out diagnosis, 2. Good use of digital technology
Expert #6	Reduced need for additional / repeat monitoring and increased diagnostic yield and accuracy. More rapid analysis and report availability. Will lead to reduced arrhythmia-based cardiology costs and improved patient outcomes
Expert #7	Improved diagnostic yield should result in improved efficiency of diagnostic pathway; early instigation of anticoagulation in cases of AF diagnoses may result in stroke prevention. The diagnostic reports are outsourced to irhythm and could therefore free-up NHS physiologists (of whom there is a national shortage) to focus on tackling other healthcare demands.
Expert #8	Avoid referrals and repeated tests

7. **Do you consider there to be any benefits from using the technology to support the creation of an environmentally sustainable health and care service?**

Expert #1	Likely to use less AA/AAA/hearing aid style batteries, less adhesive electrode patches, less requirement for use of ambulance transport / personal transport to/from hospital.
Expert #2	Ease of use; Outpatient use
Expert #3	These patches as with many other similar monitoring devices are single use. However, there are ambulatory ECG monitors that can be reused (with a new adhesive patch) and this should be considered by iRhythm.
Expert #4	Reduced transportation costs. I am told the device is recycled.
Expert #5	Yes, pre-paid postage to return device allows reduced appointments to hospital, this will ultimately support the environment and reduce the carbon footprint.
Expert #6	Yes but I do not know the exact details. Overall, reducing the number of tests for an individual patient must be a positive outcome.
Expert #7	Importantly, hospital visits by patient/carers can be minimised by fitting the device at time of clinic consultation, with no need for additional journeys to return the device (as pre-paid envelope for device return is provided).
Expert #8	no

Training for use of the technology

8. **Is there any training needed to use the technology, for example, Are healthcare professionals trained in its use? what does this involve? Are patients trained in its use? what does this involve?**

Expert #1	Training involves a short day of introduction to a webapp and training on how to prepare the patient and set up the patient for the ZIO patch. Patients are trained in the care of the device and also the use of the device as regards how to store manual symptom driven episodes.
Expert #2	Simple training on steps needed

Expert #3	Our study research nurses placed the device on our study participants and have all been trained in the procedure. This is not totally straightforward, as it requires shaving of a quarter of the chest and firm application of the device. The device is very reliable though and we only encountered one treatment failure where the device did not turn on when activated. I believe that patients (especially older ones) may struggle to consistently apply the technology reliably themselves, although it is a relatively straightforward procedure for those who have been appropriately trained.
Expert #4	In our EPACS clinical trial, it took us 15 minutes to teach a stroke nurse or junior doctor how to apply the patch and turn it on. It takes about 10 minutes to teach the patient or carer how to remove and return the device by the post. Only 2 patients preferred to return it by hand.
Expert #5	Healthcare professionals are trained to for/apply the recorder to ensure good skin contact, this is no different to skin prep technique for existing recorders. Healthcare professionals are trained to register the recorder and download recorder results using a unique serial number as a patient identifier
Expert #6	Healthcare professionals, mainly nursing/ECG staff require a very brief period of training in order to understand how the monitoring patch should be applied. Patients are instructed in its use at the time the patch is applied
Expert #7	Initial training is provided by iRhythm. It is brief and intuitive and can be readily taught to eg healthcare assistants, nurses. Patients are given simple instructions regarding its care and device operation
Expert #8	minimal

9. Do you think there is a learning curve associated with the use of the technology? If so please describe it for example from whose perspective and typical duration

Expert #1	The learning curve may well come from knowing which patients the device will be most successful in diagnosing arrhythmias. This learning curve will come from cardiac physiologist and consultant input and learning will take place over the first 6 months of use.
Expert #2	Not that I can see
Expert #3	Placement of the patches is a straightforward procedure for those who have been appropriately trained. Whist the Zio XT Patch ambulatory ECG monitor report is very structured, there is some interpretation required of the result and how this then disseminates into treating the patient. This clinical decision would usually be made under the supervision of a consultant in cardiology.

Expert #4	I have not encountered any learning curve to using the device.
Expert #5	The training required is very basic to an experienced healthcare practitioner who is familiar with fitting a range cardiac recorders. Training will take approx. 30-60 mins. This training could easily be applied to a wide range of healthcare personnel
Expert #6	No – its use is very straightforward.
Expert #7	Very simple to use with minimal learning curve required
Expert #8	minimal

10. Does training cover patient selection?

Expert #1	Training does cover patient selection and we have already developed a pathway at LHCH for patient selection.
Expert #2	Not particularly
Expert #3	This would depend on the context in which the Zio XT Patch ambulatory ECG patch is used. The decision as to whom to place the device on should be part on local/national guidelines drawn up with the involvement of cardiology, acute medicine and emergency medicine teams.
Expert #4	No
Expert #5	Patient selection is typically governed locally by resources available. In practice it is typically the requesting clinician/practitioner who assesses selection as per clinical history etc
Expert #6	Not applicable – this is a clinical decision
Expert #7	No, selection will be based on clinical judgement by physician
Expert #8	no

Incorporating the technology into current NHS management

11. How innovative is this technology, compared to the current standard of care? Is it a minor variation or a novel concept/design?

Expert #1	This is a novel concept as the device is leadless and allows patients to shower, play sports and carry on a daily routine fully. The current standard of care involves multiple electrode placement onto patients with leads attached.
Expert #2	This is one of a number of solutions for easy ECG monitoring
Expert #3	Whilst there are a few similar devices on the market (e.g. Bardy patch), I believe that this technology is very innovative. Current options to detect arrhythmia are limited with Holter limited to short periods of monitoring (24-72 hours) and longer options previously have involved invasive implantable devices (e.g. ILRs). There are smart phone based devices such as AliveCor that can pick up symptomatic arrhythmias (especially useful in palpitation and pre-syncope patients) but such devices require patient activation are no use in patients with syncope/ transient loss of consciousness (TLoC) who have lost consciousness and are unable to activate the device.
Expert #4	Substantial novel concept/ design. Due to the volume of data being generated from the duration of the recording, I understand that there is proprietary technology (algorithms) that are used to accelerate human-based interpretations of the readings.
Expert #5	This technology is innovative and novel as the recorder is 14 day, showerproof and can allow the patient to post device for analysis rather than return to a hospital or clinic. This technology suits patients who are elderly, living in rural areas and patients who are studying/working to reduce an unnecessary return visit
Expert #6	It is revolutionary compared to the currently available NHS monitoring devices but the technology for “patch” monitoring has been available for many years and used widely in other countries, especially the USA
Expert #7	Rather than a huge innovation this represents a very refined, patient-friendly and more slick version of existing Holter technology
Expert #8	Its more about usability for a prolonged monitoring period. There are other systems coming into practice which maybe as good if not better

12. What patient group is the technology suited to? Are there any specific patient selection criteria or should all patients be offered the technology? Approximately how many patients each year would be expected to use the technology, either as an estimated number, or a proportion of the target population?

Expert #1	Patients groups benefitting most from the technology will be those in the following categories: Cryptogenic Stroke, Paroxysmal Atrial Fibrillation, Cardiomyopathy patients (Arrhythmia), infrequent palpitations and syncope. Not all patients who come into LHCH will be offered this device. Current standard of care devices for 24hrs may be better suited for patients where we need to assess rate control in AF and thos who have very frequent daily symptoms. We plan to fit 80% of patients with ZIO XT and 20% with conventional 24/48hr ECG Holter.
Expert #2	Detection or suspected arrhythmias
Expert #3	Patients with unexplained syncope/ transient loss of consciousness (TLoC). Especially those with episodes less frequent than every 48-72 hours, which is the majority of patients who may only have an episode every fortnight/month or year. Those with short frequency episodes would be suitable for Holter monitoring (24-72 hours). Those with episodes months to years apart may still require implantable loop monitoring but could be investigated in the first instance with a single Zio XT Patch ambulatory ECG. Our ED (in a large university teaching hospital) sees 120,000 patients a year including 2000 patients with TLoC. Around 50% end up unexplained after ED assessment. Approximately 25% would be suitable for the technology, around 500 patients a year in a centre like ours.
Expert #4	All patients requiring cardiac monitoring for more than 1 day. This includes stroke and transient ischaemic attack patients where cardiac causes of stroke are being investigated for (e.g. atrial fibrillation and other arrhythmia's). The selection of which stroke patients to investigate more extensively is a source of research; European and USA systems would recommend all patients with embolic strokes of unknown source (ESUS), while UK guidelines have been much more conservative about who needs extended cardiac recording. An estimated 25-35% of UK stroke patients have cryptogenic strokes (i.e. strokes of unknown cause) so all these patients could all be eligible.
Expert #5	All patients are suitable and selected/assessed for a specific recorder depending upon the frequency of their symptoms. This technology suits all patients who experience less frequent symptoms such as symptoms every 1-2 weeks, patients on the Stroke/TIA pathway or Falls/Syncope pathway. Elderly patients, patients relying upon patient transport, patients living in rural areas, patients who are working are particularly suitable to aim to reduce an unnecessary return visit.
Expert #6	Other than patients who require monitoring to assess their atrial fibrillation rate control (where a conventional HOLTER, 24hr ECG would suffice), all other patients with a suspected, significant arrhythmia would be suitable for this technology. Estimate = 90% of the current patient group that undergo heart rhythm monitoring

Expert #7	Suited for the investigation of all patients with suspected intermittent heart rhythm disorder. It is particularly useful in those patients with transient impairment of consciousness where other technologies (eg patient activated lead I ECG recorders) would not be appropriate. Ambulatory monitors are one of the most commonly requested tests in cardiology and nearly all patients with suspected intermittent arrhythmia will be considered for one
Expert #8	Patients with intermittent symptoms less frequent than daily. It has potential to be used in a large number of patients especially if taken up in primary care to diagnose palpitations

13. What is the position of the technology in the care pathway? Would this technology replace or be an addition to the current standard of care?

Expert #1	This technology will replace the current standard of care (R-Test, Vista and Cardiomemo devices).
Expert #2	Diagnosis, outpatients
Expert #3	Patients with unexplained syncope/TLoC. Especially those with episodes >every 48-72 hours. This would replace Holter monitoring in most patients, which would become redudant.
Expert #4	In the stroke pathway, this is best used after the acute stroke or TIA service by secondary care to try to diagnose the case. This would replace existing Holter-based cardiac monitoring systems. This may reduce by a small degree the amount of patients who require cardiac implantable loop recorders (ILR's).
Expert #5	This technology is not designed to replace existing technology but to be offered as an additional resource for 14 day monitoring which is currently is not an option for the majority of practice. Current practise offers good resources for 24hr, 48hr, 72hr monitoring and in some cases up to 7 days, however these recorders are not waterproof/ showerproof. This technology supports the intermediate monitoring (between short and long) and can offer a resource prior to consideration of an invasive implantable loop recorder. This technology will support patient pathways for falls/syncope, palpitations and Stroke/TIA pathways

Expert #6	It would refine / replace the current standard of care. Also provides an excellent opportunity for services to review their "arrhythmia/palpitations" pathway and determine exactly which groups of patients require monitoring and which can be reassured by other less expensive methods – eg simple primary care assessment + 12 lead ECG.
Expert #7	First line investigation for suspected intermittent arrhythmia and would replace current cumbersome technology
Expert #8	diagnosis

14. Does this technology have the potential to change the current pathway? Would care take place in a different setting or with different healthcare professionals?

Expert #1	Yes. The pathway has already changed to suit the ZIO XT patch and associated patient groups. This will generally be evolving over time when we are able to realise where the device is best suited to which patient groups.
Expert #2	Possibly. No need to attend hospital for Holters
Expert #3	Yes. Patients with unexplained syncope/ TLoC would likely undergo Zio XT Patch ambulatory ECG monitoring first prior to being fitted with an ILR. This technology could be fitted in GP practices, EDs and acute medicine units. ILRs require cardiology agreement and placement in most centres at present.
Expert #4	Yes, this would make cardiac investigations of stroke patients much more integrated as this can be delivered earlier in the pathway (in line with other international standards) yet the investigation can be initiated by stroke services with a lot less burden on cardiac services.
Expert #5	Yes, this technology could change the current pathway and offer an additional longer term resource for cardiac monitoring, particularly for Stroke/TIA pathway. This technology could easily be implemented into a wide range of settings and fitted by a wide range of healthcare professionals across the entire NHS organisation. (Community, primary, secondary and tertiary care).
Expert #6	Yes – as above. Care setting maychange – this technology is far more suited to community-based services than current heart rhythm monitoring devices as the patches are small, single use and no collection/transport/hard-ware costs are incurred. Forms part of a "one-stop" pathway.
Expert #7	Its ease of use (fitting and subsequent analysis) could make this particularly suited to primary care where most low risk palpitations could be managed without subsequent involvement of secondary care services

Expert #8	Maybe have this before referral to secondary care and if normal or ventricular ectopics only when symptoms can avoid secondary care referral.

15. Would changes be needed to facilities or infrastructure in order to use the technology? Are there significant capital costs associated with introducing the technology?

Expert #1	No facilities / infrastructure changes anticipated. Capital expenditure will increase in terms of each individual device being used, but this will be offset be the down-stream cost savings driven by less consultation appointments, less need for locum / bank staff to be utilised and less long term hospitalisations of patients due to Stroke, AF, Heart Failure etc.
Expert #2	Not significntly
Expert #3	Changing where this technology is fitted (GP practices, EDs and acute medicine units) or more conventional placement in a cardiology clinic would not require changes to infrastructure. No capital costs would be required, only costs for the Zio XT Patch ambulatory ECG monitors. The reported tracings could be sent back to the cardiology ECG department service as happens in most places at present.
Expert #4	(1) Storage of these devices with an inventory system for expiry dates and serial numbers (trivial adaptation for most NHS organisations); (2) web access to cloud-based cardiac reporting systems and/or integration of the Zio service output (report and signal data) back into hospital electronic health record systems.
Expert #5	No changes to facilities or infrastructure are necessary to use this technology. Upfront capital costs will be incurred as Zio recorders are not currently factored into tariff or block contracts and do appear expensive when new to budget. This cost should then be offset against the cost saving of staff time analysing the recorder, however this exact cost can be difficult to accurately obtain.
Expert #6	No – can still be used in existing services – hospital or community based. The individual patches are purchased but costs such as physiologist time to review downloaded data, hardware costs, software costs for data analysis are all eliminated / reduced significantly.
Expert #7	No
Expert #8	Minimal change

16. Considering the care pathway as a whole, including costs and possible future costs avoided, is the technology likely to cost more or less than current standard care, or about the same?

Expert #1	Initial estimates are that Year 1 would be cost neutral and then profits should be seen in Year 2 and 3 onwards. In the long term, the technology is likely to produce an increased cost saving compared to current standard of care.
Expert #2	Probably similar
Expert #3	I would expect that costs could be reduced. Patients may be able to be discharged earlier if a suitable monitoring technology was available. Zio XT Patch ambulatory ECG monitors would pick up the cause of the patients syncope in many cases reducing need for ILR implantation, and reduce multiple outpatient and ED attendances.
Expert #4	The cost model of the technology currently is different from the standard NHS model of financing cardiac monitoring. Most NHS cardiac monitoring services put an initial outlay of a fixed equipment cost with physiologist staff cost being the bulk of the cost. This technology has a higher cost per device but has a much lower demand on staff time as it can be deployed by non-physiologist staff.
Expert #5	Overall this technology is cost neutral
Expert #6	If used appropriately and in conjunction with better training for primary care clinicians + redesign of arrhythmia/palpitations pathways, the potential is for substantial cost savings.
Expert #7	I understand current unit cost is greater that current tariff for traditional ambulatory ECG monitors however cost savings could be seen by improving diagnostic yield hence avoiding repeat testing, and through earlier treatment avoid repeated healthcare visits and in the case of AF detection reduce stroke and its attendant costs
Expert #8	More but the price is rapidly coming down as other competitor products become available

17. Is the technology likely to be able to reduce health inequalities in the NHS or improve access to care among hard-to-reach populations?

Expert #1	Yes. The technology will hopefully reduce likelihood of cryptogenic stroke and heart failure admissions related to atrial fibrillation across the populous. It will also hopefully enable earlier treatment for ventricular arrhythmias / supraventricular arrhythmias
Expert #2	No
Expert #3	I am unsure that the access to Zio XT ambulatory ECG monitors would be any different to current access to syncope/TLOC work up strategies. Changing where this technology is fitted (GP practices, EDs and acute medicine units) may improve access among hard to reach populations (e.g. rural populations)
Expert #4	Yes, patients who have difficulty commuting to secondary care cardiac services frequently miss appointments for Holter ECG's due to transport or distance issues (e.g. patients in care facilities requiring hospital transport). As much as 20% of our hospital's patients miss their Holter ECG appointments, and never rebook it so miss the opportunity to detect a potentially life-changing illness.
Expert #5	Yes
Expert #6	Possibly – as it is a single-use, one-stop suitable device, this avoids the necessity for multiple hospital visits. Patients with time constraints / transport difficulties may not be willing to undergo monitoring with existing devices
Expert #7	Its ease of use are likely to improve accessibility Eg in rural areas this technology could be provided by GP surgeries or even through domiciliary visits
Expert #8	unlikely

Current use of the technology

18. Do you know how widely used this technology is in the NHS?

Expert #1	Minimally used in the NHS in only a handful of sites. More broadly used in private health care settings.
Expert #2	No
Expert #3	I think it is used sporadically in many cardiology services (public and private) in the UK but not widespread as part of routine care pathways.
Expert #4	I am not aware of any NHS units using this as standard of care for anything more than the duration of a research project, quality improvement project or innovation project.
Expert #5	To my knowledge it's not widely used in the NHS, possibly due to it being newer technology
Expert #6	Very limited. Some small services mainly set up for research/data gathering purposes
Expert #7	I understand its use remains limited
Expert #8	Moderately widely in the private sector, but constrained by cost in the NHS

19. Are you aware of any issues which may prevent (or have prevented) this technology being adopted in your organisation or across the wider NHS?

Expert #1	Cost effectiveness across the wider NHS. The tariff currently for a long term Holter ECG is £130 in the NHS, and a single use ZIO XT patch is £290. Once an agreed tariff comes into place for this device and product cost is driven down, more NHS trusts should have this technology made more widely available.
Expert #2	No
Expert #3	No

Expert #4	The cost for the device is borne by the NHS provider while the benefits of detecting and preventing strokes are for the whole health system. There is therefore a perverse disincentive to use the technology as there is no direct benefit to the NHS provider.
Expert #5	No
Expert #6	System wide change always difficult in the NHS. The up-front cost of the patches + securing appropriate reimbursement tariff may be issues.
Expert #7	Cost
Expert #8	Cost

20. Are you aware of evidence and/or any national registers collecting data on this technology? Are you aware of any ongoing research or locally collected data (e.g. audit) on this technology?

Expert #1	iRhythm has over 22 published peer reviewed articles on the ZIO XT device.
Expert #2	No
Expert #3	No. Our research group were unsuccessful in a recent application to the British Heart Foundation entitled: 'Multi-centre open label randomised controlled trial of an immediate 14 day ambulatory ECG monitor versus standard care in acute unexplained syncope patients: The ASPIRED study'. We hope to be successful in a future grant funding application. This trial would include studying NHS resource utilisation.
Expert #4	I am not aware of any UK-based registers using this technology. There are USA-based research studies on this technology (https://jamanetwork.com/journals/jama/fullarticle/2687353; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4290477/; https://jamanetwork.com/journals/jamacardiology/fullarticle/2681476). I understand the AI-based technology is being refined by the device manufacturer through further partnerships with Google, but do not know the details of the research. My service (KCH) in partnership with Guys & St Thomas's Hospital, Croydon University Hospital and the Health Innovation Network is planning a small cross-provider Quality Improvement Project to measure the benefits of changing care pathways.
Expert #5	Yes, a local audit was carried out at South Tyneside Hospital to look at the cost effectiveness, which came out to be cost neutral. The patient yield was also analysed to capture any significant cardiac arrhythmias occurring over the 14 day period to examine

	which, if any would have been previously missed using conventional 24-72hr monitoring, the outcome was favourable as many significant arrhythmias did occur after 72 hrs and after 7 days.
Expert #6	>100 published scientific articles. I am not aware of any UK registries but irhythm have a huge data-base via its U.S activity which is being used for machine-learning purposes to improve the analysis algorithm – published in Nature medicine. Liverpool Heart & Chest has conducted a small (10 patient) evaluation of the device and found it to be very patient friendly and overwhelmingly superior to existing monitor options. We are hoping to audit our local data once this device is approved
Expert #7	There are several peer reviewed publications regarding its role in arrhythmia detection, AF detection post stroke and its tolerability
Expert #8	No

General advice

21. Please add any further comments on your particular experiences or knowledge of the technology, or experiences within your organisation.

Expert #1	This new technology offers an exciting insight into the future role that Artificial Intelligence can play in diagnostic data. iRhythm (ZIO) has a deep-learning algorithm which can analyse each patient's ECG before a second pass of the data occurs via experienced NHS cardiac physiologists. Current data suggests that deep-learning is as effective, if not better, than some human driven analysis in terms of ECG rhythm identification.
Expert #2	
Expert #3	
Expert #4	The technology was unique 4 years ago; other alternative systems have arisen in the past 4 years but most only provide the medical device (patch) and do not provide the full comprehensive AI-based monitoring system.
Expert #5	Anecdotally patient satisfaction was very positive.
Expert #6	As above. Excellent device which needs support to be rolled out to the wider NHS

Expert #7	I have used this device in the routine investigation of intermittent arrhythmia for over 2 years (in approx. 150 patients). The zio patch is unobtrusive and well-tolerated by patients. It has picked up diagnoses that would have been missed with traditional technologies with shorter monitoring periods. Additionally the irhythm cloud based system provides a comprehensive report in a timely fashion.
Expert #8	It's a good system but expensive, however the price will come down in this rapidly evolving field.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Patient survey report

Zio XT Service for detecting cardiac arrhythmias

During November and December 2019, NICE's public involvement programme posted an online survey, 26 responses were received.

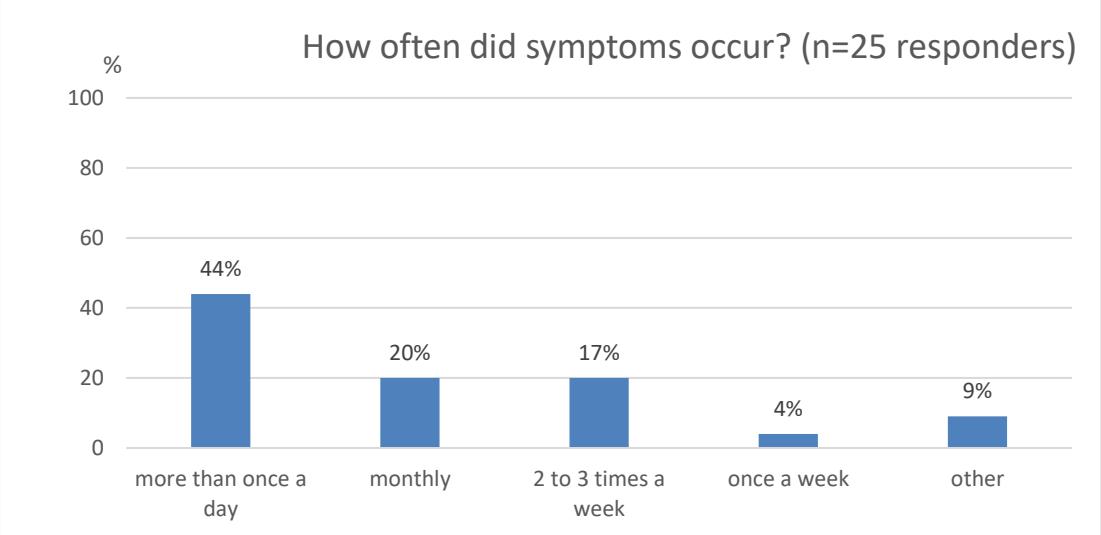
All responders confirmed that they read the information sheet provided which explains the purpose of the survey and how the information will be used. All responders consented to NICE using the information as described.

1. Responder demographics

- Mean age of responders was 56.7 years, range 29–89 years. 58% of responders were female (n=15) and 42% were male (n=11).

2. Symptoms

- All responders experienced irregular heartbeats. More than a third responders had irregular heartbeats more than once a day (n=11, 44%), and 20% had 2 or 3 times within a week (n=5).



