ACE BRIEF FOR NEW AND EMERGING HEALTH TECHNOLOGIES

Zio XT for Ambulatory ECG Monitoring for Patients Suspected to have Cardiac Arrhythmia

Document Number: HSB-M 04/2023

Date: March 2023

ACE agency for care effectiveness

Summary of Key Points

- Cardiac arrythmia (CA) is when the heart beats at an irregular rhythm. Atrial fibrillation (AF) is the most common form of CA and is an independent risk factor of stroke and heart failure.
- Patients suspected to have CA would generally undergo ambulatory electrocardiogram (ECG) monitoring. A Holter monitoring device is the standard ambulatory ECG monitor used to detect any CA events over a 24 or 48 hour period.
- The Zio XT is a single-lead ambulatory ECG patch that can monitor a patient's ECG for up to 14 days. After the monitoring period, the patch is returned to the manufacturer. An algorithm is then used to detect for CA events and produce a report based on the ECG recording.
- Zio XT was found to be safe and accurate in the detection of CA events for patients who require ambulatory ECG monitoring.
    - NICE concluded there was no significant difference in diagnostic accuracy between Zio XT and Holter monitoring.
    - Zio XT was found to improve the diagnostic yield and detection rates of CA compared to the Holter device. Diagnostic yield for Zio XT ranged from 2.3% to 32.5 % compared to 0% to 2.1% for the Holter Device.
    - Zio XT had similar diagnostic yields to other ECG devices ranging from 3% to 44.7%. This includes pacemakers and other ambulatory ECG devices like the Carnation Ambulatory Monitor, e-Patch and 30-day event monitors.
    - There is some evidence that use of Zio XT led to change in the clinical management of patients, mainly the initiation of anticoagulants. However currently there is no evidence on the direct impact of Zio XT on patient outcomes.
    - Zio XT was found to be generally well accepted by patients and is associated with high device wear time. Overall, patients wore the Zio XT from 6.1 days to 14 days.
    - Shorter waiting time and fewer follow up clinical visits were reported in patients who used Zio XT.
- Cost analysis presented in the NICE guidance showed that compared to blended strategies and based on a cost for the technology of £265 per person, Zio XT was likely to be cost saving (£3.47 to £59.80) for cardiology patients and cost incurring (£14.93 to £79.47) for stroke patients. A downstream stroke model including the costs of added risk of a recurrent stroke due to delayed or misdiagnosed patients with AF found Zio XT to be cost saving of £72.55 for no repeat testing and cost incurring of £33.79 for with or without repeat testing.
- The main limitation of the evidence is the lack of studies evaluating patient outcomes from using the Zio XT device.
- The main implementation considerations are the need for protocols to ensure both conformity of the AI algorithm to MOH guidelines and confidentiality of patient data due to the need for a third-party to process ECG data.

I. Background

Cardiac arrhythmia (CA) is the condition of irregular heartbeat when the electrical signal controlling the heartbeat malfunctions. There are two broad categories of arrhythmia: tachycardia and bradycardia. The most common form of CA is atrial fibrillation (AF). Signs and symptoms of AF include a fluttering feeling in the chest or a racing heartbeat. However, some people with AF may be asymptomatic. It is important for AF to be detected and treated as soon as possible as it is a known independent risk factor of stroke[1] and heart failure.[2]

Worldwide prevalence of AF is about 0.51%, and the condition impacts around 37 million people.[3] This prevalence has increased by 33% over the last 20 years, and is projected to increase by more than 60% by 2050.[3] In the local context, a 2008 study among Chinese residents estimated AF prevalence to be 2.6% in men and 0.6% in women, increasing to 5.8% for those aged 80 years and above.[4] AF prevalence is also predicted to increase locally due to an ageing population. Patients with AF are older, with a higher prevalence of age-related comorbidities like diabetes, hypertension and ischemic heart diseases.[5]

AF is traditionally detected using ECG, obtained either during a clinic visit or from the patient wearing a Holter monitor over 24 to 48 hours. Both are limited by the brief duration of monitoring, which may not adequately capture infrequent AF episodes.[6] In addition, the Holter device might not be comfortable to wear for long periods due to skin irritation at the locations where the electrodes are attached.

II. Technology

The Zio XT (iRhythm Technologies, Inc; San Francisco, CA) is a novel, single-use, single-lead ECG monitor that can record up to 14 days of ECG data. The device is a patch that adheres to the patient's left chest and monitors the electrical impulses of the heart, with ECG recordings stored internally within the device. It is wireless and waterproof, allowing ECG to be continuously monitored during exercise, showering and while sleeping (Figure 1).