- The common symptoms reported by responders including:

- Palpitations, heart fluttering
- black out episodes (i.e. fainted after having a shower)
- breathlessness
- pain across chest or tight chest
- rapid heart-beat
- exertion and dizziness/headedness

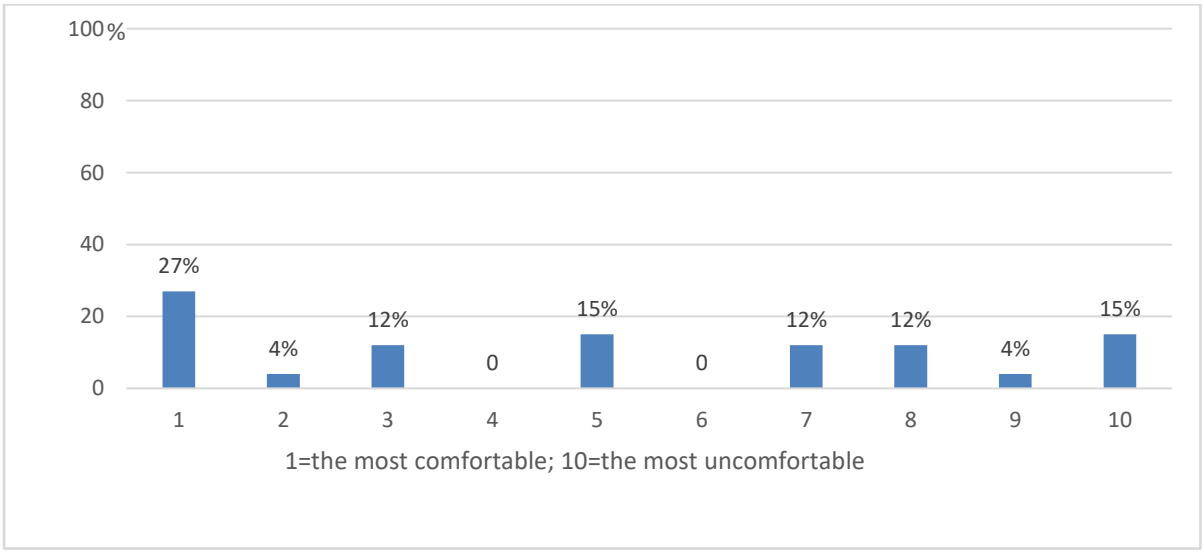
3. Device usage

- Responders had been prescribed the Zio XT Service to help detect irregular heartbeats. Most of responders were referred for remote heart monitoring by their GPs (n=10, 39%) or a specialist centre (n=8, 31%). Three responders (12%) were referred by an A&E department.

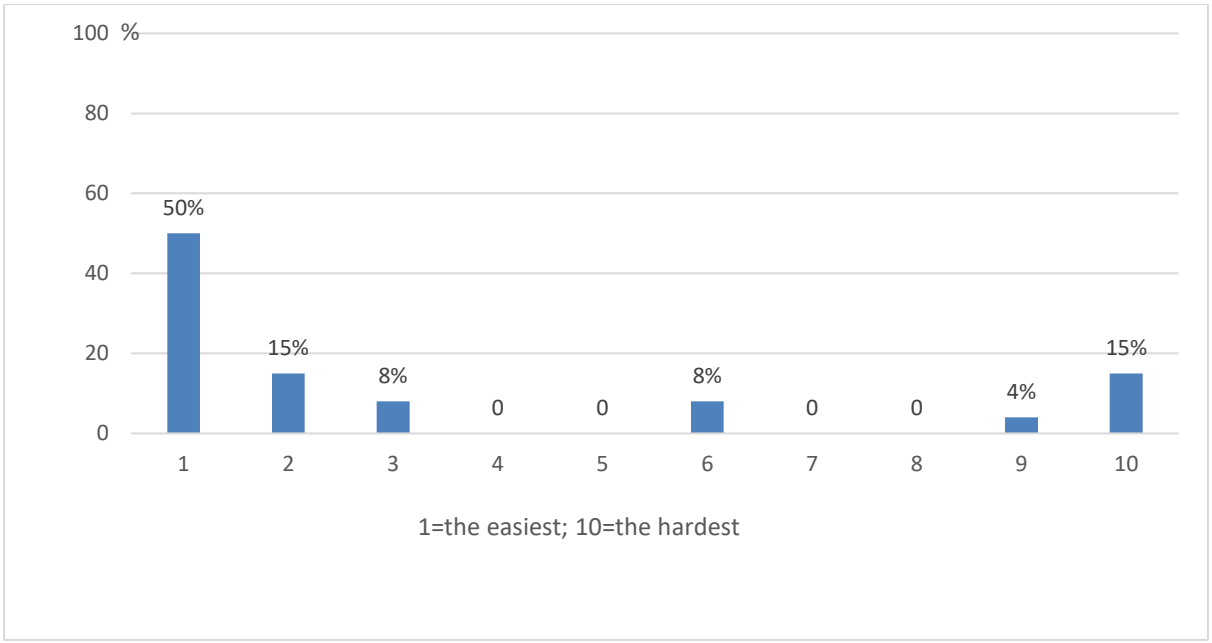
- Most responders (n=22, 85%) wore the patch for the full time prescribed (usually 14 days). Two responders did not wear the patch because it became loose or fell off.

4. Experience of using the device

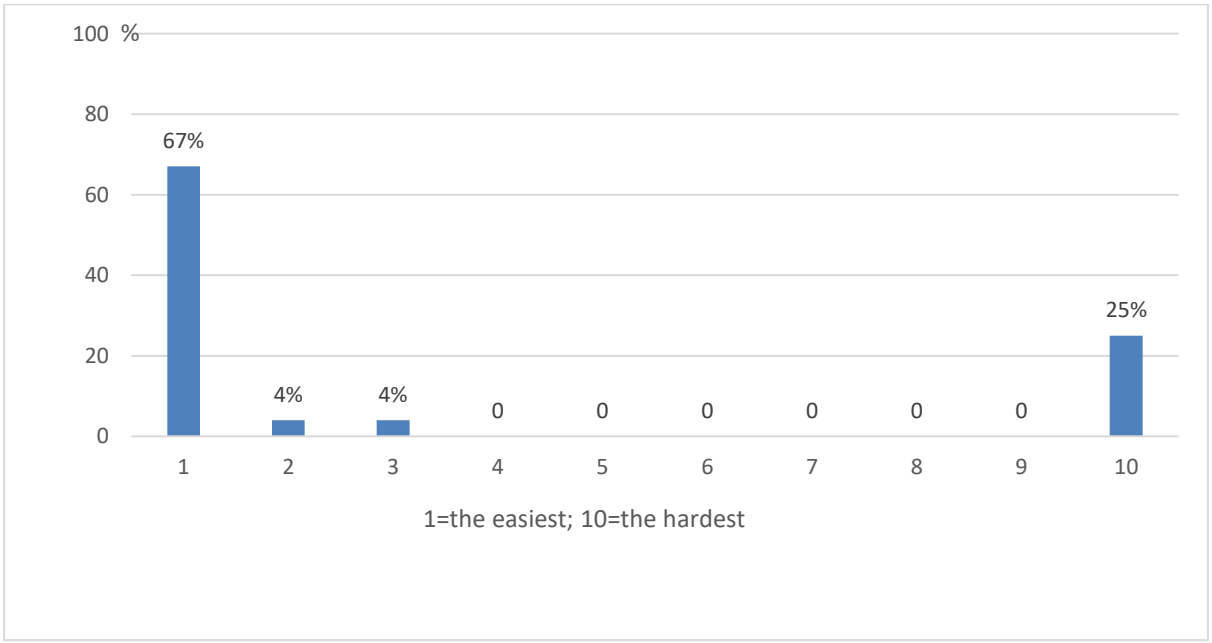
- **How comfortable was wearing the patch? (On a scale of 1 to 10, 1 being the most comfortable and 10 being the most uncomfortable) (n=26 responders)**



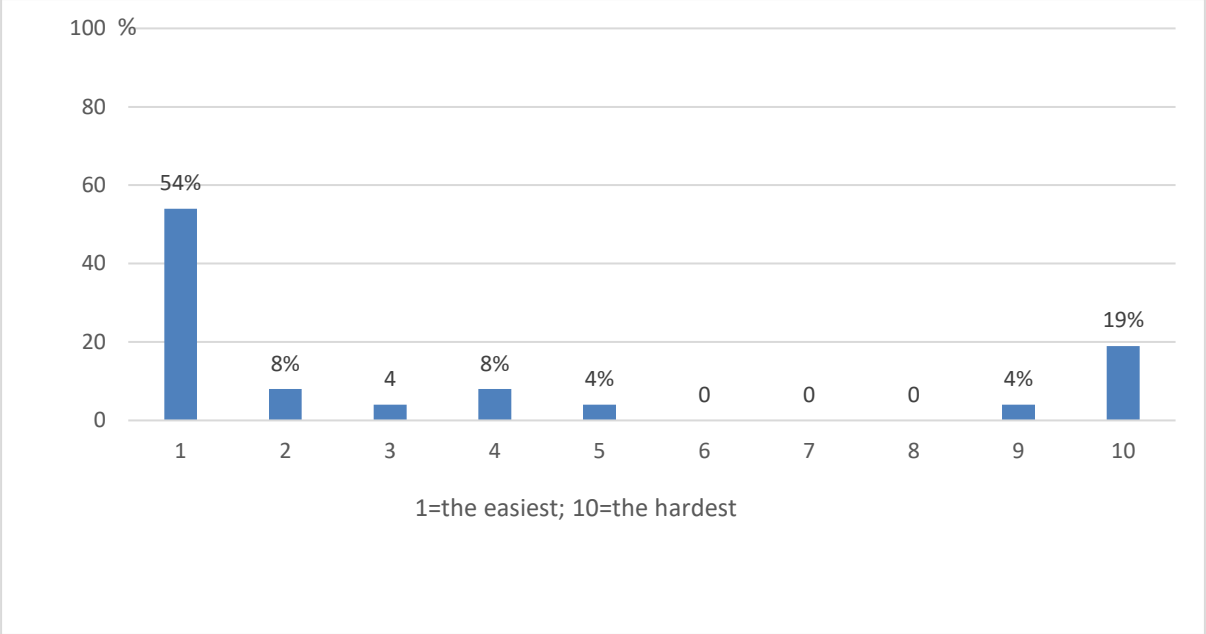
- **How easy was applying and removing the Zio patch? (On a scale of 1 to 10, 1 being the easiest and 10 being the hardest) (n=26 responders)**



How straightforward was posting the patch to the company? (On a scale of 1 to 10, 1 being the easiest and 10 being the hardest) (n=24 responders)



How easy to follow were the instructions for use? (On a scale of 1 to 10, 1 being the easiest and 10 being the hardest) (n=26 responders)



The majority of responders (n=22, 85%) considered that wearing the Zio patch did not prevent them taking part in normal activities. Most responders did not experience any side effects after using the device however four responders (15%) reported side effects mainly relating to irritation of skin.

Responders also described the positive and negative effects of using the Zio XT service.

Positive effects

Responders' statements	
1	Simple to use and simple to return
2	No negative effects at all - just some care when taking a shower to prevent the patch becoming wet which was not a problem.
3	After a couple of days, I didn't really notice it was there most of the time. It wasn't intrusive and gave me the peace of mind that my heart was being monitored 24/7 for 2 weeks. This would hopefully help identify the root cause of my recent fainting as the normal process to get an ECG was always too late (the fainting had happened and it was very likely my heart rhythm would be to normal again by the time the ECG was completed. It was very easy to fit and remove. The results of the 14 day trial where known very quickly and had a pacemaker fitted within 3 days of the results.
4	Monitoring over quite a long period without any inconvenience or discomfort. I particularly liked not having to keep a diary !
5	It showed up 28 episodes of fast heartbeat. Some I was aware of others I was not aware of.
6	I continued with normal routine and tried not to think about it too much, though I didn't over exercise during the time I wore the monitor. I did manage to press it when lifting in the garden without meaning to and as someone who sleeps on their front this was also a bit uncomfortable and ended with the button being pressed by accident. I am a very active person and enjoy good heath both mentally and physically. I was not keen to let family know about monitor so tried to wear clothes that would hide it better. Easier said than done when the weather

	is warm.
7	doesn't affect anything really quite easy to wear could go in the shower with it
8	didn't feel anything, forget i was wearing very comfortable and very good everything was fine, got on fine with it
9	I wore the Zio patch for 4 days prior to implantation of stents. Then for 10 days after implantation of 3 stents and prior to implantation of final 4th stent. The patch did not interfere with my performance of daily activities (other than not taking a bath). It did not affect my life, life style or social life. I found it very reassuring to be able to review my heart arrythmias with my cardiologist - it made sense of what I was experiencing I think my wife was slightly worried that wearing the patch was a signal that I had a serious problem with my heart
10	It indicated to the doctor that I have tacky bradycardia. It showed my heart rate during intense exercise to be 250bpm and also low heart rate at 30-35 bpm resting. This gave the doctor the ability to diagnose my condition. I was able to play tennis and run but not swim. It was slightly distracting knowing you are being monitored, and my daughters were a little worried about the device at first but I reassured them that it didn't hurt was easy to move around.
11	Comfortable and felt confident that recording was efficient. If I was out or driving and not able to write in the diary, or forgot time of irregularity, the monitor was efficient.
12	Zio didn’t interfere with any of my daily activities. My quality of life, lifestyle and social life weren’t impacted whilst wearing Zio as its discrete and hidden. After wearing the monitor and having my follow up appointment with the consultant I was reassured that the monitor showed nothing sinister and as a result I felt emotionally and mentally reassured and more positive about my heart health.
13	it affected my ability to perform daily activities it affected my quality of life, lifestyle and/or social life. Being able to shower and carry on as normal
14	did not affect my usual routines. very convenient. picked up my abnormal heart beat on day 10.
15	no effect
16	none, noticed
17	No effect on daily life or activities. was able to shower as normal. wore during sports several times. good to know it was easy to press the button if there were any issues and they would be recorded.
18	Small and easy to manage
19	very easy to use
20	There was no effect on anybody, I forgot I was using Zio patch. No problem: to perform daily activities, to quality of life, lifestyle and or/ social life and to stated of mind, emotional health and/or wellbeing.
21	no bath or shower (prevented me from taking part in steam room and swimming)
22	I couldn't bathe or shower well . I was told not to exercise in case the sweat made it peel.
23	all proactive
24	I was able to continue with normal activities. It was reassuring to wear it over a 2 week period. Friends and family were not aware I was using it - so they were not unduly concerned.
25	It did show a number of episodes even when I did not experience symptoms.
26	ability to perform daily activities

Negative effects

Responders’ statements

1	None
2	None
3	I didn't understand why I had to press the button after I had an episode as I thought that might be too late.
4	None
5	Only cosmetic
6	Did think if it had been lower it would have been less evident. I really struggled to keep a diary and did feel bad about that. On reflection I pressed my button awareness too many times when in fact only once had the symptoms that I went to see my GP about.
7	no nothing at all
8	It came off after having a shower on day 2. The nurse said it would be ok to shower but this was not the case. I would say water contact should be avoided as much as possible. I had to go back to the cardiologist and they secured it back with better tape than my plasters. It then stayed on for the duration.
9	Became detached at times and towards the end of the 7 days, this was a slight nuisance. Reddening of the skin where it was attached. The diary...see below.
10	I honestly can't think of any. I knew I needed a monitor and this one was so much better than the old Holter I had to wear.
11	None
12	None
13	it didn't stay on - lifted off and had red light so didnt give full reading
14	difficulty bathing/shower. constantly aware of patch, due to discomfort.
15	took a while to remove due to the strong adhesive. during application not all of my chest hairs around the device were removed, so some became stuck and were pulled off when removed.
16	Itchy and irritable. Worried to shower properly
17	none
18	none
19	no
20	There needs to be a way to re-attach it. I had to remove it due to a scan. Cardiology said there was no way to attach it again so i didn't wear it for the full time.
21	It was difficult (a bit) to disguise under clothes - wearing a neck scarf helped with this. It was a bit itchy at times.
22	Fell off too early. I was careful and followed all care instructions

5. Comparison with other heart monitor

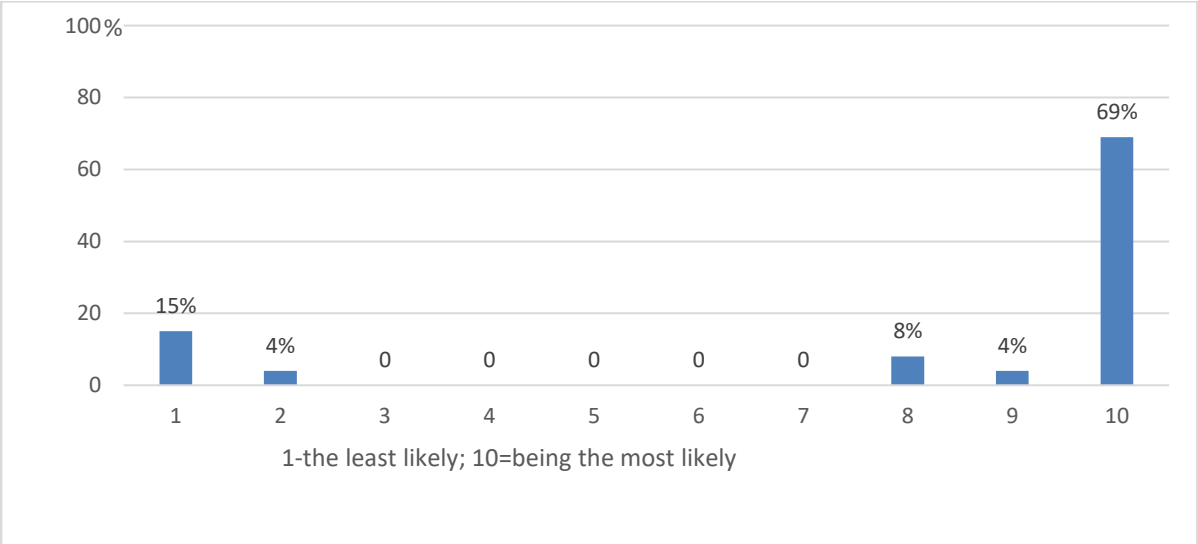
Thirteen responders (54%, n=14) had used another heart monitor before using the Zio patch, and 8 of them (57%) used Holter monitor.

If you have used other heart monitors before, how would you compare them to the Zio patch?

Responders' statements	
1	very big and uncomfortable, worn for much shorter period of time, required diary entry every half hour; would never want to use them again now I've tried Zio
2	The one I used before was attached to my chest and was suspended from my neck. I was quite careful for a couple of days but when I was hoovering or doing general housework the chest part kept separating from the necklace part. I only kept it on for about 4 days. The results were negative.

3	Zio patch was very straightforward, didn't stop me doing anything i would normally do. More space for writing about the symptoms would have been helpful.
4	The Zio patch was more comfortable and less obvious.
5	The Zio monitor was far more convenient and easier to use and wear. No wires, I could shower and do my everyday activities without a problem. With the Holter I would have to take the wires off whilst I showered and was never sure if I put them back in the right place. Zio was far more discreet as no one knew I was wearing it so no questions from work colleagues. Also, I didn't have to go back to the hospital to return it, which with the Holter I had to do which meant taking time out of work, the cost of parking and travel. This was a significant negative as i can't afford the time off work or the additional expense of petrol and parking.
6	Zio much superior
7	Bulky and inconvenient
8	very easy
9	Zio patch much more simple, you forgot it was there
10	No wires
11	It was less noticeable, it was reassuring that when I had a palpitatoin I could press a button to let the person know i had felt it. It took away the worry of being missed in a lot of data.
12	the Zio was easier to use. the previous one had a few leads which was difficult when trying to sleep
13	Zio is much more comfortable

If you needed a heart monitor in the future, how likely would you be to choose Zio patch? (On a scale of 1 to 10, 1 being least likely and10 being most likely) (n=26 responders)



- ***Additional comments about the Zio patch***

Do you have any additional comments about your experience with using Zio patch that you would like to share?

Responders' statements	
1	A helpful device and very easy to use.

2	I would totally recommend it to everyone with similar symptoms. The patch did not interfere with my life, gave me peace and comfort that my heart was being continually monitored and ultimately led to the resolution of my heart problems - this has given me my life back!
3	would recommend to anyone
4	I was happy to wear the Zio patch. I have experienced these episodes for a number of years without being able to catch any of them on record.
5	Think it was explained by my GP the readings were very normal apart from one episode. Might have been good to go over reading and have more awareness of what is normal. All in all it was a positive experience.
6	don't really think so, very easy, doesn't stop you from doing anything at all.
7	good luck to anyone else who needs to use it
8	Wearing it taught me how to recognise atrial fibrillation (and thus it's possible cause). And how hard it was for me to notice and identify brief ventricular tachycardia It was extremely helpful to have my cardiologist show me the trace on screen, explain what was going on and recommend what treatment to undertake - and why
9	I feel the diary was not adequate in that it did not really allow enough space to record all incidents. The wording for its use and layout could be rethought. I did not record all episodes of irregularity in the diary because at times it was inconvenient to do so and I was aware that the monitor would record frequency anyway. I felt that the need to use the diary for each episode raised awareness of wearing a monitor when I would have preferred to be less aware. I would have liked more feedback on my results.
10	My consultant tells my that I am one of the lucky ones who's able to have this new technology. I don't know how much they cost but I can definitely see the advantages over Holters in so many different ways. As a patient I want to know that the monitor I wear will help the doctor make his diagnosis first time. That's what the Zio did for me and I feel reassured and confident to live my life. I wish Zio was more widely available so more patients can benefit
11	None
12	Zio is premier league, the rest are just amateur!
13	Very annoyed. at not being advised of the extortionate cost of the device. £100 maybe acceptable but £1,188 is definitely NOT!!! A refund would be very welcome. The question of 'how easy was applying & removing the Zio patch' I put 2 for applying & 8 for removing but you had to choose 1 number so put 6. The question of 'If you needed a heart monitor in the future, how likely would yoube to choose Zio patch?' i scored 2 but the comments below couldn't be entered in that section Mostly due cost. It was billed at almost £1,200 & I was not advised of this before!! Very unhappy about the cost, unjustified.
14	Overall very positive. Forgot I was wearing it most of the time. Very quick to receive the results/analysis (through my doctor). Question #15. How easy was applying and removing the Zio patch? they put applying 8 and removing 5 so had to select a number in between, hence 6.
15	did not know it was water proof
16	The Zio patch did not pick anything up when I had it on for 14 days but I still continue to have the same symptoms.
17	It felt very reassuring and minimally invasive
18	I scored a 1 for the question ' if you needed a heart monitor in future, how likely would you be to choose Zio patch?' only because it did not stay on.

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies -

NICE Medical Technologies Advisory Committee

Zio Service for detecting cardiac arrhythmias

Please read the guide to completing a submission fully before completing this template.

Information about your organisation		
Organisation name	Arrhythmia Alliance	
Contact person's name	[redacted]	
Role or job title	[redacted]	
Email	[redacted]	
Telephone	[redacted]	
Organisation type	Patient/carer organisation (e.g. a registered charity)	x☐
	Informal self-help group	☐
	Unincorporated organisation	☐
	Other, please state:	
Organisation purpose (tick all that apply)	Advocacy	x☐
	Education	x☐
	Campaigning	☐
	Service provider	☐
	Research	☐
	Other, please specify:	X information support education & awareness
What is the membership of your organisation (number and type of members, region that your organisation represents, demographics, etc)? National – 60,000 patients; 40,000 HCPs		

Please note, all submissions will be published on the NICE website alongside all evidence the committee reviewed. Identifiable information will be redacted.

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies -

If you haven't already, please register as a stakeholder by completing the stakeholder registration form and returning it to medtech@nice.org.uk

Further information about registering as a stakeholder is available on the NICE website.

Did you know NICE meetings are held in public? You can register on the NICE website to attend a meeting up to 20 working days before it takes place. Registration will usually close 10 days before the meeting takes place. Up to 20 places will be available, depending on the size of the venue. Where meetings are oversubscribed NICE may need to limit the number of places we can offer.

Sources of information

What is the source of the information about patients' and carers' experiences and needs that are presented in this submission?

direct from patient feedback who have been diagnosed with various types of arrhythmias

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies -

Impact of the symptoms, condition or disease

1. How do symptoms and/or the condition or disease affect people's lives or experiences?

Arrhythmias can vary from being inconvenient to fatal. The number one killer in UK is due to an arrhythmia – sudden cardiac arrest. The most common arrhythmia (atrial fibrillation) is the leading cause of AF-related stroke. Syncope causes 6% of all A&E visits and 3% of all hospital admissions. 39% of children and 30% of adults diagnosed with epilepsy are mis-diagnosed and the vast majority have an underlying, potentially fatal, arrhythmia.

2. How do symptoms and/or the condition or disease affect carers and family?

Many people diagnosed with an arrhythmia need 24 hour care – they experience breathlessness, palpitations, anxiety, fainting (syncope), light headedness, dizziness. AF patients who survive an AF-related stroke may be severely disabled and need constant care for all bodily functions, feeding, washing, etc.

3. Are there groups of people that have particular issues in managing their condition?

Many – AF/syncope/Brugada/Long QT etc

Experiences with currently available technologies

4. How well do currently available technologies work?

There are often long waits for Holter monitoring and yield is low. Capturing the arrhythmia on an ECG is 'hit and miss' at best. Therefore any technology that can improve the detection of an arrhythmia is an improvement on the current technology. ZIO patch can be worn for 14 days at a time 24/7 even during showering etc. It has a greater yield of capturing the irregular heart rhythm. It is easy to apply and can be returned via the mail rather than the long wait for an appointment to have a Holter monitor fitted and then returning to the hospital to have it removed. You cannot wash whilst wearing a Holter monitor. The local GP can easily use the ZIO patch therefore reducing the long wait for a hospital appointment and the patient puts it into a self- address packet to return for results. It is quick, easy and cost-effective to use.

5. Are there groups of people that have particular issues using the currently available technologies?

Yes many have to rely on hospital transport to get to and from the hospital and need their carer to accompany them. There are long waiting lists for a Holter Monitor whereas a ZIO patch can be applied at the local GP surgery. Whilst wearing a Holter monitor you cannot shower or bathe. Many experience allergic reaction to the Holter monitor electrodes.

About the medical technology being assessed

6. For those <u>with</u> experience of this technology, what difference did it make to their lives?

A much quicker diagnosis, easy to capture the arrhythmia. No need for referral to hospital. Applied by local GP and then peeled off and sent back in a stamped addressed package with ease. Could shower or bathe whilst wearing the ZIO patch. Discreet and did not prevent them leading a normal active life. No need to take time off work for a hospital appointment.

7. For those <u>without</u> experience of the technology being assessed, what are the expectations of using it?

Making life easier, obtaining a diagnosis quicker, no visit to the hospital. Discreet.

8. Which groups of people might benefit most from this technology?

Additional information

9. Please include any additional information you believe would be helpful in assessing the value of the medical technology (for example ethical or social issues, and/or socio-economic considerations)

The ZIO patch can be used by all irrespective of their ethnic background. It is cost-efficient and reduces the number of visits and long waits for hospital appointments. Research has shown the yield from ZIO patch is far better than a traditional Holter monitor.

Key messages

10. In up to five statements, please list the most important points of your submission.

- **Easy to apply**
- **No need to wait for a hospital appointment**

- **Can be returned in the post**
- **Can shower/bathe whilst wearing ZIO patch**
- **Quicker diagnosis with ZIO patch than with a Holter monitor**

Thank you for your time. Please return your completed submission to medtech@nice.org.uk

Using your personal information: The personal data submitted on this form will be used by the National Institute for Health and Care Excellence for work on Medical Technologies (including reviews) and will be held on the Institute's databases for future reference in line with our privacy notice.

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies -

NICE Medical Technologies Advisory Committee

Zio Service for detecting cardiac arrhythmias

Please read the guide to completing a submission fully before completing this template.

Information about your organisation	
Organisation name	Atrial Fibrillation Association
Contact person's name	[redacted]
Role or job title	[redacted]
Email	[redacted]
Telephone	[redacted]
Organisation type	Patient/carer organisation (e.g. a registered charity) ☒ Informal self-help group ☐ Unincorporated organisation ☐ Other, please state:
Organisation purpose (tick all that apply)	Advocacy ☒ Education ☒ Campaigning ☒ Service provider ☐ Research ☐ Other, please specify:
What is the membership of your organisation (number and type of members, region that your organisation represents, demographics, etc)? National – 60,000 patients; 40,000 HCPs	

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Sources of information

What is the source of the information about patients' and carers' experiences and needs that are presented in this submission?

Patient feedback who have been diagnosed Atrial Fibrillation. This in gathered from direct contact through our helpline, patient surveys and support group meetings.

Impact of the symptoms, condition or disease

6. How do symptoms and/or the condition or disease affect people's lives or experiences?

The most common arrhythmia (atrial fibrillation) is the leading cause of AF-related stroke. AF causes breathlessness, dizziness, increased tiredness, walking short distances can cause difficult.

7. How do symptoms and/or the condition or disease affect carers and family?

Often AF reduces mobility because of being short of breath. Patient can feel dizzy so need to be watch in case of fainting or feeling faint. This impacts on their quality of life and often cannot take part in activities they once did. Anxiety and depression can follow because of the impact AF can cause on the patient and family

8. Are there groups of people that have particular issues in managing their condition?

AF/syncope

Experiences with currently available technologies

9. How well do currently available technologies work?

There are often long waits for Holter monitoring. Capturing the arrhythmia on an ECG can prove extremely difficult if not impossible. Any technology that can improve the detection of an arrhythmia is an improvement on the current technology. ZIO patch can be worn for 14 days at a time 24/7 without any restrictions. The possibility of capturing the irregular heart rhythm is much higher. It is easy to apply and can be returned via the mail rather than the long wait for an appointment to have a Holter monitor fitted and then returning to the hospital to have it removed. You cannot wash whilst wearing a Holter monitor. The local GP can easily use the ZIO patch therefore reducing the long wait for a hospital appointment and the patient puts it into a self- address packet to return for results. It is quick, easy and cost-effective to use.

10. Are there groups of people that have particular issues using the currently available technologies?

Often mobility is poor for an AF patient so getting to the hospital to collect a holter monitor can prove difficult.

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies -

About the medical technology being assessed

11. For those with experience of this technology, what difference did it make to their lives?

Because of the convenience of this technology the diagnosis process will be quicker for patients, this will reduce the anxiety often associated with a long drawn out diagnostic process.

12. For those without experience of the technology being assessed, what are the expectations of using it?

Making life easier, obtaining a diagnosis quicker, no visit to the hospital.

13. Which groups of people might benefit most from this technology?

Additional information

14. Please include any additional information you believe would be helpful in assessing the value of the medical technology (for example ethical or social issues, and/or socio-economic considerations)

The ZIO patch can be used by all irrespective of their ethnic background. It is cost-efficient and reduces the number of visits and long waits for hospital appointments. Research has shown the yield from ZIO patch is far better than a traditional Holter monitor.

Key messages

15. In up to five statements, please list the most important points of your submission.

- **Easy to apply**
- **No need to wait for a hospital appointment**
- **Can be returned in the post**
- **Can shower/bathe whilst wearing ZIO patch**
- **Quicker diagnosis with ZIO patch than with a Holter monitor**

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External Assessment Centre correspondence

Zio XT for detecting cardiac arrhythmias

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the sponsor
b) need to check "real world" assumptions with NICE's expert advisers, or
c) need to ask the sponsor for additional information or data not included in the original submission, or
d) need to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the Assessment Report Overview, and is made available at public consultation.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
Whole document (in particular 2 Overview of the technology, 3 Clinical context, 6 Ongoing data use and collection, 7 Adverse events)	**Initial questions to company – 27.09.19** 1. To confirm, has there been just one version of Zio Service (as indicated on page 10)? When did this launch? Page 10 says the Zio XT Service launched in 2016, but one submitted study (Rosenberg) was published in 2013. Has Zio Service changed significantly since 2013? 2. We note that the algorithm in ZEUS is described as AI. Please describe how the algorithm develops (is this continuous). How significant have the ongoing developments to the algorithm been? 3. How has the accuracy of the algorithm been tested (and is testing ongoing)? We note the inclusion of Hannun et al. 2019 that assesses Zio against cardiologists. Is this reported in the Zio XT Service Evaluation Tool? 4. How does the company ensure that updates to the algorithm improve the	**Responses from company – 03.10.19** **The technology** 1. To confirm, has there been just one version of Zio Service (as indicated on page 10)? When did this launch? Page 10 says the Zio XT Service launched in 2016, but one submitted study (Rosenberg) was published in 2013. Has Zio Service changed significantly since 2013? The Zio XT Service (current version) was originally FDA cleared in 2012 with a launch in the U.S. in 2013. The Zio XT Service was introduced in the UK in 2016. There have been incremental changes to the service since the initial clearance primarily to the Zio ECG Utilization System (ZEUS) software. Incremental changes to the Zio XT monitor include slight modifications for improved adhesion. In summary, the Zio Service has not changed significantly since the study by Rosenberg in 2013. 2. We note that the algorithm in ZEUS is described as AI. Please describe how the algorithm develops (is this continuous). How significant have the ongoing developments to the algorithm been? Algorithm updates are incremental and controlled through the iRhythm design control process. This pathway is taken to ensure that performance benefits are achieved prior to use in a clinical	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
	quality of results? Can you provide more information on the company design control process (what does the formal verification testing entail)? 5. We note that the advice given on the Zio technical report is actionable. Is Zio Service registered with the CQC? 6. Is every report overseen/quality assured by clinical experts or just a percentage of them? Or is it just input into the algorithm from experts over time? 7. Who receives/resolves queries entered by clinicians after they've reviewed the report? 8. What are the sources for current clinical pathways outlined on pages 24-26? 9. Was a search carried out in national regulatory databases such as those maintained by the MHRA and FDA for adverse events and outcomes associated with Zio Service? If so, what were the findings?	environment. In general, updates to the algorithm are driven by either expansion in capabilities or improvement opportunities from both qualitative/quantitative analysis. A benefit from this approach is allowing the company's data science team to identify targeted data sets needed to address the opportunity as well as continue to ensure the integrity of the data set used to train the algorithm. 3. How has the accuracy of the algorithm been tested (and is testing ongoing)? We note the inclusion of Hannun et al. 2019 that assesses Zio against cardiologists. Is this reported in the Zio XT Service Evaluation Tool? Algorithm detection performance requirements are established in conjunction with the company Medical Directors. To validate algorithm performance a mixture of labeled standards databases (e.g., MIT-BIH) as well as internal databases are used. For rhythm classification performance, the company developed a reference database of known rhythms. An internal reference database was developed to overcome the lack of a standard database containing the breath of rhythms detected by the algorithm, as well as sufficient examples of each rhythm to evaluate performance. Following algorithmic analysis, iRhythm's certified cardiac physiologists use the Quality Assurance Tool to conduct a quality review on the findings (beats, beat types, heart rates, rhythms) before posting a report for clinician review. This allows the cardiac physiologist to both	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		curate the findings into the PDF based report and to edit algorithm findings as needed. The Zio XT Service Evaluation Tool does not include algorithm accuracy statistics. However, the iRhythm clinical team reviews every final interpretation completed by a physician through our secure website. (28% of final interpretations are completed online and are thus available to iRhythm for analysis.) 99% of physicians' final interpretations online match the preliminary findings delivered in the Zio technical report. 4. How does the company ensure that updates to the algorithm improve the quality of results? Can you provide more information on the company design control process (what does the formal verification testing entail)? Performance validation against reference databases is performed on all algorithm updates. Results must meet or exceed established performance requirements to be eligible for clinical use. In practice for this testing, the reference ECG records are fed into the updated algorithm. Following analysis, the annotations from the algorithm are compared to the database reference annotations to determine algorithm performance. Results are captured in a formal test report that is reviewed and approved along with other associated design documentation. Only after approval of all required design control	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		documentation, as well as completion of regulatory assessments, can the algorithm be released into production. 5. We note that the advice given on the Zio technical report is actionable. Is Zio Service registered with the CQC (Care Quality Commission)? The Zio Service is registered with the Care Quality Commission. The approval was obtained on 25 July 2018 and our profile can be found here. Jennifer Weller is the designated authority for iRhythm. The Zio technical report is structured in order for the interpreting clinician to easily comprehend any arrhythmias or lack of arrhythmias detected during the wear time. With this information, the clinician must then utilize clinical judgment in deciding the next treatment options for the patient. The Zio technical report does not provide advisement for clinical or medical management. 6. Is every report overseen/quality assured by clinical experts or just a percentage of them? Or is it just input into the algorithm from experts over time? After the data is processed by our algorithm, every report is curated and quality assured by a cardiac technician. Our clinical team members	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		go through a rigorous training program to ensure full competency in our clinical processes. • It takes approximately 9-12months for a scanning technician to become fully competent • Prior to full competency their work is quality assured by a member of our QA team before (concurrent QA). • Once a technician achieves full competency 1-3% of their work is reviewed (retrospective QA) 7. Who receives/resolves queries entered by clinicians after they've reviewed the report? If a clinician requires more ECG data or amendments to the report, a request is made to the iRhythm clinical team. Each query/request is reviewed, addressed and the amended report is posted to our secure website. If additional information is required from the clinician, the iRhythm clinical team member will consult the clinician prior to amending the report. **Clinical pathway** 8. What are the sources for current clinical pathways outlined on pages 24-26?	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		The current Cardiology pathway has been sourced from the Liverpool Heart & Chest (LHCH) Cardiac Physiology Ambulatory Monitoring service, Liverpool. This pathway is a demonstration of how approximately 2000 patients per year are referred and progressed through a diagnosis to treatment / care management plan across the service. This information was offered and discussed at length for full understanding of each step by Dr Claire Appleby, Cardiologist LHCH. The current Stroke / TIA pathway has been sourced from the St Helens & Knowsley Hospital Trust (StHKHT) Stroke & TIA services, St Helens. This patient population has had a stroke / TIA and cardiac arrhythmia is suspected as a possible cause. This pathway is a demonstration of how approximately 1000 patients per year who access the service would be referred and progressed through a diagnosis to treatment / care management plan across the service. The information was offered and discussed at length for full understanding of each step of the pathway by Dr Andrew Hill Stoke Physician & Clinical Director of Stroke services StHKHT. The current General Cardiology pathway has been sourced from the Wirral Heart Centre (WHC), St Catherine's Community Foundation Trust, Birkenhead. This pathway is a demonstration of how approximately 4500 patients who access the service per year would be referred and progressed through a diagnosis to treatment / care management plan across the service. This information was offered and discussed at length for full understanding of each step by Mrs Nicola Williams, Cardiac Clinical Services Manager, WHC.	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		Adverse events 9. Was a search carried out in national regulatory databases such as those maintained by the MHRA and FDA for adverse events and outcomes associated with Zio Service? If so, what were the findings? A search was made of the following sites for data on adverse events and outcomes: • https://www.nice.org.uk/advice/mib101/chapter/Regulatory-information • https://www.irhythmtech.com/products-services/zio-xt • https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/detail.cfm?mdrfoi__id=4990677 • https://www.irhythmtech.com/zio_xt_precautions • https://www.fiercebiotech.com/medical-devices/irhythm-wearable-cardiac-monitor-gets-ce-mark-cardiologic-partners-to-sell-it-u-k • http://www.thegoodhealthsuite.co.uk/GP/management-staffing/i-t/153-zio-service-cardiac-monitoring-device-launches-in-uk • http://www.heartrhythmalliance.org/files/files/A-A%20US/A-A%20USA%20Which%20ECG%20is%20Right%20for%20You%20Booklet.pdf	

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		• https://www.cardiovascularbusiness.com/topics/technology-management/zio-irhythm-gains-further-recognition-key-diagnostic-cardiac • https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm • http://www.mhra.gov.uk/public-assessment-reports/ • https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/ema_group_types/ema_medicine • http://mri.cts-mrp.eu/Human/ • https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/ • http://www.crd.york.ac.uk/crdweb/Showrecord.asp?LinkFrom=OAI&ID=32016000097 • https://www.ncbi.nlm.nih.gov/pubmed/31045463 No relevant reports were identified from the MHRA. The FDA MAUDE site yielded 138 results dating from 2014, of which: • 113 were incidences of contact dermatitis • 6 were incidences of adhesive failure • 12 were cases of false negative or incorrect diagnoses being sent to the patient or physician • 8 were cases where the device was faulty or the patient management process failed No other site yielded additional information on adverse events.	

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Whole document (in particular 3 Clinical context, 9 Interpretation of clinical evidence)	**Questions to expert advisers – 07.10.19** 1) What are the main guidelines for diagnosing and managing arrhythmia? 2) Is there variation in the definition of arrhythmia? What is the standard, in particular for atrial fibrillation? 3) Are certain arrhythmias harder to detect than others? 4) What are main differences in population between different types of arrhythmia? Is there a significant systematic difference in risk factor and comorbidity across different types of arrhythmias? 5) Are there certain populations that are particularly at risk for arrhythmia? For example, some studies include a population of 'high-risk' individuals – is this a clinically defined group? 6) How would you calculate the risk of arrhythmia? Are there any standardised risk scores available?	**Response from Dr Matthew Reed – 08.10.19** 1) What are the main guidelines for diagnosing and managing arrhythmia? ESC syncope guidelines (https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Syncope-Guidelines-on-Diagnosis-and-Management-of) ESC Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death Guidelines (https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Ventricular-Arrhythmias-and-the-Prevention-of-Sudden-Cardiac-Death) NICE Transient loss of consciousness pathway (https://www.nice.org.uk/guidance/cg109) NICE Heart rhythm conditions guidelines (https://www.nice.org.uk/guidance/conditions-and-diseases/cardiovascular-conditions/heart-rhythm-conditions) 2) Is there variation in the definition of arrhythmia? What is the standard, in particular for atrial fibrillation? Not really – NICE defines Atrial fibrillation (AF) as an atrial tachyarrhythmia characterised by predominantly uncoordinated atrial activation with consequent deterioration of atrial mechanical function. (https://www.nice.org.uk/guidance/cg180/evidence/atrial-fibrillation-update-appendix-s-pdf-243739983)	

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	7) What are the benefits of longer periods of monitoring for arrhythmias? For example, is there published evidence that links longer periods to improved clinical outcomes? 8) Conversely, could there be any potential issues with extended monitoring vs a 24 or 48-hour Holter? 9) Are you aware of any devices similar to the Zio XT monitor i.e. soft biosensors for extended cardiac monitoring? 10) Do you think that this device could be superseded in the near future by other technology (i.e. app-based technologies, wearables etc)? 11) Is shaving of body hair required for Holter monitors? 12) Could a difference in the time between presenting with symptoms and receiving a clinical report have a significant clinical effect? If so, what difference in time would be considered dangerous and does this	3) Are certain arrhythmias harder to detect than others? Different arrhythmias present in different ways. Gold standard for diagnosing any arrhythmia is capturing it on an ECG. 4) What are main differences in population between different types of arrhythmia? Is there a significant systematic difference in risk factor and comorbidity across different types of arrhythmias? Yes – this is not a straightforward question. Different arrhythmias have different presenting symptoms, different types and demographics of patients who commonly are diagnosed with them and different prognoses. Typically atrial arrhythmias as less serious than ventricular arrhythmias. 5) Are there certain populations that are particularly at risk for arrhythmia? For example, some studies include a population of 'high-risk' individuals – is this a clinically defined group? See above answer to Q4 6) How would you calculate the risk of arrhythmia? Are there any standardised risk scores available? No standardised scoring systems for calculating risk of arrhythmia. CHADSVASC2 score predicts prognosis of AF however it is quite a poor prediction score. Risk depends on the history of the presenting symptoms, patient demographics and past medical history.	

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	differ depending on the population or suspected arrhythmia? 13) Are clinical outcomes likely to be clinically different between a population with suspected AF and with already diagnosed AF, when monitored with a Holter or extended continuous monitor? 14) Are there clinically defined relations between AF burden and risk of stroke or other comorbidities? 15) We understand that implantable cardiac monitors are rarely used as a first line of standard care – is this the case? Would you ever use an implantable monitor over a temporary one? Or are monitors only implanted when there is a therapeutic purpose as well?	7) What are the benefits of longer periods of monitoring for arrhythmias? For example, is there published evidence that links longer periods to improved clinical outcomes? Definitely – the longer you monitor the more chance of the patient having the monitor recording when they have an arrhythmia and therefore the more chance of picking up the culprit arrhythmia. 8) Conversely, could there be any potential issues with extended monitoring vs a 24 or 48-hour Holter? Drawback of longer monitoring is that longer implantable monitors are invasive (i.e. need an invasive surgical procedure to implant) and are more expensive. 9) Are you aware of any devices similar to the Zio XT monitor i.e. soft biosensors for extended cardiac monitoring? 2 other patches are available in the UK Bardy patch: https://www.bardydx.com (7 days only) ECG on demand: https://ecg-od.com 10) Do you think that this device could be superseded in the near future by other technology (i.e. app-based technologies, wearables etc)? More than likely in years to come, ECG monitoring devices will become smaller, easier to wear, more integrated with smartphones/watches and cheaper 11) Is shaving of body hair required for Holter monitors? Yes in hairy people	

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		12) Could a difference in the time between presenting with symptoms and receiving a clinical report have a significant clinical effect? If so, what difference in time would be considered dangerous and does this differ depending on the population or suspected arrhythmia? Potentially the earlier the clinician has knowledge of a potentially dangerous arrhythmia, the better, as the patient in theory could have another event in between the device being placed and the result being available to the clinician. 13) Are clinical outcomes likely to be clinically different between a population with suspected AF and with already diagnosed AF, when monitored with a Holter or extended continuous monitor? One would be unlikely to use a Holter or extended continuous monitor to diagnose AF in someone who has already been diagnosed with AF. In future the yield of AF (i.e. the percentage of time that the person is in AF) will help stratify treatment but evidence here is not yet available to guide clinical treatment. 14) Are there clinically defined relations between AF burden and risk of stroke or other comorbidities? As above – AF burden likely to be associated with risk of stroke but evidence is not yet available to guide clinical treatment 15) We understand that implantable cardiac monitors are rarely used as a first line of standard care – is this the case? Would you ever use an implantable monitor over a temporary one? Or are monitors only implanted when there is a therapeutic purpose as well?	

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		Cardiologists have different thresholds for implanting ILRs. Main concern is invasiveness and cost. In some places (i.e. Bristol) ILRs are implanted in the acute and emergency wards. You might implant an ILR first up if episodes are less frequent that every 2 weeks (see NICE guidance below) but you may choose to try a temporary device once or sometimes twice first. ***Criteria to determine type of ambulatory ECG*** ***For people who have:*** • TLoC at least several times a week, offer Holter monitoring (up to 48 hours if necessary). If no further TLoC occurs during the monitoring period, offer an external event recorder that provides continuous recording with the facility for the patient to indicate when a symptomatic event has occurred. • TLoC every 1–2 weeks, offer an external event recorder. If the person experiences further TLoC outside the period of external event recording, offer an implantable event recorder[1]. • TLoC infrequently (less than once every 2 weeks), offer an implantable event recorder[1]. A Holter monitor should not usually	

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		be offered unless there is evidence of a conduction abnormality on the 12-lead ECG. **Response from Dr Jacqueline Colwill – 10.10.19** What are the main guidelines for diagnosing and managing arrhythmia? Follow NICE guidelines/local guidelines Indications: *Symptomatic palpitations. Less frequent symptoms can occur sporadically with no predictable pattern so a greater chance of capturing over 14 day monitoring. *Falls/syncope *Presence of AF or paroxysmal AF and rate control *Stroke pathway - to capture/exclude AF/PAF *Known or suspicion of conduction defect such as accessory pathways etc Monitoring devices available: *24hr-72hr holter recorders *R test *Cardiocall event monitor *AliveCor *14 day Zio * Implantable loop recorder Is there variation in the definition of arrhythmia? * Definition of 'arrhythmia' covers a broad range of arrhythmias. Monitoring is largely performed to rule out significant arrhythmias which put patients at risk of harm or death (such as ventricular arrhythmias, heart blocks, AF, PAF)	

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		Sometimes also used to reassure the individual patient, particularly for symptoms of palpitations. Risk stratification - high/low risk What is the standard, in particular for atrial fibrillation? *Type of monitoring used is largely based on each individual, upon frequency of symptoms and resources available Are certain arrhythmias harder to detect than others? * Paroxysmal arrhythmias (PAF) * Infrequent symptoms (palpitations) What are main differences in population between different types of arrhythmia? Is there a significant systematic difference in risk factor and comorbidity across different types of arrhythmias? Risk factor and Co-mobitites are broad across the population: *Genetic/Family history of sudden death *Palpitations *Heart disease/LVSD/EF >35% and ventricular arrhythmia *Blackouts/falls/collapses *AF/PAF *Aged related risk factor <65 *Stroke and AF/PAF *Congenital conduction abnormalities *Post cardiac surgery *Accessory pathways and ablation *Medication side effects, particularly mental health medications *Endocrine abnormalities, electrolyte abnormalities	

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		This is merely the most common indications but is not an exhausted list Are there certain populations that are particularly at risk for arrhythmia? For example, some studies include a population of 'high-risk' individuals – is this a clinically defined group? As list above ^ *Heart disease /LVSD *Stroke *Blackouts/falls *Certain medications How would you calculate the risk of arrhythmia? *Risk is largely calculated based upon each individual presentation, history and risk factors. Risk is also calculated on each individual depending upon their results. *Arrhythmias such as ventricular tachycardia, ventricular arrhythmias, complete heart block, pauses carry a greater risk/priority to treat than atrial arrhythmias, with the exception of AF and PAF which requires adequate rate control and anti-coagulation therapy to prevent strokes. Are there any standardised risk scores available? * CHA_2DS_2-VASc risk score for AF What are the benefits of longer periods of monitoring for arrhythmias? *Monitoring for a longer period of time can be helpful where symptoms are less frequent or arrhythmias are paroxysmal For example, is there published evidence that links longer periods to improved clinical outcomes? *Clinical evidence supports longer term monitoring for PAF for stroke pathway.	