Figure 1: The Zio XT wearable ECG patch (left) and how it is worn by the patient (right). Image adapted from: *https://www.irhythmtech.com/providers/zio-service/zio-monitors*

After the recording period, the device can be returned via mail to the company who process and analyse the ECG data. A report is generated based on the recorded ECG data using a deep learning algorithm called ZEUS (Zio ECG Utilization Service) that can detect more than 13 types of cardiac arrhythmias (Table A1 in Appendix A), sinus rhythm and artifacts. The report

summarises clinically relevant information like the wear time and total analysable time after artifact removal. It also provides graphs of clinically significant arrhythmias with additional related information (e.g., number and duration of episodes, heart rate range and average heart rate). Findings from the report are further checked and validated by certified cardiographic technicians.

The Zio XT presents a few novel benefits to address the limitations of current clinical ECG measurement (including ambulatory ECG monitoring Holter devices). One main benefit is the long-term recording duration of ECG data by Zio XT (14 days) compared to a Holter monitor (24-48 hours). Also, the single-patch, waterproof and wireless Zio XT may increase the total wear duration compared to contemporary devices, such as the Holter which requires multiple electrodes connected to a wearable pouch by wires.

III. Regulatory and Subsidy Status

The Zio XT patch was approved by the United States Food and Drug Administration (FDA) in February 2012.[7] The AI system used to generate the report, the ZEUS System, was approved by the FDA in November 2014.[8] In Europe, the Zio XT was Conformité Européenne (CE) marked in December 2014.[9]

At the time of writing, a newer version of the Zio XT wearable patch has gained FDA approval. This newer product focuses on enhancing patient comfort, while providing similar functions to the current Zio XT patch.

IV. Stage of Development in Singapore

☒	Yet to emerge	☐	Established
☐	Investigational / Experimental (subject of clinical trials or deviate from standard practice and not routinely used)	☐	Established *but* modification in indication or technique
☐	Nearly established	☐	Established *but* should consider for reassessment (due to perceived no/low value)

V. Treatment Pathway

For symptomatic patients suspected to have CA, the first method of assessment would be a manual pulse palpitation to check for irregularities. This is performed on patients presenting with breathlessness, palpitations, syncope, dizziness, chest discomfort and/or stroke or transient ischemic attack.

For patients with no symptoms for CA but suspected to have CA, or when an irregular pulse is detected, a 12 lead ECG is performed to record their heart rhythm and electrical activity. Additionally, blood tests and an echocardiogram can be performed to confirm the presence

of AF. The European Society of Cardiology (ESC) recommends that all patients suspected to have AF undergo a 12-lead ECG to establish the diagnosis for AF.[10]

However, CA might not be present during the ECG session when the patient is in the clinics, hence, a need for longer term monitoring of the ECG signals. An ambulatory ECG device, the Holter, is a wearable recording device that can continuously monitor the ECG signal over 24–48 hours while the patient is not at the clinic. Patch-based wearable devices like the Zio XT present a useful option for patients who require a longer period of ambulatory ECG monitoring but do not want or need a loop recorder, which is invasively implanted.

Consultation with a local clinician found that the two main uses for patch-based wearable devices would be: (1) to diagnose CA in patients with infrequent, paroxysmal symptoms that suggest the presence of heart rhythm abnormalities; and (2) to diagnose asymptomatic but clinically significant CA in high risk patients (Personal communication: Senior Consultant from Tan Tock Seng Hospital, 16 February 2023). Another local clinician has stated that the Zio XT can be a viable alternative to the Holter (Personal communication: Senior Consultant from Tan Tock Seng Hospital, 13 February 2023).

The Zio XT could be a viable alternative or follow up to the Holter monitor in diagnosing CA, especially in asymptomatic patients. The Zio XT may result in higher diagnostic yields for CA, leading to earlier detection and management of CA, leading to downstream reduction in incidence of CA-related diseases like stroke or heart failure.

VI. Summary of Evidence

This assessment was conducted using the Population, Intervention, Comparator and Outcome (PICO) criteria (Table 1). Literature searches were performed in Pubmed, Embase, Cochrane and the International Network of Agencies for Health Technology Assessment (INAHTA) databases. The main body of evidence to inform this brief includes a health technology assessment (HTA) report by the National Institute of Health and Care Excellence (NICE), which consists of 17 published studies (with a total of 169,063 people who had ambulatory ECG recordings) and 13 abstracts. An additional 6 published studies not included in the NICE HTA guidance report were also included (one randomised controlled trial[12], three comparative studies[13,14,16] and two non-comparative studies[11,15]). Table B3 in the Appendix summarises the key evidence for Zio XT from the NICE HTA guidance. Appendix B provides an overview of the evidence base of this brief.