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		Conversely, could there be any potential issues with extended monitoring vs a 24 or 48-hour Holter? *No, not to my knowledge Are you aware of any devices similar to the Zio XT monitor i.e. soft biosensors for extended cardiac monitoring? Do you think that this device could be superseded in the near future by other technology (i.e. app-based technologies, wearables etc)? * Yes potentially, it's a growing market and other simular technology is now being developed and is available, for example Bardy Is shaving of body hair required for Holter monitors? *Yes, a good skin contact is essential Could a difference in the time between presenting with symptoms and receiving a clinical report have a significant clinical effect? If so, what difference in time would be considered dangerous and does this differ depending on the population or suspected arrhythmia? * Yes, a delay in results could have a significant clinical effect resulting in delayed treatment, cause harm or death. This impact will differ depending upon the type/origin and significance of the arrhythmia. An expectation in clinical practice, monitors should be analysed and results available within 2 working days (most centres are currently operating this service across Mon-Fri and not routinely 7 day service) Are clinical outcomes likely to be clinically different between a population with suspected AF and with already diagnosed AF, when monitored with a Holter or extended continuous monitor? *Patients who are diagnosed with AF will be offered anticoagulation therapy if suitable and often require rate control therapy and on this occasion short term holter monitoring can be used to assess their rate control whereas.....	

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		Suspected AF/PAF patients often require longer term monitoring to try to capture the arrhythmia (AF/PAF) thus to prevent a stroke/TIA. Treatment for AF/PAF is typically anticoagulation therapy which carries a bleed risk and requires supporting clinical evidence to ethically prescribe. Are there clinically defined relations between AF burden and risk of stroke or other comorbidities? *Yes, there is clinical evidence to support AF and PAF with a risk of stroke. We understand that implantable cardiac monitors are rarely used as a first line of standard care – is this the case? *Yes, an implantable device is an invasive monitor and should not be used as 1st line of standard care unless there is significant clinical evidence to support. Would you ever use an implantable monitor over a temporary one? *No Or are monitors only implanted when there is a therapeutic purpose as well? *I would only use an implanted device for diagnostic purposes **Response from Dr Gregory Lip – 12.10.19** 1) What are the main guidelines for diagnosing and managing arrhythmia? Guidelines from ESC, NICE, AHA/ACC/HRS, APHRS 2) Is there variation in the definition of arrhythmia? What is the standard, in particular for atrial fibrillation?	

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		Generally detection of 30s paroxysm 3) Are certain arrhythmias harder to detect than others? Yes. Depends on frequency 4) What are main differences in population between different types of arrhythmia? Is there a significant systematic difference in risk factor and comorbidity across different types of arrhythmias? Clearly there are differences between atrial and ventricular arrhythmias 5) Are there certain populations that are particularly at risk for arrhythmia? For example, some studies include a population of 'high-risk' individuals – is this a clinically defined group? Yes Yes 6) How would you calculate the risk of arrhythmia? Are there any standardised risk scores available?	

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		There are risk scores for incident AF eg C2HEST, Framingham, CHARGE-AF 7) What are the benefits of longer periods of monitoring for arrhythmias? For example, is there published evidence that links longer periods to improved clinical outcomes? Monitor longer, more likely to detect 8) Conversely, could there be any potential issues with extended monitoring vs a 24 or 48-hour Holter? Service strain 9) Are you aware of any devices similar to the Zio XT monitor i.e. soft biosensors for extended cardiac monitoring? Other patches Monitoring devices PPG on smartphone 10) Do you think that this device could be superseded in the near future by other technology (i.e. app-based technologies, wearables etc)? Yes	

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		11) Is shaving of body hair required for Holter monitors? Possibly 12) Could a difference in the time between presenting with symptoms and receiving a clinical report have a significant clinical effect? If so, what difference in time would be considered dangerous and does this differ depending on the population or suspected arrhythmia? Possibly 13) Are clinical outcomes likely to be clinically different between a population with suspected AF and with already diagnosed AF, when monitored with a Holter or extended continuous monitor? Depends on outcome 14) Are there clinically defined relations between AF burden and risk of stroke or other comorbidities? Yes 15) We understand that implantable cardiac monitors are rarely used as a first line of standard care – is this the case? Would you ever use	

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		an implantable monitor over a temporary one? Or are monitors only implanted when there is a therapeutic purpose as well? Yes Not usually No **Response from Dr James Teo – 13.10.19** Disclaimer: I am responding to this questionnaire as a stroke neurologist, not as a cardiologist or electrophysiologist. I do not specialise in arrhythmia detection, and my clinical practice only covers arrhythmia's which lead to strokes. The questionnaire tries to lump all arrhythmia's together, when they are not comparable since most are distinct diseases with distinct pathophysiologies, distinct syndromes and distinct populations affected. 1) What are the main guidelines for diagnosing and managing arrhythmia? NICE helpfully provides guidelines on this topic: https://www.nice.org.uk/guidance/conditions-and-diseases/cardiovascular-conditions/heart-rhythmconditions https://pathways.nice.org.uk/pathways/heart-rhythm-conditions European Society of Cardiology also publishes extensive guidelines on this:	

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		https://www.escardio.org/Guidelines/Consensus-and-Position-Papers/Arrhythmias-and-Electrophysiology-Consensus-Position-Papers There is also joint ACC/AHA/ESC (North America and Europe) guidelines specific to Atrial Fibrillation: https://www.ahajournals.org/doi/full/10.1161/circ.104.17.2118 2) Is there variation in the definition of arrhythmia? What is the standard, in particular for atrial fibrillation? I am not sure the first part of this question is answerable since arrhythmia are a collection of distinct diseases. The definition for atrial fibrillation is internationally standardised for Europe and North America (see: https://www.ahajournals.org/doi/full/10.1161/circ.104.17.2118) 3) Are certain arrhythmias harder to detect than others? Paroxysmal arrhythmia's (i.e. episodic arrhythmia's) are obviously harder to detect as they are not present all the time. This includes paroxysmal atrial fibrillation, non-sustained ventricular tachycardia's, supraventricular tachycardia's. 4) What are main differences in population between different types of arrhythmia? Is there a significant systematic difference in risk factor and comorbidity across different types of arrhythmias?	

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		This question assumes that there are commonalities between arrhythmia types. Each arrhythmia-type are distinct pathophysiological entities with distinct epidemiological patterns. 5) Are there certain populations that are particularly at risk for arrhythmia? For example, some studies include a population of 'high-risk' individuals – is this a clinically defined group? *Responses – Dr James Teo, 12/10/2019* This question lumps all arrhythmia's together. This makes the question unanswerable. For atrial fibrillation, known risk factors include females, elderly, those with history of hypertension, ischaemic heart disease or mitral valvular disease and those with chronic alcohol use. 6) How would you calculate the risk of arrhythmia? Are there any standardised risk scores available? This question lumps all arrhythmia's together. This makes the question unanswerable. 7) What are the benefits of longer periods of monitoring for arrhythmias? For example, is there published evidence that links longer periods to improved clinical outcomes? Longer periods of cardiac monitoring increases detection of arrhythmia's, and arrhythmia's can only be treated if diagnosed. There is a wealth of literature on this topic from Holter ECG's, Implantable	

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		Loop recorders to Inpatient telemetry. References specific to the Zio: https://eurjmedres.biomedcentral.com/articles/10.1186/s40001-019-0383-8 https://www.frontiersin.org/articles/10.3389/fneur.2014.00266/full 8) Conversely, could there be any potential issues with extended monitoring vs a 24 or 48-hour Holter? Main issues are: A. tolerability of extended monitoring - Holters have poor tolerability due to the wired interfaces and the actual ECG recording time is often <70% of wear time. B. interim interpretation of positive results from a recording - Patch-based recorders and Holters record continuously and are only interpreted at the end of the recording. This means that positive results early in the reading may not be acted upon until the end of the recording (ie. Delayed in the context of extended monitoring). This is however extremely rare in the context of Holter ECG's since the yield of arrhythmia detection is so low from just 24-48hr Holters). Also, many NHS services have waiting list of 1-4 weeks to deploy a Holter ECG and 1-2 weeks to interpret a 24-48hr Holter ECG (ie. current waiting list of standard of care exceeds the	

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		duration of Zio extended monitoring). 9) Are you aware of any devices similar to the Zio XT monitor i.e. soft biosensors for extended cardiac monitoring? Bardy produces another patch-based recorder There are other patch-based recorders which rely on manual downloading of the recording but these require extensive human interpretation. 10) Do you think that this device could be superseded in the near future by other technology (i.e. app-based technologies, wearables etc)? Wrist-based wearables already exist but these are usually not continuous (due to battery life) and only record for 30-60 second bursts. The signal quality is also not comparable to medical-grade chest wall leads from a precordium patch. *Responses – Dr James Teo, 12/10/2019* 11) Is shaving of body hair required for Holter monitors? Yes 12) Could a difference in the time between presenting with symptoms and receiving a clinical report have a significant clinical effect? If so, what difference in time would be considered dangerous and does this differ depending on the population or suspected arrhythmia? The arrhythmia that my clinical practice is focused on is paroxysmal atrial fibrillation which is commonly asymptomatic so this question is not answerable.	

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		13) Are clinical outcomes likely to be clinically different between a population with suspected AF and with already diagnosed AF, when monitored with a Holter or extended continuous monitor? This question is ambiguous. It is not clear if the clinical outcomes comparison is: - between a population with suspected AF and with already diagnosed AF; or - between a population when monitored with a Holter or extended continuous monitor? 14) Are there clinically defined relations between AF burden and risk of stroke or other comorbidities? Yes. Increased AF burden is associated with increased risk of stroke. https://jamanetwork.com/journals/jamacardiology/fullarticle/2681476 https://www.ncbi.nlm.nih.gov/pubmed/19843914 Current AF treatment guidelines for stroke prevention do not factor this into clinical decision-making; this is likely due to the difficulty measuring AF burden without extended cardiac monitoring. 15) We understand that implantable cardiac monitors are rarely used as a first line of standard care – is this the case? Would you ever use an implantable monitor over a temporary one? Or are monitors only implanted when there is a therapeutic purpose as well? Implantable cardiac monitors are rarely used as first line of standard care in United Kingdom (it is	

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		used commonly in North America). An implantable monitor may be indicated if there was difficulty deploying a non-invasive one for extended periods (e.g. skin reaction to adhesive). The last component of the question is unclear, as it is unclear why any investigation would be done without a therapeutic purpose. **Response from Dr Anthony Shannon – 14.10.19** 1) What are the main guidelines for diagnosing and managing arrhythmia? There is a NICE CG for atrial fibrillation and a number of European / heart rhythm society documents. In general, we follow NICE180 for AF but for all other diagnosis and management this is left to individual cardiology practice. There is a clesr national deficiency in this respect. 2) Is there variation in the definition of arrhythmia? What is the standard, in particular for atrial fibrillation? There remains some disagreement regarding the diagnosis of AF on ecg monitoring devices – ie the AF burden and at what point anticoagulation is deemed appropriate (also in the setting of AF diagnosed via pacemaker interrogation – clinical studies are ongoing. Most cardiologists agree that a 30 second episode of AF is the minimum required to diagnose "PAF".	

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		3) Are certain arrhythmias harder to detect than others? Given that AF carries the greatest risk (stroke) and is the most common, sustained arrhythmia – this is the focus but can be hard to detect given that some patients have no symptoms and other have only intermittent symptoms. The common practice of using multiple days of short term ECG monitoring is often fruitless. More prolonged, less intrusive/patient friendly methods of ECG monitoring are v desirable. 4) What are main differences in population between different types of arrhythmia? Is there a significant systematic difference in risk factor and comorbidity across different types of arrhythmias? AF is more common in older patients and particularly in those with certain risk factors. Alcohol excess is the most common "cause" of AF in a patient of any age. In general, atrial arrhythmias such as SVT present more commonly in younger adult and are often associated with specific symptoms. Risk factos clustering is not so relevant. AF or paroxysmal AF is more common in middle age / older age and although it can occur in otherwise healthy people, it is more commonly associated with co-morbidities such as obesity, obstructive sleep apnoea, type 2 diabetes, hypertension, ischaemic heart disease and heart failure. Alcohol xs is also a very frequent lifestyle risk factor. Ventricular arrhythmias are much less common than atrial arrhythmias and are often associated with structural heart disease such as ischaemic heart disease and/or severe left ventricular systolic dysfunction.	

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		5) Are there certain populations that are particularly at risk for arrhythmia? For example, some studies include a population of 'high-risk' individuals – is this a clinically defined group? As above. One additional group are patients with TIA/stroke. If such a diagnosis is made in a younger person without risk factors for vascular disease, then embolic stroke due to an episode of AF might be suspected. Even in older patients (where the prevalence of AF is highest), the ability to detect a new diagnosis of AF is increasingly felt to be important. Often the CT scan / MRI brain scan might suggest an embolic cause of stroke, even in a patient who has vascular disease risk factors. For these patient groups, current practice is to offer ECG monitoring post discharge. The current monitors are often too short in duration and the diagnostic yield is low. More prolonged ECG monitoring in these groups of patients to identify AF/PAF is of extreme value. 6) How would you calculate the risk of arrhythmia? Are there any standardised risk scores available? There are no algorithms or scores in current clinical practice which are used to determine future risk of any arrhythmia. CHADS2VASC2 score is used to determine the risk of thrombo-embolic events in patients with a confirmed diagnosis of AF/PAF 7) What are the benefits of longer periods of monitoring for arrhythmias? For example, is there published evidence that links longer periods to improved clinical outcomes?	

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		There are 22 unique studies into clinical effectiveness of the ZIO patch. PUBMED systematic literature review: "Cardiac arrhythmia detection outcomes among patients monitored with the Zio patch system" Yenikomshian et al, Oct 2019. Findings from the review suggest that long-term, continuous, uninterrupted monitoring with Zio results in longer patient wear times and higher cardiac arrhythmia detection rates compared with outcomes reported in previous reviews of short-duration (24-48 h) cardiac rhythm recording studies. 8) Conversely, could there be any potential issues with extended monitoring vs a 24 or 48-hour Holter? There would require some auditing around skin reaction to the device. 9) Are you aware of any devices similar to the Zio XT monitor i.e. soft biosensors for extended cardiac monitoring? I have only heard of Bardy as being a company who produce a soft biosensor for Cardiac Monitoring. There are other companies such as Cardioscan, CardioSTAT, Novacor and GE who produce extended Cardiac Monitors, but these rely on conventional press-stud connection with gel electrodes. 10) Do you think that this device could be superseded in the near future by other technology (i.e. app-based technologies, wearables etc)? Unlikely at present. 11) Is shaving of body hair required for Holter monitors?	

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		Yes. It reduces impedance between the device and the skin and will ultimately reduce artefact content on the report. 12) Could a difference in the time between presenting with symptoms and receiving a clinical report have a significant clinical effect? If so, what difference in time would be considered dangerous and does this differ depending on the population or suspected arrhythmia? The may be system wide benefits in terms of shorter pathways such as preventing A&E attendances in worried-well patients and reducing/eliminating un-necessary investigations. In terms of AF/PAF – there is evidence that delayed diagnosis exposes patients to a higher risk of stroke (assuming other risk factors are present). Patients with heart block require urgent assessment for pacemaker implantation and other arrhythmias may require anti-arrhythmic medication to prevent relapse or hospitalisation. I would suggest a delay of no more than 5 days from monitoring completion to report availability is acceptable. 13) Are clinical outcomes likely to be clinically different between a population with suspected AF and with already diagnosed AF, when monitored with a Holter or extended continuous monitor? Patients with known, permanent AF do not require extended monitoring devices – at most, these patients may require 24 hr (HOLTER) devices to assess AF rate control if their symptoms are troublesome. This patient group will be treated according to	

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		guidelines and their prognosis will depend on concomitant risk factors / life-style and NOT the arrythmia. Patients with suspected AF will have an adverse outcome if their arrhythmia (particularly AF/PAF) is not diagnosed promptly. Failure to make a diagnosis (often due to inadequate periods of ECG monitoring) may result in patients presenting with TIA/Stroke. Many patients with AF/PAF do NOT have symptoms of any arrhythmia and therefore present de novo with conditions such as decompensated heart failure, TIA and stroke. 14) Are there clinically defined relations between AF burden and risk of stroke or other comorbidities? CHADS2VASC2 defines the relationship between certain CVD risk factors, the presence of AF/PAF and stroke. There are ongoing studies looking at AF burden and stroke risk – this is NOT yet part of any stroke risk algorithm. Current NICE/ESC guidelines dictate merely that once a diagnosis of AF/PAF has been secured, then treatment for the prevention of embolic events such as stroke should be determined by the CHADS2VASC2 risk score only. 15) We understand that implantable cardiac monitors are rarely used as a first line of standard care – is this the case? Would you ever use an implantable monitor over a temporary one? Or are monitors only implanted when there is a therapeutic purpose as well? Yes, this is the case. Implantable (loop-type) recorders (ILRs) are used almost exclusively for patients with loss of consciousness / syncope when a cardiac arrhythmia has been suspected but a	

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Whole document (in particular 2 Overview of the technology, 3 Clinical context, 5 clinical evidence review)	**Further questions to company – 10.10.19** 1. In section 2.2. you outline 5 studies that provide evidence for the diagnostic accuracy of Zio – could you tell us how this was calculated? E.g. the sensitivity and specificity for the Barrett study 2014. 2. Is there evidence to suggest that Zio is better at detecting certain types of arrhythmia over others? 3. In appendix D, you outline confidential information about a study at London	diagnosis has not been made using existing modes of ECG monitoring. These ILRs require a small procedure to insert, carry infection risk and require a procedure for removal. ILRs are diagnostic devices only and carry no therapeutic activity. They are expensive in terms of the devices themselves and the surveillance costs as they send continuous ECG reports to the implanting site. They are not appropriate as "default" / "workhorse" ECG monitoring devices. It is possible that with the availability of more prolonged cutaneous ECG monitoring patches, the overall requirement for ILRs may be reduced. **Responses from company - 15.10.19** 1. In section 2.2. you outline 5 studies that provide evidence for the diagnostic accuracy of Zio – could you tell us how this was calculated? E.g. the sensitivity and specificity for the Barrett study 2014. Barrett 2014: the sensitivity and specificity were calculated according to the same formula used for several of the other papers in the submission, as described below. The confusion matrix was constructed from the numbers in table 1.	

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	North West University Healthcare NHS Trust. Are the findings likely to be published? 4. The paper, Solomon, M. D., et al. (2016). "*Incidence and timing of potentially high-risk arrhythmias detected through long term continuous ambulatory electrocardiographic monitoring*." BMC Cardiovascular Disorders 16(1): 35., includes over 120,000 patient records between November 2011 and December 2013. Is there any overlap between this and any other published study, such as Schultz (2019), Schreiber (2014), Go (2018), Eisenberg (2014) etc? Are you aware of an overlap between any of the other populations? 5. We have noticed that the CE marking certificate you have provided expired on 1 October 2019. Do you have an up-to-date one?	Table 1 contains the number subjects with or without arrythmia events detected by the Zio patch and the Holter monitor in the total wear time that were confirmed by physician investigators. There were no false positives reported, so all positives were true positives. So for the patch: • The true positive count was 96 (36 cases positive by patch and negative by Holter, plus 60 positive by patch and Holter). • The true negative count was 49, the number of subjects negative by both the patch and Holter. • The false negative count was 1 (positive by Holter and negative by patch). The sensitivity was therefore 98% (96 true positives divided by 96 + 1 false negative). The specificity was therefore 100% (49 true negatives divided by 49 + 0 false positives). The positive predictive value was 100% as there were no false positives reported. The negative predictive value was 98% (49 true negatives divided by 49 + 1 false negative).	

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		Regarding the other studies listed, Eysenck 2019 compares the accuracy of diagnosis across a range of modalities, including Zio. Eisenberg 2014, Turakhia 2015 and Steinhubl 2018 demonstrate diagnostic efficiency in detecting silent AF. 2. Is there evidence to suggest that Zio is better at detecting certain types of arrhythmia over others? As described in Hannun (2019), the detecting capabilities of the Zio XT Service are state of the art. The performance of the deep neural network (DNN), referred to as the artificial intelligence algorithm in our clinical submission, was compared to a consensus committee of board-certified practicing cardiologists, most of whom were subspecialized in rhythm abnormalities. The algorithm met or exceeded the averaged cardiologist performance for all 12 rhythm classes (Atrial fibrillation and flutter, AV Block, Bigeminy, Ectopic Atrial Rhythm, Idioventricular Rhythm, Junctional rhythm, Noise, Sinus rhythm, Supraventricular tachycardia, Ventricular tachycardia, Wenckebach). When the specificity was fixed at the average specificity achieved by cardiologists, the sensitivity of the DNN exceeded the averaged cardiologist sensitivity across all rhythm classes. The DNN and the averaged cardiologist performance tended to be lower on similar classes, such as ventricular tachycardia and ectopic	

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		atrial rhythm (EAR). As reported in the paper, "Manual review of the discordances revealed that the DNN misclassifications overall appear very reasonable. In many cases, the lack of context, limited signal duration, or having a single lead limited the conclusions that could reasonably be drawn from the data, making it difficult to definitively ascertain whether the committee and/or the algorithm was correct." The model had a lower performance than cardiologists in classifying ventricular tachycardia, but interestingly had higher sensitivity (94.1%) than the averaged cardiologist (78.4%). The study authors concluded that "manual review of the 16 records misclassified by the DNN as ventricular tachycardia showed that 'mistakes' made by the algorithm were very reasonable," for the reasons listed above. The findings reported in Hannun (2019) illustrate that deep learning algorithmic approaches, whose performance improves as more data become available, can utilize the growing availability of digitized ECG data to improve the accuracy of ECG interpretation. iRhythm is demonstrating new insights through digital enhancements that eclipse others in the ambulatory monitoring field. In the commercial Zio XT Service, each patient record is first analysed by the algorithm and then reviewed by a cardiac physiologist through iRhythm's Quality Assurance Tool. These highly trained physiologists examine the algorithm output, paying close attention to high risk, difficult to detect arrhythmias. Modifications are made prior to physician interpretation, and	

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		eventually are utilized to further train the algorithm in future releases. As previously shared, 99% of physicians' final interpretations online match the preliminary findings delivered in the Zio technical report. 3. In appendix D, you outline confidential information about a study at London North West University Healthcare NHS Trust. Are the findings likely to be published? The study investigators will present their findings at an upcoming health economic conference and also plan to submit an abstract to a primary care or cardiology conference. The findings may be written up for an online journal as well, following the collection of further clinical pathway and economic information. 4. The paper, Solomon, M. D., et al. (2016). "*Incidence and timing of potentially high-risk arrhythmias detected through long term continuous ambulatory electrocardiographic monitoring*." BMC Cardiovascular Disorders 16(1): 35., includes over 120,000 patient records between November 2011 and December 2013. Is there any overlap between this and any other published study, such as Schultz	

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<tr><td></td><td></td><td>(2019), Schreiber (2014), Go (2018), Eisenberg (2014) etc? Are you aware of an overlap between any of the other populations?

Patient overlap may occur in the retrospective data studies. Likely overlap is listed below based on the dates of the records sent for each study. We are able to confirm by checking individual patient records; please let us know if this is of interest.

<table><tr><th>Study</th><th>Inclusion Criteria</th></tr><tr><td>Turakhia 2013</td><td>All patients who had completed Zio Patch monitoring from January 1, 2011 to December 31, 2011</td></tr><tr><td>Tung 2015</td><td>Patients who were monitored between January 2012 and June 2013 and whose indication for monitoring was TIA or stroke</td></tr><tr><td>Eisenberg 2014</td><td>Data reviewed from 524 consecutive patients referred to a five-physician, academic electrophysiology practice between May 28, 2010, and January 11, 2013</td></tr><tr><td>Solomon 2016</td><td>Over 120,000 patient records between November 2011 and December 2013</td></tr></table></td><td></td></tr>
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Go 2018	All Kaiser Permanente patients identified with PAF between October 2011 and October 2016	Solomon 2016 Wineinger 2018
Wineinger 2018	13,293 individuals identified with PAF from November 2014 through September 2016	Go 2018

5. We have noticed that the CE marking certificate you have provided expired on 1 October 2019. Do you have an up-to-date one?

Please see attached certificate (see appendix 2)

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Whole document (in particular 3 Clinical context, 5, Clinical evidence review, 9 Interpretation of clinical evidence)	**Further questions to expert advisers – 21.10.19** 1. What is the most likely setting for use of a device such as Zio XT Service? E.g. would it be prescribed by a GP or by a cardiologist? 2. Is Zio likely to be more, less or equally accurate when compared with Holter monitoring over the same period of time (for example 24 hours)? 3. How could the diagnostic accuracy for these technologies be verified? What would be the reference standard? 4. If a Holter monitor is indicated for use, is this fitted at the first appointment, or would patients need to return to have a Holter fitted? 5. Typically, is there high refusal or drop out by patients for Holter monitors? The dropout rate in one study was 20% - does this seem representative?	**Response from Dr Gregory Lip – 21.10.19** 1. What is the most likely setting for use of a device such as Zio XT Service? E.g. would it be prescribed by a GP or by a cardiologist? Either 2. Is Zio likely to be more, less or equally accurate when compared with Holter monitoring over the same period of time (for example 24 hours)? Based on validations, similar. Holters usually for 24-48 hours. Ziopatch for 14 days 3. How could the diagnostic accuracy for these technologies be verified? What would be the reference standard? ECG recording 4. If a Holter monitor is indicated for use, is this fitted at the first appointment, or would patients need to return to have a Holter fitted? Depends on local facilities	

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	6. From your experience, how many times is the test using a Holter monitor repeated in order to rule out AF?	5. Typically, is there high refusal or drop out by patients for Holter monitors? The dropout rate in one study was 20% - does this seem representative? Seems a bit high 6. From your experience, how many times is the test using a Holter monitor repeated in order to rule out AF? In my AF clinic, I can order a 7 day Holter. On rare occasion I would repeat **Response from Dr Anthony Shannon – 21.10.19** 1. What is the most likely setting for use of a device such as Zio XT Service? E.g. would it be prescribed by a GP or by a cardiologist? It is most likely prescribed by a Cardiologist at either Liverpool Heart and Chest Hospital site or Knowsley Cardiovascular Service. 2. Is Zio likely to be more, less or equally accurate when compared with Holter monitoring over the same period of time (for example 24 hours)? It is likely to be equally as accurate as most standard 24 hour Holter devices (albeit some 24 hr Holters have multiple ECG leads compared to just one on the ZIO patch), but in comparison to	

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		current 7 day Holter devices, a ZIO is likely to be much more accurate with a higher diagnostic yield of data. 3. How could the diagnostic accuracy for these technologies be verified? What would be the reference standard? I imagine accuracy could be determined by assessing inter-observer variability. I understand that iRhythm have compared the diagnostic accuracy of ZIO against a consultant panel and also against the diagnostic accuracy of a pacemaker over a similar time frame, and the ZIO has come out very favourably in terms of diagnostic accuracy compared to both consultants and pacemakers over 14 days. 4. If a Holter monitor is indicated for use, is this fitted at the first appointment, or would patients need to return to have a Holter fitted? Where possible, our intention is to have the monitor fitted at the first appointment visit to avoid multiple hospital visits for patients. If this is not possible, then an appointment can be made for the patient to attend as an outpatient. 5. Typically, is there high refusal or drop out by patients for Holter monitors? The dropout rate in one study was 20% - does this seem representative?	

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		For the last week, we had an initial 13% DNA/Cancellation rate, but because our clerical team regularly update the appointment lists, we have been able to fit waiting list patients in quickly into the slots left vacant. This has meant much improved clinical activity with overall drop-out rates <10%. The patients who do drop-out or refuse (aside from holidays / unwell), are quite often those who may not have the time to get out of work on multiple days to attend for three separate appointments (Consultation, Holter on, Holter off). I am currently waiting on our Digital Systems team to provide me with some longer term data regarding the amount of DNA / Cancellations we have had at LHCH. 6. From your experience, how many times is the test using a Holter monitor repeated in order to rule out AF? A 24 hour Holter monitor may only be requested once depending on frequency of symptoms (symptoms <24hrs apart) and we may generally opt for a longer term Holter such as an R-Test / Vista to be worn for 7 to 14 days to try and catch evidence of Atrial Fibrillation in patients with symptomatic episodes >24hrs apart. If these methods are unsuccessful on the first couple of occasions, then implantation of an Implantable Loop Recorded (ILR) – which can be used continuously for approximately 3 years – may be the next course of action. Obviously this would depend on the individual	

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		consultant's threshold for referring to ILR and also the patient consenting to ILR over external loop recorder. Occasionally GP's do refer patients in directly to an LHCH consultant for ILR if symptoms are very infrequent. **Response from Ms Jacqueline Colwill – 22.10.19** 1. What is the most likely setting for use of a device such as Zio XT Service? E.g. would it be prescribed by a GP or by a cardiologist? Zio service could easily be prescribed both in primary care by GP or by a Cardiologist. I could see GP's favouring Zio service as it is very easy to fit in a GP practise and additionally will include an analysed report. Equally Zio would be also favoured in secondary/tertiary care by a Cardiologist or healthcare professional to offer the additional resource of longer term monitoring for a selected group of patients. 2. Is Zio likely to be more, less or equally accurate when compared with Holter monitoring over the same period of time (for example 24 hours)? Zio should be equally accurate when compared to Holter, as the data is analysed and quality controlled by a team of qualified Cardiac Physiologists based at Zio.	

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		3. How could the diagnostic accuracy for these technologies be verified? What would be the reference standard? Both technologies (24hr Holter and Zio) rely on independent and autonomous teams to analyse data accurately. The same principle applies to both technologies…training, competency and quality control processes would be required for both technologies whether it's Zio analysing or in-hospital holter analysis. It would be important and valuable to know and recognise what level of training/qualifications staff have received to ensure competency is standardised, verified and maintained. Diagnostic accuracy should be verified for both technologies using the same quality control processes which could be randomly sampled by Cardiac Physiologists/Cardiologists, however this would be labour intensive. The reference standard for analysis of both holter/Zio would be performed by a qualified/competent healthcare professional. Currently Cardiac Physiologists are qualified and registered with RCCP/AHCS to perform this role. 4. If a Holter monitor is indicated for use, is this fitted at the first appointment, or would patients need to return to have a Holter fitted? In practice the Holter monitor should if possible be identified at referral/screening (if indicated) then fitted pre - 1st appointment so results are ready and available for 1st appointment for discussion with Cardiologist/healthcare professional, if not then at the patient's first appointment. This may vary between centres as it is often down to availability of resources in each department. In some situations a patient	

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		will need to return to have Holter fitted, often as a result of new clinical information from the patient's history taking which was not identified on the original referral letter. 5. Typically, is there high refusal or drop out by patients for Holter monitors? The dropout rate in one study was 20% - does this seem representative? No, personally I don't think 20% dropout is a true reflection, the vast majority of patients in my service all attend for holter monitors. I would evaluate dropout in my practice to approx 5% and often related to factors such transport/time of day/carer or work commitments. Patients are not always availability to attend 2 appts to fit and return monitor largely due to work or family commitments and very occasionally due to lifestyle factors (such as; is it visible, can I have a bath/shower). A small group of vulnerable patients with confusion, dementia, learning difficulties or children may refuse the test or pull it off before it's completed. 6. From your experience, how many times is the test using a Holter monitor repeated in order to rule out AF? I have very occasionally seen a Holter monitor repeated or an implantable loop recorder requested in its place to try to capture Paroxysmal AF (PAF) but this varies from one consultant to another. We are aware there is a gap in long term monitoring and a normal 24hr ECG holter does not exclude PAF. In my practice generally holter monitors are not repeated, for	

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		example; a 72hr ECG monitor is performed and if results are negative for PAF then 14day Zio patch or implantable loop recorder may be considered. **Response from Dr Mark Tanner – 26.10.19** 1) What are the main guidelines for diagnosing and managing arrhythmia? **NICE, European Society of Cardiology and American Heart Association provide such guidelines** **2)** Is there variation in the definition of arrhythmia? What is the standard, in particular for atrial fibrillation? **The definition of arrhythmia is generally accepted as any deviation from physiological sinus rhythm however it is not standardised in terms of specific diagnostic criteria eg duration of arrhythmia. AF is typically defined in the research setting as R-R irregularity in the absence of p waves lasting > 30 beats, but this does not have an established clinical implication (eg whether to treat with anticoagulation or not)** **3)** Are certain arrhythmias harder to detect than others? **Arrhythmia is challenging to diagnose when it is intermittent. The most**	

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		challenging arrhythmia to diagnose is when it is asymptomatic, brief, and occasional **4)** What are main differences in population between different types of arrhythmia? Is there a significant systematic difference in risk factor and comorbidity across different types of arrhythmias? **In general terms arrhythmia increases with age and co-morbidity. Life-threatening arryhthmias are associated with increasing age, structural heart disease, myocardial ischaemia, and co-morbidity.** **5)** Are there certain populations that are particularly at risk for arrhythmia? For example, some studies include a population of 'high-risk' individuals – is this a clinically defined group? "**High risk" patients are those with prior arrhythmia, pathological ECG changes, structural/ ischaemic heart disease, or arrhythmogenic cardiomyopathy** **6)** How would you calculate the risk of arrhythmia? **Accurate risk calculators are lacking but risk increases with age and co-morbidities**. Are there any standardised risk scores available? **Very limited data. The only commonly used validated arrhythmia risk score is that for predicting risk of sudden cardiac death in Hypertrophic Cardiomyopathy (Eur Hear J 2014 35(30):2010-20)**	

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		7) What are the benefits of longer periods of monitoring for arrhythmias? For example, is there published evidence that links longer periods to improved clinical outcomes? **Longer periods of monitoring increase the likelihood of detected intermittent arrhythmia. Eg The CRYSTAL AF study demonstrated a large increase in detection rate of AF in post cryptogenic stroke patients when long term monitoring (with ILRs) was compared to standard Holter monitoring.** 8) Conversely, could there be any potential issues with extended monitoring vs a 24 or 48-hour Holter? **There may be issues of compliance/inconvenience with longer monitoring periods** 9) Are you aware of any devices similar to the Zio XT monitor i.e. soft biosensors for extended cardiac monitoring? **CardioSTAT longterm ECG recorder** **10)** Do you think that this device could be superseded in the near future by other technology (i.e. app-based technologies, wearables etc)? **Not entirely (at least in the near future) as not all patients will necessarily have access to or the ability to use such technology**	

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		11) Is shaving of body hair required for Holter monitors? **Yes** **12)** Could a difference in the time between presenting with symptoms and receiving a clinical report have a significant clinical effect? **Could be relevant in cases of malignant arrhythmia/bradycardia**. If so, what difference in time would be considered dangerous and does this differ depending on the population or suspected arrhythmia? **If reports turned around in a sensible time (eg < 7 days) likely only to be relevant in high risk population (eg syncopal patients)** 13) Are clinical outcomes likely to be clinically different between a population with suspected AF and with already diagnosed AF, when monitored with a Holter or extended continuous monitor? **In the former the outcome is to make an initial diagnosis and in the latter to help refine treatment** **14)** Are there clinically defined relations between AF burden and risk of stroke or other comorbidities? **This is controversial and poorly defined. There is some evidence that a lower burden is linked to a lower stroke risk but a casual association has not been established. There are ongoing randomised trials looking at AF duration (as detected in the pacemaker population) and stroke risk/benefits of anticoagulation**	

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		15) We understand that implantable cardiac monitors are rarely used as a first line of standard care – is this the case? Would you ever use an implantable monitor over a temporary one? **Rarely but a reasonable option in recurrent but very infrequent syncope.** Or are monitors only implanted when there is a therapeutic purpose as well? **16)** What is the most likely setting for use of a device such as Zio XT Service? E.g. would it be prescribed by a GP or by a cardiologist? **Mostly cardiologists but its simplicity including the reporting system would make it suitable for use by GPs or stroke specialists** **17)** Is Zio likely to be more, less or equally accurate when compared with Holter monitoring over the same period of time (for example 24 hours)? **Likely equally accurate (although theoretically as only 1 lead might reduce diagnostic accuracy)** **18)** How could the diagnostic accuracy for these technologies be verified? What would be the reference standard? **Reference standard would be Holter monitor**	

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		19) If a Holter monitor is indicated for use, is this fitted at the first appointment, or would patients need to return to have a Holter fitted? **My understanding is that in most NHS institutions patients usually return later for fitting** **20)** Typically, is there high refusal or drop out by patients for Holter monitors? The dropout rate in one study was 20% - does this seem representative? **Sounds a feasible figure due to tolerability of wearing device continuously and risk of patient not returning device** **21)** From your experience, how many times is the test using a Holter monitor repeated in order to rule out AF? **Depends on ongoing suspicion of AF; usual post CVA (and asymptomatic) a single monitoring period is used to "rule out", if ongoing intermittent infrequent symptoms then may need to be repeated several times to obtain symptom/rhythm correlation** **Response from Dr Matthew Reed – 28.10.19** 1. What is the most likely setting for use of a device such as Zio XT Service? E.g. would it be prescribed by a GP or by a cardiologist?	

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		Whilst the Zio XT could be prescribed by a GP and likely fitted at the hospital (although could be fitted in a GP practice), I suspect this would likely prescribed by an acute or general medicine consultant or cardiologist 2. Is Zio likely to be more, less or equally accurate when compared with Holter monitoring over the same period of time (for example 24 hours)? The fidelity and accuracy of the Zio is similar to a Holter over a 24 hour period but because it is able to monitor over an extended period this gives it a much greater pick up rate. 3. How could the diagnostic accuracy for these technologies be verified? What would be the reference standard? There is no gold standard for patients undergoing outpatient investigation, the fidelity and accuracy of both 24 hr Holter and Zio could be tested against a standard 12 lead electrocardiogram over a short period (3-4 seconds) or standard in hospital wired monitoring over a longer period (ie hours) 4. If a Holter monitor is indicated for use, is this fitted at the first appointment, or would patients need to return to have a Holter fitted?	

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		Usually at first appointment 5. Typically, is there high refusal or drop out by patients for Holter monitors? The dropout rate in one study was 20% - does this seem representative? There are patients who do not comply as with all investigations but generally well tolerated. I don't have a local figure for Holter dropout rate. 6. From your experience, how many times is the test using a Holter monitor repeated in order to rule out AF? Patients don't tend to get repeated Holter's to rule out AF, mainly to rule in as pick up rate so poor especially if AF yield (ie amount of time patient in AF) low. No AF on 2 week monitoring would be reassuring but does not definitely rule out AF as it can be paroxysmal (i.e. only now and then) **Response from Dr James Teo – 28.10.19** 1. What is the most likely setting for use of a device such as Zio XT Service? E.g. would it be prescribed by a GP or by a cardiologist?	

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		Secondary care clinician in outpatients. This includes all kinds of secondary care physicians including stroke physician, acute physician, stroke neurologist, cardiologist. 2. Is Zio likely to be more, less or equally accurate when compared with Holter monitoring over the same period of time (for example 24 hours)? Zio is likely to be more accurate for a fixed period of time (24 hours), there is likely to be less artefact and more analysable rhythm (patients remove the monitors during showers). 3. How could the diagnostic accuracy for these technologies be verified? What would be the reference standard? This has been extensively verified by FDA and MHRA already. The device is already in use in USA and in UK (in private sector). I am not aware of the reference standard used for Holter ECG's or ECG monitoring systems; I would expect the Zio XT service had a similar reference for the FDA and MHRA submissions. 4. If a Holter monitor is indicated for use, is this fitted at the first appointment, or would patients need to return to have a Holter fitted?	

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		This is normally requested but the patient usually has return for a Holter fitting (waiting list 7-60 days), and return again for a Holter removal. Reporting delay ranges from 2-14 days. 5. Typically, is there high refusal or drop out by patients for Holter monitors? The dropout rate in one study was 20% - does this seem representative? Our study EPACS showed a ~25% drop-out from Holter. Other European or Canadian studies show a drop-out rate of 20-28% depending on population and duration of recording. 6. From your experience, how many times is the test using a Holter monitor repeated in order to rule out AF? The UK stroke guidelines does not have a minimum duration of recording unlike European guidelines or North American guidelines. As such, there is a significant variation in practice (some centres do a single 24-hour only while others do repeated Holters). In our centre, an average of 1.5 to 2x per patient.	

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6 Ongoing use and data collection	**Question to company – 31.10.19** We understand that as part of the ongoing review process, Quality Clinical Managers review 1-3% of all reports on a daily basis. Are the reports selected on a random basis?	**Response from company – 06.11.19** The reports are randomly selected for retrospective QA but split across cardiac technicians. For example, for every 100 reports completed by Cardiac Tech A, 1-3 are randomly selected for retrospective review. If those 1-3 reports are all normal (i.e., no arrhythmias detected), the reviewer may opt to manually select higher complexity reports from that Cardiac Tech instead.	
9 Interpretation of clinical evidence	**Further questions to company – 18.11.19** 1. How would you expect Zio to compare in terms of diagnostic accuracy against a Holter monitor (if ECG was used as a reference standard, for example)? 2. Your submission includes one recent study that assesses the diagnostic accuracy of a continuous ambulatory cardiac monitor (Spyder) vs. a loop recorder against ECG recording as reference standard (Mamchur, 2019) for detecting AF. We note the study has a relatively small sample size (n=32, n=17 for Spyder arm).	**Response from company – 20.11.19** 1. How would you expect Zio to compare in terms of diagnostic accuracy against a Holter monitor (if ECG was used as a reference standard, for example)? There are two studies in which a Zio monitor and Holter monitor were worn simultaneously: Barrett (2014) and Rosenberg (2014). However, neither included a reference standard ECG recording. In Barrett a physician checked all ECG recordings from Zio and Holter to determine accuracy. We calculated sensitivity and specificity from the reported 2x2 tables in the paper, which we assume are based on the physician judgement. Zio performs better than the Holter monitor in our analysis, with similar (100%) specificity but higher sensitivity (99% vs. 63%). Accordingly, more patients will be diagnosed with Zio than Holter, with no false positives.	

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	a) How would you expect the results for the Spyder monitor to compare with Zio? b) Are you aware of any other studies that directly assess the accuracy (sensitivity/specificity) of any continuous monitoring device compared with standard care or against ECG as reference standard?	All recordings in Rosenberg were assessed by cardiologists to confirm diagnoses. Diagnostic accuracy was the same in the 24 hours when both devices were worn, but the fact that Zio could be worn for longer than the Holter monitor led to an increase in overall detection rate in 43 additional patients with Zio than Holter. In Hannun (2019), the Zio algorithm performed as well or better than expert cardiologist interpretation. The algorithm met or exceeded the averaged cardiologist performance for all 12 rhythm classes (Atrial fibrillation and flutter, AV Block, Bigeminy, Ectopic Atrial Rhythm, Idioventricular Rhythm, Junctional rhythm, Noise, Sinus rhythm, Supraventricular tachycardia, Ventricular tachycardia, Wenckebach). When the specificity was fixed at the average specificity achieved by cardiologists, the sensitivity of the DNN exceeded the averaged cardiologist sensitivity across all rhythm classes. Eysenck (2019) compares several monitoring modalities, including Zio, to a pacemaker. Pacemakers have high accuracy, and Ciconte et al 2017 said they were the diagnostic gold standard. Compared to concurrent pacemaker recordings, the overall AF burden found by Zio had an R squared of 0.99 with an MSE of 0.24, the most accurate of all included modalities, including the event monitor (Novacor R test). Additionally, Zio more accurately indicated the presence or absence of AF than the R Test (odds ratio 12.3 (95% CI 1.4 to 110.3; p = 0.025). To reach a Zio vs. Holter comparison, we can couple Eysenck with Sejr (2017) which compares the Novacor R test and Holter. In this study, Holter identified cardiologist-confirmed AF in 3/191 patients plus 1 false positive	

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		but missed 2 true positives detected by the R test. We calculate this is a sensitivity of 60% and specificity of 99.5%. During the same time period (day 1 and 2) R test identified cardiologist-confirmed AF in 5/191 patients including the 3 who were detected by Holter plus 2 false positives. We calculate this as a sensitivity of 100% and specificity of 99%. Therefore, we conclude that the R test has a higher accuracy than Holter. It is difficult to reliably compare accuracy across different study protocols, patient characteristics and outcome assessments. But in the absence of other data, the studies above suggest that the accuracy of Zio exceeds that of Holter. The hierarchy of accuracy would therefore be Holter < R test < Zio and pacemaker. 2. Your submission includes one recent study that assesses the diagnostic accuracy of a continuous ambulatory cardiac monitor (Spyder) vs. a loop recorder against ECG recording as reference standard (Mamchur, 2019) for detecting AF. We note the study has a relatively small sample size (n=32, n=17 for Spyder arm). a) How would you expect the results for the Spyder monitor to compare with Zio? The sensitivity and specificity values were calculated by the study authors, with physician confirmation of an arrhythmia based on analysis of the transmitted ECG recording used as the gold standard. In this study, the sensitivity of Spyder was 80.1% and the specificity 73.1%. The accuracy of Spyder is considerably lower than for Zio as reported by Barrett. However, Mamchur is a very small study and therefore conclusions should be drawn	

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		cautiously. Without additional data, we can say that there is no reason to believe that Zio is worse and it could be more accurate than Spyder. b) Are you aware of any other studies that directly assess the accuracy (sensitivity/specificity) of any continuous monitoring device compared with standard care or against ECG as reference standard? Unfortunately no; the systematic literature review we submitted includes everything that we found that was relevant.	
9 Interpretation of clinical evidence	**Webinar with the company - 05.12.19** KiTEC had a presentation and general discussion with the company about the background to the development of Zio XT Service and how the performance of the algorithm is evaluated. The full details around the AI development process are Commercial in Confidence.		

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10 Economic evidence	**Further questions to company -06.12.19** 1. It's not very clear whether the cost associated with a clinician reviewing the report (after the results become available) and making a decision on the diagnosis/treatment has been included in the analysis. Could you please give more detail on whether the PLICS cost estimate includes this parameter for the comparators (Holter and CER) and whether this is included in the cost of the technology? 2. In the stroke downstream model it's not very clear how the different waiting times for the results associated with the technologies were	**Response from company – 06.12.19** 1. It's not very clear whether the cost associated with a clinician reviewing the report (after the results become available) and making a decision on the diagnosis/treatment has been included in the analysis. Could you please give more detail on whether the PLICS cost estimate includes this parameter for the comparators (Holter and CER) and whether this is included in the cost of the technology? The technology costs in the model include the cost of fixing, removing, analysing and reporting the results of the test. If the patient returns to outpatients for review, then this is costed additionally as a single OP attendance – the cost of further investigations and follow-up are not considered. If the patient is discharged back to primary care on the basis of the report, without any further hospital follow-up, then there is no additional cost. 2. In the stroke downstream model it's not very clear how the different waiting times for the results associated with the	

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	used in the model, particularly how they impact the risk of stroke. Could you please give more detail on this?	technologies were used in the model, particularly how they impact the risk of stroke. Could you please give more detail on this? Because the difference in waiting times between technologies can be quite substantial, especially if repeat testing was required, effectively doubling the wait time, some patients who ultimately are found to need anticoagulation are likely to remain untreated for significant periods. We therefore used the following approach to estimate the excess risk: • Identify a cohort of patients who actually have underlying AF (30% - using 3-year data from the CRYSTAL-AF study) • Assign a baseline risk of stroke in these patients, assuming AF + no anticoagulation (using data from the placebo arm in the EAFT study) • For each technology, use the positive diagnostic yield to estimate the proportion of the cohort in whom the AF is diagnosed at each monitoring pass • Apply the technology-specific wait times to assess how long the patient would continue to have been at the baseline risk of stroke. • From the point that the diagnosis was made, the lower risk for anticoagulated patients was applied to the remainder of the year* (using data from intervention arm in the EAFT study) • For patients with underlying AF that is not diagnosed in any arm, the higher risk of stroke (AF + no anticoagulation) was applied • For the 70% of patients without AF, a baseline risk of recurrent stroke for non-AF patients was used (Based on data from EAFT and Burn et al)	

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		* Note that there is likely to be a further delay from the point where the report becomes available and the time when anticoagulation is started, but this depends on local NHS trust mechanisms rather than the monitoring technology used. As this delay will not vary between technologies, it will not impact on the incremental difference between arms. This element was therefore omitted. The overall results of the stroke downstream model principally depend on the differences in diagnostic yield between technologies, but as a number of clinicians highlighted to us the long delays that could be incurred and the potential for Zio to mitigate this, we elected to include this element as an additional factor.	
10 Economic evidence	**Further questions to experts – 12.12.19** 1. Risk of stroke in AF patients. We have a figure for risk of stroke in untreated AF patients - 12%- which has been taken from the EAFT study, and the additional risk of stroke associated with AF from Burn et al. (1994) – OR 1.24. We have concerns about the date of these references. In your opinion, are these references representative/appropriate to use? Are there more recent references or	**Response from Dr Gregory Lip – 12.12.19** 1. Risk of stroke in AF patients. We have a figure for risk of stroke in untreated AF patients - 12%- which has been taken from the EAFT study, and the additional risk of stroke associated with AF from Burn et al. (1994) – OR 1.24. We have concerns about the date of these references. In your opinion, are these references representative/appropriate to use? Are there more recent references or better sources to use for these risk of stroke in AF patients?	