Table 1: PICO criteria

Population	Patients suspected to have CA
Intervention	Zio XT wearable ECG monitor patch
Comparator	Other ambulatory ECG monitoring devices including Holter
Outcome	Safety, clinical- and cost-effectiveness
Abbreviations: CA, Cardiac arrhythmia; ECG, Electrocardiogram	

Safety

The use of the Zio XT is deemed to be relatively safe, with no serious adverse events reported. A total of 138 adverse events reported to FDA MAUDE (Manufacturer and User Facility Device Experience), consisting mostly of contact dermatitis. It should be noted there were 12 cases

of false negatives or incorrect diagnoses reported which the manufacturer, iRhythm, suggests were due to faulty hardware or misinterpreting the report.[17] In terms of clinical outcomes, Gupta et al. (2022) reported that the use of Zio XT showed no increased risk of adverse outcomes (all cause death, ischemic stroke or transient ischemic attack, other arterial thromboembolic event and hospitalised heart failure) compared to 24-hour Holter and 30-day cardiac event monitor.[13]

Effectiveness

Accuracy

Based on three studies included in the NICE guidance that looked at diagnostic accuracy of Zio XT, NICE concluded there was no significant difference in diagnostic accuracy between Zio XT and Holter monitoring.[17] The company calculated accuracy data based on one included study and found that Zio XT had a 99% sensitivity, 100% specificity, 98% positive predictive value and 98% negative predictive value when using the clinical investigator's decision as the gold standard.[17] Another study in the NICE report compared Zio XT with an event recorder (Novacor R Test) and found that Zio XT was more accurate in detecting AF (R^2 value: Zio XT 0.99, Novacor R Test 0.029), when referencing cardiac pacemaker as the gold standard.[18] There is also evidence for high agreement concordance with Holter monitoring for AF event detection found in another study within the report, where 25 CA events recorded by the Holter device was also identified on Zio XT in the same 24-hour period.[18]

Based on a technical study included in the report, NICE considered the diagnostic performance of the fixed deep neural network used as part of Zio XT's algorithm (ZEUS) was adequate when compared with a committee of cardiologists.

Patient Experience and Wear Time

Evidence from the NICE HTA guidance report showed that patients generally preferred using the Zio XT patch compared to the Holter monitor, as it is easier to wear and also more comfortable.[18] The report attributed these findings to the fact that the Zio XT had no external wirings and hence can be worn under the patient's clothes, be more discreet and be worn during sleep. Also, the Zio XT is waterproof which allows the patient to wear it even during showers and exercise.

Across the evidence base included in this brief, the total device wear time of the Zio XT ranged from 6.1 days to 14 days out of an intended 14 days.[11,14,18] One study had a median wear time of 27.4 days, out of an intended 28 days.[12] Table C2 in the Appendix C shows the individual device wear times (if measured).

Diagnostic Yield and occurrence of CA

Compared to Holter monitoring, the Zio XT had a higher diagnostic yield (2.3% to 32.5% versus 0% to 2.1%)[12,13,15-17] and a higher number of CA events detected (87 to 96 events versus 61 events)[12,13,15-17] (Table 2). This is consistent with the evidence described in the NICE HTA guidance showing higher diagnostic yields with the Zio XT over total wear time, compared to 24-hour Holter monitoring.[18] The longer monitoring time for Zio XT of 14-days, compared to

Holter which only monitors between 24-48 hours could have contributed to the increased diagnostic yield of the Zio XT.

Table 2: Overall key effectiveness parameters between Zio XT, Holter and other comparators

	Zio XT	Holter	Other ECG Monitoring Modalities*
Diagnostic yield	2.3% to 32.5%	0% to 2.1%	3% to 44.7%
Number of CA events	87 to 96	61	122
*Composite of routine clinical follow-up plus a pulse check and heart auscultation, Carnation Ambulatory Monitor, ePatch, 30-day event monitor and cardiac pacemaker. A more detailed comparison based on individual studies can be found in Table C1 in the Appendix.			

When comparing the diagnostic yield of Zio XT with other ambulatory ECG monitoring device, the results were mixed. It was higher for Zio XT (6%) compared to the 30-day event monitor (3%), though the difference was not statistically significant (p=0.07). The number of detected events for Zio XT (86.7 events) were lower compared to the Carnation Ambulatory Monitor ECG patch (121.7 events). Similarly, Zio XT detected CA events compared to pacemakers (32.5% versus 44.7%). Table C1 in the Appendix summarises the diagnostic yields from the studies in the evidence base.