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	better sources to use for these risk of stroke in AF patients? 2. Risk and cost of complications: In addition to risk of stroke we would like to include risk of bleeding due to anticoagulant use as a consideration of the economic model. Is it reasonable to consider risk of bleeding as a complication as well as risk of stroke? Are you aware of any references that give data for risk or cost of bleeding due to anticoagulant therapy in AF patients?"	>>> Those studies are in the era where AF patients not on OAC or aspirin. EAFT also a clinical trial. 2. Risk and cost of complications: In addition to risk of stroke we would like to include risk of bleeding due to anticoagulant use as a consideration of the economic model. Is it reasonable to consider risk of bleeding as a complication as well as risk of stroke? Are you aware of any references that give data for risk or cost of bleeding due to anticoagulant therapy in AF patients?" 1: Olesen JB, Lip GY, Lindhardsen J, Lane DA, Ahlehoff O, Hansen ML, Raunsø J, Tolstrup JS, Hansen PR, Gislason GH, Torp-Pedersen C. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: A net clinical benefit analysis using a 'real world' nationwide cohort study. Thromb Haemost. 2011 Oct;106(4):739-49. doi: 10.1160/TH11-05-0364. Epub 2011 Jul 20. PubMed PMID: 21789337. 2: Olesen JB, Lip GY, Hansen PR, Lindhardsen J, Ahlehoff O, Andersson C, Weeke P, Hansen ML, Gislason GH, Torp-Pedersen C. Bleeding risk in 'real world' patients with atrial fibrillation: comparison of two established bleeding prediction	

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		schemes in a nationwide cohort. J Thromb Haemost. 2011 Aug;9(8):1460-7. doi: 10.1111/j.1538-7836.2011.04378.x. PubMed PMID: 21624047. **Response from Dr James Teo – 12.12.19** (1) The references are definitely out of date. Nowadays, stroke risk in AF is calculated using a risk-scoring system which is individualised. This is called CHADS2Vasc. The spread of CHADS2Vasc scores varies from population to population, so the stroke risk varies from population to population. I have recently published on the KCH population: https://journals.plos.org/plosone/article/comments?id=10.1371/journal.pone.0225625 A large primary practice cohort study from 2017 showed the increased rates of prescribing. https://bmjopen.bmj.com/content/7/9/e015363 It might be worthwhile to refer to NICE's prior guidance (and reference documents) on stroke prevention in AF https://www.nice.org.uk/guidance/cg180 I have no doubt there is economic modelling on this which you could use. (2) With respect to bleeding risk, this has been difficult to calculate in real world. I have been part of UCL/KCL collaborative that has also tried to study this but the data is from the 1998-2010: https://link.springer.com/article/10.1186/s12916-019-1438-y	

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		During this period, all anticogulation was Vitamin-K-based (warfarin), and the newer lower risk anticoagulants only entered market in 2013/4 onwards. **Response from Dr Matthew Reed – 13.12.19** The current most common clinical tools that are used for both of these are the CHAD2DS2-VASC score for the risk of stroke with AF (or simplified CHADS2 score) and the HAS-BLED score. The CHA2DS2-VASc score is recommended by the American College of Cardiology and American Heart Association(ACC/AHA) [January CT et al. Circulation 2014;130 (23): 2071-104; https://www.ncbi.nlm.nih.gov/pubmed/24682348] and by the European Society of Cardiology (ESC) [Camm AJ et al. Eur Heart J. 2012; 33(21): 2719-47; https://www.ncbi.nlm.nih.gov/pubmed/22922413] to stratify embolic risk in atrial fibrillation. Anticoagulation is recommended in patients with CHA2DS2-VASc ≥ 1 (ESC) or ≥ 2 (ACC/AHA). The HAS-BLED score can be used to assess the individual bleeding risk of patients with atrial fibrillation. A score ≥ 3 indicates high risk (Pisters R. Chest. 2010; 138(5): 1093-100; https://www.ncbi.nlm.nih.gov/pubmed/20299623). **Response from Dr Mark Tanner – 18.12.19** Q1	

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		Stroke risk in AF is determined by a number of cardiovascular risk factors and there are a number of validated risk scores eg ATRIA, CHADS and CHADSVASC to predict individual annual stroke risk. The CHADSVASC score is the most widely used, and referenced in AF guidelines (eg NICE and European Society Cardiology). This link gives a nice summary and references https://www.chadsvasc.org/ Q2 *Is it reasonable to consider risk of bleeding as a complication as well as risk of stroke?* Bleeding risk is not a complication of stroke but it is an inevitable complication of anticoagulation. Importantly risk factors for bleeding eg age and hypertension are also risk factors for stroke so the stroke risk in AF is tracked by bleeding risk. The above link also includes a validated bleeding risk calculator. I have attached a pdf of a systematic review, network meta-analysis and cost-effectiveness analysis of anticoag in AF	
10 Economic evidence	**Further questions to experts – 19.12.19** Evidence suggests around a quarter of patients have a positive result following a 24 Holter assessment post stroke.	**Response from Dr Gregory Lip – 19.12.19** 1. What proportion of patients would you expect to have a negative scan? A quarter have a positive Holter, the others negative.	

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	1. What proportion of patients would you expect to have a negative scan? 2. What proportion of patients would have an inconclusive scan? 3. What would constitute an inconclusive scan and how would this differ from a negative scan? 4. How would an inconclusive scan be followed up?	2. What proportion of patients would have an inconclusive scan? Depends on competency of the ECG dept. 3. What would constitute an inconclusive scan and how would this differ from a negative scan? Poor quality tracing. Machine not working. 4. How would an inconclusive scan be followed up? Repeat. **Response from Dr Mark Tanner – 19.12.19** Evidence suggests around a quarter of patients have a positive result (by positive result I assume you mean AF) following a 24 Holter assessment post stroke. I think 25% is very much the upper limit reported (ranges reported between 0-25%) 1. What proportion of patients would you expect to have a negative scan? >90- 95% 2. What proportion of patients would have an inconclusive scan? <1-5% - usually it is clear whether there is AF or not 3. What would constitute an inconclusive scan and how would this differ from a negative scan? I take inconclusive to mean AF cannot be confidently excluded or confirmed and often relates to	

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		difficulties in interpretation due to artefact or indeterminate shorter bursts or arrhythmia. A negative scan means no AF seen. 4. How would an inconclusive scan be followed up? Depends on clinical suspicion of AF **Response from Dr Matthew Reed – 28.12.19** I think questions 1 and 2 are very difficult to answer in post stroke as not all patients undergo rigourous testing with 24hr Holter as it is such a poor test for detecting AF and certainly is no use for looking at longer term AF burden (% of time a patient is in AF). I am also probably not the person to ask as secondary stroke prevention is not my area. A positive 24 hour Holter would be one demonstrating Atrial fibrillation which was thought to have contributed to the stroke. A negative 24 hour Holter would be similar to an inconclusive scan ie no AF picked up during the 24 hour monitoring period. It would not be possible to conclude that occult AF was not present as the time period tested is so short. It is only with 14 day patch monitors that we are picking up occult AF as a probably cause of stroke and are able to look at AF burden. I don't think we are clear either how much AF somebody needs to have i.e. their AF burden/% of time a patient is in AF to put them at risk of stroke. It is likely a graduated risk but I haven't seen any evidence yet to help clinicians decide whether to anticoagulate based on a patients AF burden. An inconclusive 24 hr tape	

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		would not be very helpful as you don't know whether the patient doesn't have any AF or whether you haven't monitored for long enough so if you have a high clinical suspicion then your next option would be to go for longer monitoring. Unfortunately what tends to happen (with stroke/palpitations/syncope) is that patients get repeated negative 24 hour tapes.	
10 Economic evidence	**Further question to experts – 20.12.19** The company estimates a time from the initial decision to monitor to the availability of results of 73 days for a Holter and 88 days for a cardiac event recorder. These consist of time delays prior to fitting the devices, recording time and time from return to availability of results. For Holter this is 36 days delay from the initial decision to fitting the device, 2 days for monitoring and device return and a further 32 days following return for the results to be available. For Zio Service the company estimates zero days for fitting the device (fitted at initial consultation), 15 days for monitoring and	**Response from Dr James Teo – 20.12.19** Our EPACS trial measured the time. I would say we got results within 14-21 days generally. We are currently doing a care pathway pilot across 4 hospitals with the Health Innovation Network to validate the impact of this. The audits I forwarded is part of that baseline evaluation before we deploy patches. **Response from Dr Gregory Lip – 20.12.19** For Zio Service the company estimates zero days for fitting the device (fitted at initial consultation), 15 days for monitoring and return of the patch and a further 4 days for return of the results.	

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	return of the patch and a further 4 days for return of the results. Do you think the use of Zio Service will lead to earlier initiation of anti-coagulation therapy compared to Holter by 54 days (73 – 19) in patients with a positive result? Specifically, are delays from device return to availability of results likely to be shortened to 4 days (time to return of Zio results) with Zio Service and would this translate into a concomitant reduction in time to initiation of anticoagualation (where appropriate)?	all these figures are so variable, depending on the hospital Most try to have a WL of <4 weeks to get the Holter, and the report turnround is maybe 2-3 weeks Do you think the use of Zio Service will lead to earlier initiation of anti-coagulation therapy compared to Holter by 54 days (73 – 19) in patients with a positive result? Specifically, are delays from device return to availability of results likely to be shortened to 4 days (time to return of Zio results) with Zio Service and would this translate into a concomitant reduction in time to initiation of anticoagualation (where appropriate)? maybe **Response from Dr Mark Tanner – 20.12.19** Do you think the use of Zio Service will lead to earlier initiation of anti-coagulation therapy compared to Holter by 54 days (73 – 19) in patients with a positive result? Yes Once a positive result is obtained (ie detection of AF) this should trigger prompt initiation of anticoagulation. Regarding the figures, there is likely to be considerable regional variation but from my experience in the 2 institutions I currently work in these figures would appear a realistic estimate. Specifically, are delays from device return to availability of results likely to be shortened to 4 days (time to return of Zio results) with Zio	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		Service and would this translate into a concomitant reduction in time to initiation of anticoagualation (where appropriate)? Once again a reduction in the time from device return to results availability should result in a concomitant reduction in time to initiation of anticoagulation. **Response from Mr Anthony Shannon – 23.12.19** The current process at Liverpool Heart and Chest Hospital is approximately a 3 to 4 week wait for a 7 day Holter device from consultant initially seeing the patient in clinic, 1 week wearing the device and then 48 hours (maximum) turn-around time in analysing and uploading results. I would suggest the whole current process would take around 30 to 37 days on average from request to report becoming available. ZIO would reduce this by having the device fitted on the day of initial consultation, 14 days wearing the patch and then 4 days for results (18 days average). Effectively, these numbers suggest that we could almost halve the waiting time for diagnosis of arrhythmia by implementing ZIO leading to earlier intervention / initiation of anti-coagulant therapy. **Response from Dr Matthew Reed – 28.12.19**	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		Yes I would agree that 15 days for monitoring and return of the patch and a further 4 days for return of the results is realistic. Obviously the earlier a significant result is achieved, the earlier therapy can be initiated so again, yes I think that is realistic. **Response from Dr Jacqueline Colwill – 05.01.20** This is an interesting question and somewhat subjective. In clinical practice there is variance around the country on the time from the initial decision to monitor to the availability of results for all monitoring devices (including holter, event and Zio) This variance is largely due to waiting times, priority and resources available. All devices could in theory be fitted at initial consultation. Most routine referrals (incl Zio) are not fitted at initial consultation and are placed on a diagnostic waiting list with an aim to have the device fitted within 6 weeks (as per diagnostic waiting list target). In my clinical experience this also includes Zio being placed on a waiting list. However an urgent patient could have any monitor fitted on the same day as referral and analysed immediately on its return. If resources permit, all devices could and should be fitted at the time of initial consultation.	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		To conclude, I feel Zio's claim of zero days to fit device is somewhat misleading as the same claim could be applied to any device including Holter. I personally do not think this data (Holter compared to Zio (73 – 19) is an accurate reflection on real life clinical practice and therefore I cannot support this claim that Zio will reduce the time for initiation of anticoagulation. (where appropriate) Zio devices support a valuable role in monitoring services by offering longer term (14 day) continuous ECG recording, the monitors can also be returned via postal service and thus avoid an unnecessary revisit by the patient.	
10 Economic evidence	**Further question to company – 02.01.20** I have a question regarding the costs of Zio Service. In the case of an inconclusive test, if a further test with Zio Service is undertaken on the same patients, would this incur a further charge of £310?	**Response from company – 06.01.20** In answer to your question, clinicians tell us that, in the unlikely event of an inconclusive Zio test, they would rarely repeat the test, but would be more likely to move to investigate other reasons for the patient's symptoms, discharge, or, if indicated, ask for an implantable loop recorder test. If the Zio test is repeated, the cost would be the same as the first test.	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
10 Economic evidence	**Further questions to expert advisers – 14.01.20** Considering patients undergoing investigations for symptoms in a cardiology department: Would patients typically have an outpatient consultation with the clinician following a negative result after monitoring with Holter or CER? Do you think patients would have an outpatient consultation after a negative result from Zio Service? Considering patients undergoing investigations following a TIA or a confirmed or suspected stroke: How likely is it that patients would undergo further monitoring following a negative finding after holter monitoring or CER?	**Response from Dr Mark Tanner – 14.01.20** Considering patients undergoing investigations for symptoms in a cardiology department: Would patients typically have an outpatient consultation with the clinician following a negative result after monitoring with Holter or CER? Not routinely; usually only if ongoing concerns Do you think patients would have an outpatient consultation after a negative result from Zio Service? Again, not routinely Considering patients undergoing investigations following a TIA or a confirmed or suspected stroke: How likely is it that patients would undergo further monitoring following a negative finding after holter monitoring or CER? It would be unusual to have repeat monitoring in this setting **Response from Dr Matthew Reed – 14.01.20** Considering patients undergoing investigations for symptoms in a cardiology department: Would patients typically have an outpatient consultation with the clinician following a negative result after monitoring with Holter or CER?	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		Not always – commonly clinicians just write to GP and patient with result. If positive clinician may just arrange treatment rather than a further appointment Do you think patients would have an outpatient consultation after a negative result from Zio Service? Again not always – we didn't arrange as routing in our study – up to individual clinicians and result of Zio Considering patients undergoing investigations following a TIA or a confirmed or suspected stroke: How likely is it that patients would undergo further monitoring following a negative finding after holter monitoring or CER? NICE guidance released today (!) suggests going to an ILR if stroke cause still unknown after initial testing (https://www.nice.org.uk/news/article/implantable-cardiac-monitors-detect-atrial-fibrillation-after-stroke-of-unknown-cause-recommended-for-routine-nhs-adoption?utm_campaign=revealling&utm_medium=social&utm_source=twitter) **Response from Dr James Teo – 14.01.20** Considering patients undergoing investigations following a TIA or a confirmed or suspected stroke: How likely is it that patients would undergo further monitoring following a negative finding after holter monitoring or CER?	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		Due to the lack of capacity and yield for standard 24-hour holter monitoring or CER (waiting times ranging from weeks to months), I have tended to give up after a the first negative test even if this does not match European or USA guidelines. **Response from Dr Jacqueline Colwill – 14.01.20** Considering patients undergoing investigations for symptoms in a cardiology department: Would patients typically have an outpatient consultation with the clinician following a negative result after monitoring with Holter or CER? No, generally for negative results, results are sent in a written letter to patient/GP and patient is discharged back to GP. Patients are informed of this process during the consultation. Patients would be advised to see their GP (for possible re-referral) if symptoms get worse or more frequent. Do you think patients would have an outpatient consultation after a negative result from Zio Service? No, as above, generally for negative results, results are sent in a written letter to patient/GP and patient is discharged back to GP Patients are informed of this process during the consultation. Patients would be advised to see their GP (for possible re-referral) if symptoms get worse or more frequent.	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		Considering patients undergoing investigations following a TIA or a confirmed or suspected stroke: How likely is it that patients would undergo further monitoring following a negative finding after holter monitoring or CER? This decision would be taken on an individual basis by the clinician, however routinely further long monitoring is not performed unless there is suspicion or evidence to support repeat testing such as patient symptoms. If further monitoring is indicated this would then possibly be an indication for an implantable loop recorder. Regular spontaneous pulse checks are advised to be carried out by GP and healthcare professionals at any opportunity such as when performing blood pressure checks, annual health checks etc. as well as educating the patient to report any irregularities with their heart beat. **Response from Dr Gregory Lip – 14.01.20** Considering patients undergoing investigations for symptoms in a cardiology department: Would patients typically have an outpatient consultation with the clinician following a negative result after monitoring with Holter or CER? Depends on the patient profile Do you think patients would have an outpatient consultation after a negative result from Zio Service?	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		Depends on the patient profile Considering patients undergoing investigations following a TIA or a confirmed or suspected stroke: How likely is it that patients would undergo further monitoring following a negative finding after holter monitoring or CER? Depends on the patient profile, and clinical index of suspicion	

[Insert additional rows if required]

Appendix 1

Minutes from company teleconference on 03.10.19

iRhythm sponsor
TC_Minutes_03.10.1

Appendix 2 [Insert additional appendices as required]

Document received from company by e-mail on 15.10.19

CE Mark Zio Dec 2019.pdf

Document received from company by e-mail on 03.01.20

Zio Service 5 Yr CERT.pdf

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

DHT005 Zio XT Service for detecting cardiac arrhythmias

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from King's Technology Evaluation Centre to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **[13 January 2020]** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

[Insert date submitted to Sponsor]

NICE National Institute for Health and Care Excellence

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
10.2.4.2 NHS and unit costs *"The EAC believes the NHS reference cost for 2017/18 for cardiology services of £141 is a more suitable source."* The EAC stated that "*the PLICS data from 2016/17 is based on information gathered voluntarily in a limited number of NHS Trusts. The NHS reference cost is representative of national practice"*	We propose that the base case revert to using the original cost source derived from PLICS (of £158 per test) or, if a cost based on NHS Reference costs are used, the base case should use a blended cost from NHS reference costs of £214	We understand the EAC's rationale for preferring the reference cost for cardiology services but we continue to believe that the PLICS-derived estimate remains the most accurate representation of true NHS costs, on the basis that it represents an average cost of ECG (as an outpatient procedure) across all specialities. Although we recognise that in 2016/17, the collection of PLICS was not yet mandatory, 62 providers contributed to the 2016/17 dataset and the PLICS cost used for EY51 (OPROC – Outpatient procedures) was based on data from 329,000 tests. If using the PLICS cost of £158 is not accepted, then we propose that a blended cost from the NHS reference costs is used, rather than just taking the cost for Cardiology. In the current NHS Reference Costs, the following specialty-specific costs for cardiac monitoring are listed for relevant outpatient services: • Cardiology: £141 • Stroke medicine: £328 • Transient Ischaemic Attack: £172 Although we recognise that Cardiology accounts for around two-thirds of the tests represented in the NHS Reference costs, the range of cost is large, across 62 specialty outpatients: a median value of £214 per test, IQR = £153-£307. We therefore believe that the PLICS cost of £158 used in the company's modelling is a conservative estimate, that does not justify further down-rating.	The EAC has considered the available evidence on the cost of Holter monitoring and remains of the view that the best available estimate of the cost of the procedure is the NHS reference cost for Cardiology. The EAC notes the uncertainty in the cost of this procedure and has undertaken sensitivity analysis on this parameter.

NICE National Institute for Health and Care Excellence

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
10.3.1 Base case results "*The EAC included an outpatient assessment cost after all test results regardless of the technology used*" *"The inclusion of an outpatient assessment prior to discharge following a negative test result in the cardiology model increased the costs of the technology more than the comparator since Zio Service produces more negative results.* *The EAC revised the cardiology model to combine inconclusive and negative results for 24hr Holter and CER, negating the need to estimate the probability of a negative result.*	**In the cardiology model:** We request that the base case revert to the original assumption in the sponsor's economic submission that: 1. A follow-up outpatient appointment would not be required if the patient's test was negative (and therefore conclusive for a diagnostic 'rule out' of clinically significant arrhythmia) 2. For this to occur, it will also be necessary to revert the base case back to the original assumption that different management pathways are followed for	Currently, all results from Holter or cardiac event recorder tests are reviewed by senior clinicians. In the Cardiology pathway, these clinicians would, typically, not require a face-to-face follow-up outpatient appointment with the patient to relay negative test results (confirm that no clinically significant arrhythmia is the cause of their symptoms). Common practice would be for this follow-up to take place in primary care, community or integrated care structures. This clinical pathway was reflected in the original Cardiology model. In contrast, a test result in a stroke patient would require a follow-up appointment, regardless of whether it was positive, negative or inconclusive, as it cannot be assumed that an arrythmia isn't present, due to the nature of the referral. This difference in the clinical pathway was reflected in the original Stroke model Due to factors relating to wear time, patient compliance and other practical benefits, the Zio service delivers a significantly higher diagnostic yield – information to rule in or rule out clinically significant arrythmia – than the comparator. Importantly for comparing the cost of the Zio service pathway vs the comparator, arrhythmia can be ruled out (negative test) in significantly more patient with Zio than the comparator (29.9% for Zio vs 11.4% for Holter). Clinical opinion confirms that it is this ability to confidently rule out arrythmia in the cardiology pathway, and therefore discharge the patient back into the community, that	The EAC has contacted clinical experts regarding the likelihood of an inconclusive test and the care pathway following a negative test. The clinical experts did not provide a clear definition of the difference between an inconclusive test and a negative test. On consideration of the evidence, the EAC concluded that the majority of Holter results would be considered a negative result. The resulting clinical evidence may then be inconclusive given a failure of monitoring to detect an arrhythmia. For this reason, and the lack of data on the number of negative or inconclusive tests following Holter monitoring the EAC decided to combine these test outcomes in the model. The EAC considered that ambiguity on diagnosis following a negative finding with Holter would ideally be resolved through further discussion of symptoms with the patient. Such an appointment would seem valuable in assessing whether a further period of monitoring is required or not. Hence the EAC

	inconclusive and negative test results	contributes to the economic value of the Zio Service. To not allow the distinction between the follow-up of a negative test vs an inconclusive test, and to incorrectly assume all patients are followed-up in outpatients regardless of test result, ignores a significant element of the potential cost and system benefit of the Zio System. The inclusion of outpatient appointments for all test results is counter conducive to NHS England strategic intentions to reduce unnecessary secondary care follow up appointments.	included a follow-up appointment following a negative result. The EAC has undertaken further discussion with clinical experts. The response has been varied and indicates that further outpatient visits following a negative finding after Holter monitoring sometimes occur. The EAC has undertaken sensitivity analysis in which these costs are excluded.

NICE National Institute for Health and Care Excellence

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
10.2.4.4 Adverse events and Table 10 Base Case Costs *The EAC believes the cost of anticoagulant therapy including the cost of increased incidence of major bleeds should be included in the model. The EAC considers the cost projections in the NICE costing report accompanying the Clinical guideline on the management of atrial fibrillation [CG180] to be the most appropriate source of data since the guidelines consider oral anticoagulants as well as warfarin and the proportion of patients given no therapy.* EAC base case - cost of anticoagulation therapy including costs of bleeds = £452 (NICE clinical guidance CG 180, Atrial Fibrillation management – costing report upgraded to 2017 / 2018 prices	Remove the cost of anticoagulation therapy from the model	Clinical management of atrial fibrillation post stroke is independent to every individual and should reflect current NICE guidance as well as current availability of anticoagulation as per local prescribing guidelines. To generalise a clinical management plan may not reflect current clinical practice and penalise localities. A review of anticoagulant prescribing patterns in England show that: • There have been substantial changes in the patterns of use of warfarin/DOACs over the past 5 years • The magnitude and nature of these changes show wide differences across CCGs To use a cost source from the 2014 CG180, even with an upgrade of cost to 2017 / 2018 prices, will not reflect the change in clinical practice to the prescribing of anticoagulation drugs which has happened since publication of CG180, and will therefore potentially introduce inaccuracies and bias to the cost outcome of this current evaluation.	The EAC considers the cost of anti-coagulation therapy to be relevant to a consideration of the impact of diagnosis of AF on the downstream costs of stroke. The EAC accepts there is uncertainty in the estimation of these costs, but considers the NICE guidance to provide a robust estimate relevant to the UK.

NICE National Institute for Health and Care Excellence

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The diagnostic accuracy of the Zio XT Service compared with Holter monitoring is unclear, however overall clinical opinion suggested that there may be no significant difference in accuracy. The current evidence would benefit from further research into the diagnostic accuracy of Zio XT Service against standard practice and an appropriate reference standard.	There is over emphasis in the report on the lack of evidence comparing accuracy of Zio to the comparator and the uncertainty that this leads to in the overall conclusions. Comparison should focus instead on diagnostic yield	A gold standard ECG analysis is not available against which to compare the accuracy of Zio or its comparators. As far as we know, clinical accuracy data are absent for Holter and event recorders as well One study, Eysenck (2019) did compare the accuracy of several monitoring modalities, including Zio, to a pacemaker. The investigators stated that dual chamber permanent pacemakers are considered the reference standard in arrhythmia detection, with high sensitivity and specificity for atrial and ventricular waveforms via endocardial electrodes. Zio was the only device that showed 100% AF detection concordance with the pacemaker. Compared to concurrent pacemaker recordings, the overall AF burden found by Zio had an R squared of 0.99 with an MSE of 0.24, the most accurate of all included modalities, including the event monitor (Novacor R test). Additionally, Zio more accurately indicated the presence or absence of AF than the R Test (odds ratio 12.3 (95% CI 1.4 to 110.3; p = 0.025). Zio provides an arrhythmia detection service, and should not be viewed as a diagnostic device. The service provides the Clinician with curated AI-led information about the patient's heart rhythm. The Clinician makes the final diagnosis**.** As Zio XT is a service to provide the clinician with critical information to make a diagnosis of arrhythmia (including, critical information to rule out clinically	The EAC understands that increased diagnostic yield is a main stated benefit of Zio XT Service. The EAC does conclude that 3 pivotal comparative studies indicate "the use of 14-day Zio XT Service increased diagnostic yield compared with 24-hour Holter monitoring over total wear time". The EAC also believes that it is important to note though the Zio XT Service is not intended for diagnosis, its accuracy in detecting true arrhythmias is important to further understand the value of an increased diagnostic yield. The accuracy of results from Zio XT Service potentially has an impact on clinical outcomes. The EAC assessed the available published evidence and consulted NICE clinical experts to conclude "The diagnostic accuracy of Zio XT Service compared with Holter monitoring is unclear, however overall clinical opinion suggested that there may be no significant difference in accuracy" and also describes the Eysenck (2019) study that "indicated that Zio XT Service may be more accurate in detecting the

		significant arrhythmia), the diagnostic '*yield*' is more pertinent to measure and compare than any fundamental difference in the sensitivity of the technology. Diagnostic yield can only be as good as the wear time, regardless of accuracy and is proven to increase with duration of monitoring. • A Holter will continuously monitor the heart rhythm for the period that it is worn, regardless of whether the patient has any symptoms. Wearing a Holter monitor for longer than 24-48 hours is universally considered to be impractical and is rarely employed for longer than 48 hours and 24 hours is generally considered to be the normal wear time. • The Zio biosensor also continuously monitors heart rhythm for the period of time that it is worn, but by virtue of being worn for 14 days (with no issues with patient compliance or artefact), is far more likely to capture an intermittent problem – hence a greater diagnostic yield than Holter. The Zio service incorporates a tool to give you performance statistics of the biosensor in terms of mean analysable time. This is not available with the Holter systems.	presence or absence of AF than the Novacor R Test (an external event/loop monitor, described as current standard practice) but less accurate than pacemaker data (described as gold standard)". The EAC maintains that further published evidence comparing the accuracy of Zio XT Service with standard care would be helpful to support this.

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 11. Summary of base case results Stroke model. Cost saving per patient: -£70.81	Given the changes in the stroke model base case outlined by the EAC, we cannot replicate this result. It would help us understand how this figure has been arrived at.	We are especially puzzled by some of the statements, in the stroke model, regarding the EAC making changes to the base case to include an outpatient follow-up appt regardless of test result. The EAC report, in its summary of the impact of the changes to the base case,: (page 106): *The inclusion of an outpatient assessment after all Zio results in the stroke model increased the costs of the technology.* We would like to note that in the company's economic submission, the stroke model included an outpatient review for <u>all</u> patients, regardless of the test result, so we seek an understanding of how the EAC has adjusted the base case in this regard. Also (on page 92) in the assumptions for the stroke model, the report states "*Some patients with an inconclusive/negative result will be discharged, others will undergo further tests"*. This is incorrect. As stated above, all patients in the stroke model are reviewed in outpatients, regardless of the test result.	The stroke model submitted by the company include a 'review no repeat' branch following a negative result for both the current care and for Zio Service. In the current care pathway this branch was associated with a cost of an outpatient assessment appointment and the cost of monitoring with either Holter or CER. In the Zio Service this branch was associated with the cost of Zio Service only. In its revision of the model the EAC added the cost of an outpatient assessment to the 'review no repeat' branch of the Zio Service arm. There were further branches of the model where an outpatient assessment had been included following a positive or inconclusive test under the current pathway but not in the arm representing Zio service. These included a positive outpatient assessment following a negative result from inpatient monitoring, and a review leading to placement of an ILR following a negative/inconclusive test. The EAC made further amendments to the following parameters as detailed in

			the report. The parameter pNorepeat was amended from 0.73 to 0.719 to align the probability of patient not undergoing a further test to the figure of 73% derived from HES data after allowing for the small proportion of patients whose test is positive with Holter. The parameter nRepeat was amended from 1.44 to 1.465 to more closely match the number of repeat tests observed in the HES data. The overall cost of monitoring with Holter or CER (cCER and cHolter) was amended from £185.12 to £168.12. The assumption that the EAC reported regarding the company's submission refers to the clinical decision regarding the request for a further test following a negative/inconclusive test. The EAC accepted the company's assumption that the majority of patients receiving a negative/inconclusive test would not undergo further testing. As stated above, the EAC notes that the company's model did not include the cost of an outpatient assessments after some assessments with Zio Service.

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 25 of 156 Eisenberg (2014) No conflicts of interest for the published content, funding unclear	The company was not involved with funding this study.	To make clear that the company was not involved in the funding of this study	We have amended this to "Not funded by company".

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 29 of 156 Rho (2018)	Add, the company was not involved with funding this study.	To make clear that the company was not involved in the funding of this study	We have amended this to "Not funded by company".

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 38 of 156 Agarwal (2015)	The setting was NIH Atherosclerosis Risk in	To clarify the setting for the study	We have added the following to the table "The setting was the US national Institutes of Health Atherosclerosis Risk

Setting unclear	Communities (ARIC) Study population		in Communities (ARIC) Study population"

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Country of origin unclear.	Country of origin: US	To clarify country of origin	See response to issue 8, above.

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 11.1 (no page number available) Neither of the studies use a gold standard reference.	Delete this sentence	Rosenberg, et al. did use a 12 lead ECG at the start of the study for all participants: "electrocardiogram performed in the clinic prior to enrollment that was interpreted as sinus rhythm (56 patients) or AF, atrial flutter, or atrial tachycardia (11 patients)...."	We have changed to clarify that the "judgement of clinical experts was used as reference standard". The study reports that ECG data was used prior to enrolment in the study, but it is unclear if and how the ECG data was used within the study.

Issue 11

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 3 of 156 Acknowledgements Currently omits to include Dr Joe Mills	Add to the list of acknowledgements: Dr Joe Mills, Consultant Cardiologist, Liverpool	Dr Mills has been consulted during the development of this report and therefore should be included in the list of acknowledgements	Thank you. Dr Mills was not consulted by the EAC in the development of this Assessment Report.

	Heart and Chest NHS Foundation Trust, no conflict declared.		

Issue 12

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 9.2.1 (no page numbers available) This section refers to 3 models: cardiology model, stroke model and downstream stroke model. There are 2 Figures referred to: "cardiology and downstream stroke models", however, only figures of the stroke model and downstream stroke model are provided in the report. A figure of the cardiology model is not included. Figure 1 is the stroke model, but is incorrectly labelled as the cardiology model.	Include a figure of the cardiology model. Correct error in the labelling of Figure 1		This has been amended.

Issue 13

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 7. No page numbers available "Estimate derived from data on all patients undergoing echocardiogram monitoring or stress testing. The EAC has some concerns regarding the applicability of this data to the population in the company's models."	Should read "Estimate derived from data on all patients undergoing electrocardiogram monitoring or stress testing. The EAC has some concerns regarding the applicability of this data to the population in the company's models."	Echocardiogram has been mistakenly written for electrocardiogram	We have amended echocardiogram to electrocardiogram in economic section of the report (as referencing EY51Z).

Issue 14

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 8. No page numbers available "Estimate derived from data on all patients undergoing echocardiogram monitoring or stress testing. The EAC has some concerns regarding the applicability of this data to the	Should read "Estimate derived from data on all patients undergoing electrocardiogram monitoring or stress testing. The EAC has some concerns	Echocardiogram has been mistakenly written for electrocardiogram	See response to issue 13 above.

population in the company's models."	regarding the applicability of this data to the population in the company's models."		

Issue 15

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
10.2.4.2 NHS and unit costs. No page numbers available The EAC was unable to source a better estimate of the cost of ambulatory echocardiogram monitoring in the NHS.	Should read "The EAC was unable to source a better estimate of the cost of ambulatory electrocardiogram monitoring in the NHS."	Echocardiogram has been mistakenly written for electrocardiogram	See response to issue 13 above.

Issue 16

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
10.2.4.3 Resource use No page numbers available The EAC notes that this parameter is derived from data on all patients undergoing echocardiogram monitoring or exercise stress tests in the NHS.	Should read "The EAC notes that this parameter is derived from data on all patients undergoing electrocardiogram monitoring or exercise stress tests in the NHS.	Echocardiogram has been mistakenly written for electrocardiogram	See response to issue 13 above.

Issue 17

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
9.2.3 No page numbers available The EAC considered an estimate of the cost of £142 derived from the NHS reference cost for echocardiogram or stress testing in a cardiology department ……	Should read "The EAC considered an estimate of the cost of £142 derived from the NHS reference cost for electrocardiogram or stress testing ……."	Echocardiogram has been mistakenly written for electrocardiogram	See response to issue 13 above.

Issue 18

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 98 *The EAC contacted clinical experts to enquire on the suitability of these references. The clinical experts suggested they may not be inappropriate.*	Consider changing to "The EAC contacted clinical experts to enquire on the suitability of these references. The clinical experts suggested they may be appropriate	This statement contains a double negative and perhaps could be reworded to read more clearly	We have amended this to "they may be appropriate".

Issue 19

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
*S*ection 9.2.1. *P*age 94. Downstream stroke model The EAC changed the base case of the Downstream Stroke Model to include diagnostic costs as well as the cost of stroke treatment. The report states (page 106) that the '*the biggest change the EAC made to the downstream stroke model was the inclusion of additional test costs*'.	Please could the EAC remove the additional test costs from the Downstream Stroke Model to avoid the possibility of double counting the test costs as these are already included in the stroke process model (Stroke Model)	In Section 2.3 of the Sponsor's Economic Submission (***Assumptions used to extrapolate clinical outcomes***) it states that ***No costs of monitoring are included in this model, as this element has already been captured in the process model.***	The EAC considers the costs of monitoring to be relevant to all analyses. Therefore, it has included these costs in all analyses. This is not double counting; monitoring costs are accrued as they occur in each model.

The report also states (p113) '*The EAC amendments to the downstream stroke model increased the cost for Zio Service when compared to current care. The main change was the inclusion of test costs*'			

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical engagement report

Zio XT Service for detecting cardiac arrhythmias

This report documents the decision made regarding the suitability of the evidence for progression to committee for guidance development. It has been prepared by the technical team at NICE with input from the chair and a committee member of the Medical Technologies Advisory Committee. It highlights the key issues raised in the evidence review so far.

This report is based on:

- the evidence and views presented by the company in a submission of evidence to NICE which presents the technology description, clinical evidence and an outline of economic information available
- views from clinical expert advisers
- a briefing from the external assessment centre (EAC) based on their review of the clinical evidence and an outline of the economic evidence
- discussions by the topic lead team at a meeting on 8 November 2019. Other attendees at the meeting were:
    - EAC representatives:
        - Anastasia Chalkidou, KiTEC
        - Jamie Erskine, KiTEC
        - Yael Rodriguez Guadarrama, KiTEC
    - Expert Advisers
        - Joseph Mills, Consultant Cardiologist
        - Mark A Tanner, Consultant Cardiologist and Honorary Clinical Senior Lecturer
- Consultation responses received on the draft technical engagement report

The technical report should be read with the supporting documents available for the development of for this technology.

1. Summary of the technical engagement report

This technical engagement report contains 2 appendices:

- Appendix A: EAC technical engagement briefing document
- Appendix B: Technical engagement consultation responses

1.1 Proposed next steps for guidance development:

- This technology should proceed to the NICE medical technologies advisory committee (MTAC) for guidance development.

The technology is available and currently being used in a small number of NHS sites, with more widespread use in the UK private sector. There is published evidence which the EAC considers is of adequate quality for guidance development. There is very limited published information on the economic impact of the technology but the EAC considers there is enough information to build an appropriate economic model to inform guidance development.

1.2 Summary of key issues identified during technical engagement:

- Limited evidence on diagnostic accuracy of the technology
- Further information needed regarding the AI algorithm used to detect events
- Limited evidence on the impact of the technology on clinical outcomes
- Heterogeneity of patient populations
- Uncertainty in parameters for the economic model
- Generalisability of the economic model across different NHS pathways

1.3 Equality considerations

Some clinical experts suggested that use of Zio XT Service may improve accessibility for people who have difficulty travelling to secondary cardiac centres. Use of this technology requires fewer hospital appointments and could in the future be fitted in other settings such as GP practices.

2. Considerations for guidance development

1. Is the technology ready for use in, and available to the NHS?	
Information available	Zio XT Service is CE-marked as a class 2a device and is in the process of being re-certified. The company (iRhythm Technologies) is registered with the CQC. Expert advisers said that Zio XT Service is being used in a small number of NHS sites, but is more widely used in private practice. No significant issues were identified by expert advisers regarding the technology's safety, usability or practical aspects.
Preliminary response and rationale	No issues with its use and availability to the NHS. A technical assessment carried out by ORCHA will confirm if the technology meets NHS Digital's standards for digital technologies.
Summary of technical engagement responses	The company confirmed that the new CE mark (class 2a) has been received. Responses received agreed that the technology is mature enough for guidance development.
2. Is there sufficient evidence to take this topic to the Medical Technologies Advisory Committee for guidance development? Is the evidence robust and of good quality?	
Information available	The EAC identified 30 relevant clinical studies (including 16 studies submitted by the company, 1 additional full text study and 13 abstracts). Of these, the company and EAC considered 4 comparative studies to be pivotal; 1 UK-based RCT and 3 prospective comparative studies. Three of the studies compared Zio XT Service with 24-hour Holter monitor and 1 compared it with an external loop recorder. Two studies were conducted in an NHS setting. The EAC considered these studies to be of adequate quality, concluding that the available evidence for the technology is sufficient for guidance development. The economic evidence base for Zio XT Service consists of 5 studies (1 budget impact analysis and 4 studies containing cost or resource use data). The EAC considered the first stage (1-year time horizon) of the company's planned cost model appropriate but details provided for stage 2 of the model were insufficient to assess feasibility. Some uncertainties within the clinical and economic evidence base were noted (see section 3), however it was not believed that these would prevent guidance development.
Preliminary response and rationale	There is enough evidence available to proceed to guidance development. Uncertainties within the clinical and economic evidence base can be considered by MTAC.
Summary of technical engagement responses	Responses received agreed that there is sufficient evidence to take this topic to the Medical Technologies Advisory Committee for adoption recommendations

3. Are there any concerns about how this technology would be used in NHS clinical practice or any implications for the treatment pathway?	
Information available	The company presented 3 clinical pathways where Zio XT Service could be implemented for ambulatory monitoring (cardiology, stroke and general medicine). These pathways have been validated by NHS professionals. According to expert advisers, the amount of training needed is minimal and no significant facilities / infrastructure changes would be needed to use Zio XT Service. No significant capital costs were identified, aside from the cost for purchasing the Zio XT patches. The EAC did not believe that significant changes to IT infrastructure would be needed.
Preliminary response and rationale	There are no significant concerns about using Zio XT Service in NHS clinical practice. Expert opinion suggests that Zio XT Service could be easily implemented into the existing care pathway and may improve efficiency of care for patients. It could be used in several different patient pathways and the clinical outcomes and economic impact may differ between these settings.
Summary of technical engagement responses	No concerns were raised.
4. Are there any other implications for guidance development?	
Information available	No other implications were identified and no concerns surrounding guidance development were raised by any of the expert advisers.
Preliminary response and rationale	No additional implications for guidance development have been identified.
Summary of technical engagement responses	No other implications were raised.

3. Key issues identified in the evidence review

These issues have been identified by the topic lead team from the submission of evidence provided by the company and the EAC review of the submission and advice received from expert advisers.

Before technical engagement	Following technical engagement
Issue 1: there is limited clinical evidence on the diagnostic accuracy of the technology. No clinical studies primarily investigated the diagnostic accuracy of Zio XT Service against the 24-hour Holter monitoring.	It was noted that Barrett et al. (2014) may provide additional useful evidence. The EAC have been asked to investigate the evidence from the first 24 hours of this study where both the Holter and Zio XT technologies were worn by the patient. In their response to technical engagement the company stated that Zio XT is a diagnostic service not device, and that it is the clinician who makes the final diagnosis. The company therefore believe diagnostic yield is a more relevant measure of effectiveness, and state that evidence-based diagnostic yield will be a key parameter in the economic model for all the monitoring modalities being modelled.
Issue 2: further information is needed regarding the reliability of the AI algorithm used to detect arrhythmic events. Any developments to the AI algorithm may affect the diagnostic accuracy of the device.	A technical assessment, providing more information on the reliability of the AI algorithm and how it has been developed and validated, will be available to inform committee discussions. In their response to technical engagement the company provided further proprietary information about the deep-learned ECG analysis algorithms used within the Zio XT Service.
Issue 3: it is unclear from the available studies whether an increase in diagnostic yield with Zio XT Service is associated with improved clinical outcomes.	The EAC are not aware of any studies to support this link. In their response to technical engagement the company stated that, based on results from Kaura et al. (2019), 8 times as many post stroke patients with AF will be appropriately treated as a result of monitoring with the Zio Service than would be following monitoring with Holter. The company believe that the incremental clinical gain from treatment is indisputable, given that treating AF in these patients is known to reduce the risk of further stroke/TIA by 60-70%.

Issue 4: The EAC considers the comparative study populations to be heterogenous. The distinct populations of some of the studies may limit generalisability of results to the broader population of people being referred for ambulatory monitoring in the NHS.	Further clinical advice may be sought to help better understand which outcomes may be generalisable across different patient populations and pathways and which ones are not. It may be appropriate to consider the use of Zio XT Service in different populations separately. In their response to technical engagement the company state that despite the heterogenous nature of the populations studied, there is considerable consistency across the studies in terms of diagnostic yield, and that this suggests results are likely to be generalisable.
Issue 5: there may be uncertainty associated with some of the key parameters in the economic model. This is mainly due to limited evidence for diagnostic accuracy and the lack of direct evidence linking Zio XT Service diagnostic yield to clinical outcomes.	The impact of uncertainty in the parameters will be explored by the EAC using sensitivity analysis. In their response to technical engagement the company agrees that sensitivity analysis can be used to explore the impact of uncertainty in the parameters. It also states that their planned economic model separates the process outcomes of the different monitoring approaches from the downstream clinical benefits.
Issue 6: consideration may be needed around the generalisability of the economic model across different NHS pathways. The company presented several validated clinical pathways which could incorporate testing with Zio XT Service. The EAC have noted that the cost and diagnostic yield of usual care will be highly dependent on the clinical pathway and this will impact on the incremental cost of Zio XT Service in the planned cost modelling.	The EAC will conduct sensitivity analyses, where appropriate. Further clinical expert advice may also be obtained to help address this issue. In their response to technical engagement the company state that, to look at some of the differences in populations, different economic models have been planned. The company note that the critical issue for the modelling is the comparison between alternative technologies, length of monitoring and subsequent yield.

4. Issues for information

Issue	Comments
Ongoing studies	The company and EAC identified 2 ongoing studies. Both studies are RCTs which will compare 2 weeks monitoring of the Zio XT Service with standard care. One study is based in Canada and Germany and has enrolled 856 participants aged 75 years or over with a history of hypertension and without known AF. The primary endpoint is the rate of new diagnosis of AF (or flutter) within 6 months of randomisation and is expected to be completed in 2019. The other is a UK-based study which plans to enrol 2,500 people at high-risk for AF. It has a primary endpoint of proportion of participants diagnosed with AF after 2.5 years of follow-up (see section 9.2 of the EAC assessment report for further information).
Equality considerations	Some experts have suggested that Zio XT Service could increase the accessibility for hard to reach populations to cardiac ambulatory monitoring.

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Appendix A: EAC technical engagement briefing

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

DHT005 Zio XT Service for detecting cardiac arrhythmias

Technical engagement briefing report

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Contains confidential information	No

Number of attached appendices	Appendix A – Decision Problem

Purpose of the technical engagement briefing report

The purpose of this EAC report is to provide the technical team at NICE with an overview of the evidence submitted by the company in their part 1 evidence submission. The aim is to provide the team with information to help inform its decision on whether there is sufficient evidence to move to a part 2 economic submission or whether further evidence generation is required.

NICE has commissioned this work and provided the template for the report.

Declared interests of the authors

Description of any declared interests with related companies, and the matter under consideration. Please refer to NICE's Policy on managing interests for board members and employees.

The Kaura (2019) study was carried out, in part, at King's College Hospital NHS Foundation Trust. The King's Technology Evaluation Centre is part of the King's Health Partnership network.

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"Copyright belongs to King's Technology Evaluation Centre."

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Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

Overview of decision problem and technology

The company submission is largely consistent with this decision problem and the available evidence conforms to these populations and outcomes. See Appendix A for a description of the decision problem.

The Zio XT Service (iRhythm Technologies) consists of 3 components: the Zio XT biosensor, the Zio ECG Utilisation Service (ZEUS) system and the Zio XT technical report. The Zio XT biosensor is an adhesive patch with a I-Lead ambulatory electrocardiogram (ECG) recorder. The ZEUS system is a proprietary software platform that is used to store, analyse and sort the recorded ECG data. The Zio XT technical report is a clinically actionable summary of the recorded and analysed data, generated by the ZEUS system and the Zio clinical team.

The technology can be used as described in the decision problem. Despite the information in the clinical submission, however, there are still some unknowns regarding the proprietary algorithms used to interpret the recorded ECG data. The most recent versions of the algorithms have been described as making use of artificial intelligence and deep-learning techniques. However, it is not clear how version changes and system learning will affect the outcomes captured in the clinical evidence.

Overview of clinical evidence

Summary of evidence base

The company's submission included 22 studies that were reported as fulltext; the EAC included 16 of these 22 studies. One further study reported as fulltext was added by the EAC (Rho et al. 2018). The EAC excluded 6 studies from the company's selection (Camm et al. 2015, Chen et al. 2015, Lutsey et al. 2016, Mullis et al. 2019, Muse et al. 2018, Hannun et al. 2019) due to population being out of scope or the outcomes being irrelevant to the performance and efficacy of the device. The EAC added 13 abstracts, totalling 30 studies overall. Most of the included studies were observational in design and lacked direct comparators or were reported as abstracts (see table 2 in the assessment report). The company and the

EAC considered 4 comparative studies to be the most relevant to the decision problem: 1 UK-based RCT (Kaura et al. 2019), 3 prospective comparative studies (Barrett et al. 2014, Eysenck et al. 2019, Rosenberg et al. 2013).

Quality of evidence

The EAC considers the 4 comparative studies to be of adequate quality. Three of the studies prospectively compared 14 day Zio XT Service with 24 hour Holter monitoring, while 1 compared 14 day Zio XT Service to the Novacor R-test (an external event recorder). Unlike the 3 other comparative studies, the RCT included asymptomatic patients (people with stroke/TIA), therefore results may not be generalisable to a broader cohort of people with suspected cardiac arrhythmia. There was a high withdrawal rate in the comparator which may have biased results. The authors carried out a power calculation indicating that the study was adequately powered for the primary outcome. An independent power analysis carried out by the EAC found the RCT to be underpowered due to the high drop out rate from both arms of the study. The study is highly likely to be underpowered for the secondary outcomes that included anticoagulation use and mortality.

The further 3 comparative studies included heterogenous populations. Barrett et al. (2014) included a broad population from a US hospital which included people referred for ambulatory monitoring for 6 different types of arrhythmia. Some participants had pre-existing arrhythmias and were referred for reasons other than symptomatic arrhythmia. The study population in Eysenck et al. (2018) was relatively small (n=21). No power calculation was reported so it is unclear whether the study was adequately powered. There were a high percentage of men and therefore results may not be as generalisable to women. The order of devices was randomised which helps mitigate against order effects. All patients had pacemakers of varying brands which may bias results. This may limit generalisability, due to the presence of other cardiac pathology, and did not allow assessment of external ambulatory monitors in ‘healthy’ individuals. Rosenberg et al. (2013) carried out a blinded study in a US hospital setting where the experts who determined whether the ECG traces showed AF or not were blinded to the source technology. Blinding was not mentioned in the other studies. It is unclear whether the 2 groups within the study

were adequately matched. The groups are described as comparable by the study, but reported as significantly different ($p<0.0001$). No power calculation was reported.

The UK setting of Kaura et al. (2019) and Eysenck et al. (2019) make them potentially more applicable to the NHS setting.

Many studies were at least in part funded by the company (including the 3 within participant comparative studies) which may introduce a source of bias.

Key outcomes

Key outcomes included diagnostic yield, clinical outcomes and patient experience. Diagnostic yield indicates how much information is gathered to help establish a diagnosis, whereas diagnostic accuracy indicates how well a device correctly identifies an event (or non-event). A high yield without corresponding accuracy may mean a diagnostic process is inefficient and inaccurate.

Diagnostic accuracy is an important outcome that was not directly assessed against standard 24 hour Holter monitoring in the key studies. Using odds ratios, Eysenck (2019) indicates that Zio XT Service may be more accurate in detecting the presence or absence of AF than the Novacor R Test (an external event/loop monitor, described as current standard practice) but less accurate than pacemaker data (described as gold standard). Overall, clinical experts suggested that there may be no significant difference in accuracy between Zio XT Service and Holter monitoring, though 1 noted that because of the increased number of leads (1 for Zio XT Service and 3 for Holter monitoring) the Holter may, theoretically, be more accurate. Conversely, 1 expert noted that Zio XT Service may be more accurate for a fixed period of time (24 hours), as there is likely to be less artefact and more analysable rhythm (for example, patients remove the Holter monitors during showers).

The diagnostic yield appeared to be consistently higher for Zio XT Service compared with Holter monitoring (as a result of extended monitoring). This may affect clinical management but it is not clear how this translates to clinical outcomes for the patient. Experts noted that extended monitoring would be particularly useful for populations suspected of infrequent arrhythmias. Evidence indicates that Zio XT Service has relatively high patient acceptance and compliance.

Though the key studies were of adequate quality to infer some conclusions (despite a number of flaws, such as small sample sizes), no further pooled analysis was carried out by the company. The company stated that the evidence for the efficacy and safety of the Zio XT Service is extremely heterogeneous, in terms of populations, methodology, devices used and outcomes reported. Clinical experts noted that arrhythmia is a broad condition encompassing distinct pathophysiologies, syndromes and populations which are not directly comparable. The EAC concurs that a meta-analysis carried out with the current clinical evidence would not be robust.

Further research required

There are 2 key gaps in the evidence that should be considered. Firstly, a better understanding of the diagnostic accuracy of Zio XT Service against an appropriate reference standard would be required to understand whether its use translates to appropriate clinical management. Secondly, a larger analysis focused on utilisation and resulting clinical outcomes may provide greater insight on how providers respond to newly-detected arrhythmia.

Overview of economic evidence

Economic evidence submitted by the company

The EAC considers that only 3 of the studies presented in the company evidence submission document contain relevant economic evidence for the decision problem. Only the study conducted by Kaura et al. (2019) performed a cost-minimisation analysis; Ghosh et al. (2018) and Chandratheva et al. (2017) report cost data only.

Kaura et al. (2019) reports a randomised non-blinded trial comparing Zio XT Service with 24-hour Holter-based monitoring strategy. The primary outcome of the study was the detection rate of AF at 90 days. The authors observed an AF detection rate of 16.3% in the Zio XT Service group compared with 2.1% in the Holter-based monitored group. Using these estimates the authors conducted a budget impact analysis complementing with parameters retrieved from the literature. The analysis applied a time horizon of 1 and 5 years and include monitoring costs and stroke health care costs. Implementation of Zio XT Service is cost saving for King's College

Hospital over 1 (£113,630) and 5 years (£162,491) for a target population of 1053 patients.

Ghosh et al. (2018) and Chandratheva et al. (2017) are 2 conference abstracts comparing Zio XT service with Holter-monitoring. Ghosh et al. (2018) concluded Zio XT Service is costlier than a 24-hour Holter monitor (£440 vs £367). Chandratheva et al. (2017) compared Zio XT Service to a 72-hour Holter monitor, a 3-day patch and in-clinic monitoring strategy. The authors concluded Zio XT Service is cost-saving (-£269, -£351, -£370) compared to 72-hour Holter, 3-day patch and in-clinic monitoring. Although both studies report contrary results regarding cost per patient, both studies concluded Zio XT service is more efficient in terms of time to report. As these studies were reported as conference abstracts, there was not enough information to clarify why the results are contradictory.

Economic evidence identified by the EAC

The EAC conducted a literature search and identified no additional economic analysis of the technology. However, 5 studies containing economic data were identified. Two of these studies (Steinhubl et al. (2019) and Eysenck et al. (2019)) were included as part of the clinical evidence submitted by the company although were not considered as part of the economic evidence.

The characteristics of study design, methods and primary outcomes of Steinhubl et al. (2019) have been described in the assessment report. The authors reported a statistically significant increase of AF-related therapeutic interventions including anticoagulant therapy, cardioversion procedures and cardiac ablation in the group actively monitored with Zio in comparison to a matched control group at 1 year. Emergency department or inpatient stays with AF diagnosis was the only parameter that did not achieve statistically significant difference. Nonetheless, emergency visits or inpatient stays for any other cause was significantly reduced in the group monitored with Zio XT Service. Cardiology or primary care visits were also significantly higher in this group. Three-year overall cost will be reported in a future publication.

A number of conference abstracts presented by Eysenck et al. (2017a, 2017b and 2018) containing economic data from the REMAP-AF trial were identified. All the studies compared the AF detection, diagnostic accuracy, patient satisfaction, and cost efficacy of different external ambulatory ECG monitors against the intervention considered as usual practice in the study setting (Novacor 'R'). The first abstract presented in 2017 (Eysenck et al. (2017a)) included Zio XT Service, NUUBO's shirt-based ELR, Bardy Patch, and Qardio Belt. The second abstract presented in 2017 (Eysenck et al. (2017b)) did not include Bardy Patch and Qardio Belt. Both analyses enrolled 20 patients whom had a permanent pacemaker advanced Holter implanted that served as the gold standard for estimation of diagnostic accuracy. The first study only reports that usual practice is the the least costly alternative without providing further detail. In the second study the authors report a mean cost per patient of £212 for Zio XT Service, £321 for NUUBO shirt-based external loop recorders and £28 for usual practice (Novacor 'R'). No details are provided on the design of the studies. The results of the abstract presented in 2018 are included in the authors' most recent publication in the Journal of Interventional Cardiac Electrophysiology (Eysenck et al. (2019). The characteristics of the study design, methods and primary and secondary outcomes of the study have been described in the full assessment report. This study included Zio XT Service, NUUBO Vest and Carnation Ambulatory Monitor as the comparators. The study reports a mean monitoring cost derived from the device unit cost, staff costs, patient travel costs and consumables costs for the Novacor R-test. According to the study Zio XT Service has the lowest travel time cost (measured in minutes) however is the costliest monitoring strategy (£284). The technology is followed in cost by the Carnation Ambulatory Monitor (£242), NUUBO Vest (£195) and Novacor R-test (£15).

Critique of identified economic evidence

Although there are a number of published studies containing economic evidence, the estimates and methodologies are highly heterogeneous hindering generalisability and lowering quality of the results.

Kaura et al. (2019) is the only study found that conducted any form of economic analysis. The analysis is poorly reported and may make some challengeable

assumptions. In the main body text there are no details of the methodology employed. The information provided in the supplementary appendix is limited to screen dumps from the model results. The authors used figures from Hospital Episodes Statistics, an estimate of prevalence from Sanna et al. (2004), and a 1-year recurrent stroke risk from Hart et al. (2007) to estimate the maximum number of preventable strokes. The assumptions the model makes regarding sensitivity and specificity, and how they were used to estimate the potential strokes prevented with Holter monitors and Zio XT Service, is not clear. The strategies outlined for both technologies incorporate the use of an implantable loop recorder with a higher diagnostic yield for a small proportion of negative results. This adds complexity to the modelling as the proportion of positive results when this test is applied is not independent from previous tests, therefore an adjustment should be made. Cost of usual care was extracted from NHS Reference Costs whereas the cost of Zio XT Service was obtained from the manufacturer. It is unclear if these costs include the time of NHS staff and overheads, as well as the cost of medical therapy to treat the diagnosed AF. The figures from Xu et al. (2018) for 1-year total cost of stroke and 1-year medical cost were £22,429 and £13,452, respectively. The study did not perform any type of sensitivity analysis to explore uncertainty around the parameters that populated the economic model.

Only Steinhubl et al. (2019) report health care resource. Although the findings reached statistical significance, no information is provided on the monitoring strategies employed in the control group. Additionally, that increase is not linked to clinical outcomes such as quality of life, morbidity or mortality. The rest of the studies only report cost data and time to report efficiency (time to report) of Zio Service XT contrasted with the comparators. However these estimates are not used to perform any type of further economic analysis.

Critique of proposed company economic model

The company intends to develop a 2-stage cost-minimisation model to capture the difference between Zio XT Service and usual clinical practice on the detection of AF and the reduction on health care cost from avoided stroke costs. The first stage is a 1-year time horizon decision tree. The second is 5-year time horizon analysis

intended to capture the consequences of stroke due to undiagnosed AF in three month time intervals. The structure of the second stage is yet to be defined. The key parameters of the model outlined by the company are diagnostic yield, Holter-based test use and re-use, cost of comparators, clinical pathway and risk of stroke associated with underdiagnosis of AF.

The EAC considers the model structure proposed by the company for the first stage to be appropriate given the absence of clinical outcomes in the literature. Nonetheless, the EAC has some concerns regarding a cost model based on the model structure and assumptions reported by Kaura et al. (2019). There is a high a level of uncertainty around key parameters of the model. Firstly, the value proposition of the technology relies on the increased diagnostic yield of Zio XT Service in comparison with usual practice. The elevated diagnostic yield is well supported by the body of evidence identified by the EAC. However little is known about the diagnostic accuracy of the technology. Secondly, there is a lack of clarity around the clinical pathway currently implemented in the NHS. As correctly noted by the company there are a number of different alternatives currently in place. The cost and diagnostic yield of usual care will be highly dependent on the clinical pathway and this will impact on the incremental cost of Zio XT service.

Conclusions

The clinical evidence consists of 30 studies – only 4 of which are considered pivotal as they are comparative and compare 14 day Zio XT Service with 24 hour Holter monitoring or external event monitoring. One UK-based RCT was included which meets the requirements for the NICE Evidence Standards Framework best practice standard evidence for digital health technologies with measurable benefits through active monitoring. The individual studies are of moderate quality to infer conclusions (with some significant flaws, such as the RCT being underpowered), however the populations are heterogenous and therefore results cannot be pooled. There is adequate evidence to suggest Zio XT Service increases diagnostic yield compared with 24 hour Holter monitoring. However there are gaps in evidence regarding its diagnostic accuracy and clinical outcomes.

The published economic evidence consists of 1 study performing an economic analysis and 4 studies containing economic evidence – 3 studies contain cost data and 1 study contains health care resource use. The EAC considered the first stage of the economic model structure planned by the company to be appropriate. Methodological adjustments should be made in order to address the issues previously highlighted in the case that the model is based upon the results of Kaura et al. (2019). More detail regarding the second stage of the model is needed in order to provide a statement about its feasibility and reliability.

There is a considerable degree of uncertainty around key parameters that populate the economic model. Firstly, as noted by the clinical evidence, though there is a sufficient body of evidence to support the claim of a higher diagnostic yield, there is little information about the diagnostic accuracy. Hence an assumption of perfect sensitivity might lead to overestimating potential benefits. Secondly, there are various clinical pathways currently used within the NHS that could be deemed as standard practice. Particularly, the number of Holter monitors used to rule out AF remains uncertain. Preliminary information from clinical experts suggests that a 24 hour Holter tends to be only requested once, unless clinical indications suggest a repeated test is necessary. A longer term Holter monitor may be worn for 7 to 14 days in patients with symptomatic AF episodes more than 24 hours apart. UK stroke guidelines do not have a minimum duration of recording. As such, there is a significant variation in practice (from single 24-hour to repeated Holters). This parameter has a direct impact in the true cost of the comparator.

The EAC believes there is enough clinical and economic evidence to proceed with an economic analysis for the first stage of the company proposed economic model. The EAC also believes the uncertainty around diagnostic accuracy and number of Holter test repetition could be partially addressed by further clinical expert advice and extensive sensitivity analysis. The description outlined by the company on the second stage of the model is insufficient to fully assess its feasibility. The company appears to be proposing a simple decision tree, however a Markov model might provide a stronger design and allow the incorporation of mortality from other causes as a competing risk. More information is needed on the second stage of the company economic model.

Appendix A Decision Problem

Decision problem	Scope	Proposed variation in company submission	EAC comment
Population	Adults (18 years or older) with suspected cardiac arrhythmia referred for ambulatory ECG monitoring.	None.	
Intervention	Zio ECG monitoring service (Zio Service).	Zio XT ECG monitoring service (Zio XT Service).	Addition of "XT" to name of intervention.
Comparator(s)	Current pathway for ambulatory cardiac arrhythmia detection, which includes Holter and/or event monitoring (external and implantable).	Current pathway for ambulatory cardiac arrhythmia detection, which includes Holter and/or event monitoring.	Company has removed "(external and implantable)". The company states that implantable cardiac monitors are rarely used as a first line of standard care and are not directly comparable. Clinical experts agreed that implantable devices are rarely used as a first line of care. They are more likely used for diagnosis. The EAC feels that the implantable comparators should be included as a potential indication of the diagnostic accuracy of Zio XT Service.
Outcomes	Procedure-related outcomes: • Diagnostic yield and accuracy (sensitivity and specificity) • Number of symptomatic and asymptomatic arrhythmia events detected over total wear time • Ability to quantify atrial fibrillation (AF)	Remove the following: • Health-related quality of life,	The company suggests removing "Health-related quality of life" as an outcome as there is no evidence to demonstrate this. The EAC suggests retaining this outcome in case future evidence comes to light.

	burden (amount of time spent in AF) • Time to first arrhythmia event and time to first symptomatic event • Time to return device, analysis and report production • Test failure rate • Signal quality Clinical management outcomes: • Time to diagnosis or rule out of cardiac arrhythmia • Time to initiation of preventative treatment • Impact of test results on clinical decision making • Total number of hospital outpatient appointments for testing • Total number of hospital outpatient appointments or admissions for device-related complications • Number of outpatient visits and staff time for undertaking and analysing diagnostic tests • Morbidity (including stroke, thromboembolism, heart failure, and		

	complications associated with preventative treatment) • Mortality Patient outcomes: • Patient compliance (average wear time and analysable wear time) • Ease of use (for patients and healthcare professionals), including training requirements • Device acceptability and patient satisfaction • Health-related quality of life • Device-related adverse events		
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	None.	
Subgroups to be considered	• Adults referred for ambulatory ECG monitoring, who experience asymptomatic arrhythmia events	Changes to subgroups: Adults referred for ambulatory ECG monitoring, *with*	The company states that the primary care referral pathway is included within the general medicine pathway as a route to diagnostic services but will not be considered separately

	• Adults referred for ambulatory ECG monitoring in primary care • Adults referred for ambulatory ECG monitoring in secondary care	*symptoms of arrhythmia* Adults referred for ambulatory ECG monitoring*, without symptoms of arrhythmia (e.g., patients with cryptogenic stroke or TIA)* Adults referred for ambulatory ECG monitoring in secondary care	within the economic modelling. The company's suggested changes include subgroups with symptomatic or non-symptomatic adults. One RCT and 2 non-comparative studies were found in asymptomatic patients. No evidence was found in primary care settings.
Special considerations, including those related to equality	The area of skin in which the Zio XT patch is applied will need shaving if hair is present. Some religions forbid cutting or shaving bodily hair. Zio XT Service is not approved for paediatric use. Religion and age are protected characteristics under the Equality Act. Contraindications are listed the instructions for use for Zio XT Service.	The company notes that traditional approaches to ECG monitoring also require shaving of bodily hair for electrode placement on the body.	The EAC acknowledges this note about the comparators for Zio XT Service.
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristics? No	None.	
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality? No	None.	

	Is there anything specific that needs to be done now to ensure MTAC will have relevant information to consider equality issues when developing guidance? No	None.	
	Cardiac arrhythmias can develop in people of any age but are more common in people over 60 years. Women tend to be at higher risk of certain arrhythmias, including atrioventricular nodal tachycardia, whereas men are 3 times more likely to develop atrial fibrillation at any age. However, of those people who develop atrial fibrillation, women have a much higher incidence of morbidity and mortality. Age and sex are protected characteristics under the Equality Act. People whose first language is not English or who cannot write may not be able to give written information on their symptoms while using the Zio Service.	None.	

Appendix B: Technical engagement consultation responses

Technical engagement response form

Zio XT Service for detecting cardiac arrhythmias

As a key stakeholder you have been invited to comment on the technical engagement report for this technology evaluation.

We need your comments and feedback on the questions/issues below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the NICE technical team to amend or update the judgement and rationale in the technical report.

Deadline for comments: **Friday 29 November 2019** at **5pm**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which describes the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted]. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: ‘academic/commercial in confidence information removed’.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate. **Comments received during engagement may be published in the interest of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

About you

Your name* (if you are responding as an organisation rather than a registered stakeholder please leave blank)	
Organisation name (if you are responding as an individual rather than a registered stakeholder please leave blank)	**iRhythm Technologies, Inc.**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

* Please note, any personally identifiable information will be removed from this section prior to publication on the NICE website.

Questions for engagement

Please provide your comments on the below questions:

1	Is the technology mature enough for guidance development?	Yes
2	Is there sufficient evidence to take this topic to the Medical Technologies Advisory Committee for adoption recommendations?	Yes
3	Are there any other concerns about medical technologies guidance development on this technology?	No
4	Have we included the correct stakeholders in this evaluation? (see stakeholder list)	Yes

Key issues

Please provide your comments on the below key issues and how you think NICE could address these:

1	There is limited clinical evidence on the diagnostic accuracy of the technology. No clinical studies	Zio XT is a service, not a diagnostic device. The service provides the Clinician with curated AI-led information about the patient's heart rhythm. The Clinician makes the final diagnosis. Zio XT provides an arrhythmia detection service, backed by a sophisticated deep learning algorithm and expert clinical quality assurance. [redacted]

	primarily investigated the diagnostic accuracy of Zio XT Service against the 24-hour Holter monitoring.	As Zio XT is a service to provide the clinician with critical information to make a diagnosis of arrhythmia (including, critical information to rule out clinically significant arrhythmia), the diagnostic '*yield'* is more pertinent to measure than any fundamental difference in the sensitivity of the technology. Diagnostic yield is proven to increase with the duration of monitoring. • A holter will continuously monitor the heart rhythm for the period that it is worn, regardless of whether the patient has any symptoms. Wearing a holter monitor for longer than 24-48 hours is universally considered to be impractical and is rarely employed for longer than 48 hours and 24 hours is generally considered to be the normal wear time • The Zio biosensor also continuously monitors heart rhythm for the period of time that it is worn, but by virtue of being worn for 14 days, is far more likely to capture an intermittent problem • The method of detection using events monitor in that they are designed to be triggered by events or patient when symptoms occur vs continuous recording (Zio service and Holter) A gold standard ECG analysis is not available against which to compare the accuracy of Zio. As far as we know, clinical accuracy data are absent for Holter and event recorders as well. Eysenck (2019) compared several monitoring modalities, including Zio, to a pacemaker. The investigators stated that dual chamber permanent pacemakers are considered the reference standard in arrhythmia detection, with high sensitivity and specificity for atrial and ventricular waveforms via endocardial electrodes. Zio was the only device that showed 100% AF detection concordance with the pacemaker. Compared to concurrent pacemaker recordings, the overall AF burden found by Zio had an R squared of 0.99 with an MSE of 0.24, the most accurate of all included modalities, including the event monitor (Novacor R test). Additionally, Zio more accurately indicated the presence or absence of AF than the R Test (odds ratio 12.3 (95% CI 1.4 to 110.3; p = 0.025). The Draft Technical Engagement Report states that *it was noted that Barrett et al. (2014) may provide additional useful evidence. The EAC have been asked to investigate the evidence from the first 24 hours of this study where both the Holter and Zio XT technologies were*

		worn by the patient. It should be pointed out that Zio and holter have a different approach to arrhythmia detection: With Zio, the rhythm over the entire wear period is analysed, compared with a day by day approach with holter [redacted]*
2	Further information is needed regarding the reliability of the AI algorithm used to detect arrhythmic events. Any developments to the AI algorithm may affect the diagnostic accuracy of the device.	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

		[redacted]**
3	It is unclear from the available studies whether an increase in diagnostic yield with Zio XT Service is associated with improved clinical outcomes.	The Zio Service is a diagnostic service not a therapeutic technology. There is a long-standing and undisputed evidence-based consensus that, in post stroke patients, the presence of AF increases the risk of further stroke/TIA and that treating the AF with anticoagulants reduces this risk by around 60-70%. The monitoring approach used to make a diagnosis of AF is relevant to this clinical benefit as regards to the proportion of patients with AF (particularly those with paroxysmal or silent AF where the arrhythmia is difficult to capture with current monitoring approaches) that are identified through monitoring. In post-stroke patients, it has been estimated that the underlying prevalence of AF is around 30% (Ref: 3 year data from CRYSTAL-AF). In Kaura 2019, Zio identified 16% of post stroke patients as having AF (just over half of the total estimated number of patients with AF), 24-hr Holter 24 only identified up to 2%. If it is assumed that all patients identified as having AF are appropriately treated, this means that 8 times as many patients with AF will be appropriately treated as a result of monitoring with the Zio Service than would be following monitoring with Holter. Provided these are true positive results, the incremental clinical gain from anticoagulation is indisputable.
4	The EAC considers the comparative study populations to be heterogenous. The distinct populations of some of the studies may limit generalisability of results to the broader population of	Zio is a versatile service which has been used in a variety of settings to detect arrhythmias. Despite the heterogenous nature of the populations studied, there is considerable consistency across the studies in terms of diagnostic yield. For symptomatic patients, Zio has a positive diagnostic yield in the range 60-70%, with negative diagnostic yield of 20-30%, giving a consistent combined rule in and rule out (positive and negative) yield of >90%. This consistency of results across different populations suggests that the results are quite likely to be generalisable. To accommodate some of the differences in population, different economic models have been constructed to look at multiple populations. Acknowledging the heterogenous nature of the population studied, there is also poor baseline data about the current nature of services between primary and secondary care.

	people being referred for ambulatory monitoring in the NHS.	
5	There may be uncertainty associated with some of the key parameters in the economic model. This is mainly due to limited evidence for diagnostic accuracy and the lack of direct evidence linking Zio XT Service diagnostic yield to clinical outcomes.	Please refer to the comment in 1 regarding the point about diagnostic accuracy. A key parameter in the economic modelling is based on **diagnostic yield** from the clinical studies and substantial patient data on file. On this basis, the modelling uses an evidence-based diagnostic yield for all the monitoring modalities being modelled. Expert opinion has been sought on other key parameters, such as the pathway taken by patients on different diagnostic outcomes (positive, negative, inconclusive). As stated in the draft Technical Engagement Report, the impact of any uncertainty in the diagnostic yield and other parameters will be explored using sensitivity analysis. As regards the lack of direct evidence linking the Zio Service to clinical outcomes, the economic model examines separately the process outcomes of the different monitoring approaches from the downstream clinical benefits, to allow the relative impact of different levels of uncertainty to be taken into account.
6	Consideration may be needed around the generalisability of the economic model across different NHS pathways. The company presented several validated clinical pathways which could incorporate testing	This issue assumes an incremental *cost* of Zio where in fact modelling will show that there is an incremental saving in comparison to the comparator, directly attributable to pathway. To accommodate some of the differences in population, different economic models have been constructed to look at multiple populations. However, although the absolute diagnostic yield will vary between populations depending on the underlying prevalence of arrhythmias, the critical issue for the cost consequences is the comparison between technologies, length of beat-to-beat monitoring and subsequent yield. Thus, for instance, the positive diagnostic yield for the Zio service is around 60-65% in a symptomatic palpitations population but only 16% in a post-stroke population, the corresponding figures for a Holter monitor are 20-25% and 2% respectively. Clearly, in this context, the cost per positively identified patient will vary; this caveat also applies to the comparator technologies. The consequence is that the incremental results will show substantially less variation than might have been expected.

	with Zio XT Service. The EAC have noted that the cost and diagnostic yield of usual care will be highly dependent on the clinical pathway and this will impact on the incremental cost of Zio XT Service in the planned cost modelling.	

Any other issues

Please add any comments/issues/key questions to be answered that have not been captured above and you would like to make the NICE technical team aware of:

*	[redacted]