The summary of evidence from the NICE report found about 46-70% of CA events detected occur within 48 hours[18], meaning at least a third to half of CA events could remain undetected by the Holter monitor due to its shorter monitoring period compared to Zio XT. This trend is consistent with previous reviews.[19,20]

Clinical Utility

Clinical Management

NICE has stated from their evidence review that the use of Zio XT does have an impact on the clinical management of the patients.[18] This was also observed in the RCT by Gladstone et al. (2021) which reported a higher indication of oral anticoagulant therapy due to AF for the group using the Zio XT compared to standard care, at 6 months (4.1% vs. 0.5%).[12] However, the study by Gupta et al. (2022) did not observe any significant difference in clinical management between Zio XT, 24-hour Holter and the 30-day event monitor.[13] There are no studies that have looked at how Zio XT impacts patient outcomes directly.

Impact on Public Healthcare System

Lang et al. (2022) have noted that patients who received Zio XT ambulatory ECG monitoring had a significantly shorter wait time to receiving their device and the results of the recording compared to patients who used Holter monitoring.[14] The number of visits required by the patient was also lower by a median of two visits for the Zio XT group.

Cost Effectiveness

A de novo cost analysis included in the NICE report compared the 14-day Zio XT with a blended strategy based on a 24-hour Holter monitor or cardiac event recorder. Costs associated with diagnosis of patients were analysed within two care pathway models: a cardiology model and a stroke model. A scenario analysis was included as the downstream stroke model. NICE considered the downstream stroke cost model to the most informative. The models were

tested in two scenarios: (1) no appointment after a negative result with no repeated test and (2) no appointment after any negative result, with or without repeat test. Table 3 describes each model analysed and what scenarios were used to test the models.

Table 3: Cost analysis models and scenarios

Care Pathway Models	
Model	**Description**
Base case	
Cardiology Model	Cost associated with the diagnosis of patients with symptomatic palpitations or syncope
Stroke Model	Cost associated with the diagnosis of patients who have had a stroke or transient ischemic attack
Downstream Stroke Model	Economic consequences of increased risk of a recurrent stroke due to delayed or missed diagnosis of atrial fibrillation
Scenario Analyses	
	Description
1	No additional appointment needed after a negative result, and no repeated test
2	No additional appointment needed after any negative result, whether or not the test is repeated
Adapted from NICE Guidance Report[18]	

Using a cost for the technology of £265 per person, cost modelling by NICE showed that Zio XT was cost saving or broadly cost neutral.[18] Across all models and scenarios, Zio XT ranged from cost savings of £72.55 to cost incurring of £79.47. The degree of cost saving or cost incurring for each scenario for each model is detailed in Table 4. Zio XT was found to be cost saving in both scenarios in the cardiology model and cost incurring in both scenarios in the stroke model. For the downstream stroke model, Zio XT was cost saving only if the test was not repeated. Overall, NICE concluded that Zio XT was likely to be cost saving or cost neutral, but it highlighted the uncertainty about resource use of adopting Zio XT which would impact on the results significantly.

Table 4: Degree of cost saving or cost incurring for each model and scenario

Model	**Scenario**	**Cost Saving/Incurring**	**Amount (£) per patient per year**
Cardiology Model	No repeat test done	Cost Saving	£59.80
	With or without repeat test done	Cost Saving	£3.47
Stroke Model	No repeat test done	Cost Incurring	£14.93
	With or without repeat test done	Cost Incurring	£79.47
Downstream Stroke Model	No repeat test done	Cost Saving	£72.55
	With or without repeat test done	Cost Incurring	£33.79
Adapted from NICE Guidance Report[18]			

Five other studies within the NICE evidence base analysed the cost effectiveness of Zio XT compared to other devices including Holter monitoring. Two studies reported that Zio XT was cost saving while another two reported the opposite .[18] A feasibility study by Khan et al. (2020) investigating the use of Zio XT for long-term continuous heart monitoring in a stroke clinic

reported that for 84% of patient's out-of-pocket costs were less than USD$100 for the device. [11] They suggest their approach may be more cost effective than using a Holter monitor, which has low sensitivity in detecting PAF in stroke patients.[11]

Ongoing Trials

A search on the ScanMedicine (NIHR Innovation Observatory) database was done and a total of three trials were found. One trial is comparing health outcomes and changes to treatment between patients wearing a Zio XT patch and those wearing a Holter monitor. Another is assessing if the use of Zio XT leads to increased detection of non-sustained ventricular tachycardia compared to 48 hour monitoring. The third trial is assessing the capability of Zio XT to predict who might develop AF. Table 5 summarises the details of these ongoing trials.

Table 5: Ongoing trials for Zio XT

Trial Name	Estimated Enrolment	Aim of Trial	Estimated Completion Date
A Multi-centre Cohort Study Comparing Health Outcome Data From Holter Monitoring to 14 Day Zio Monitoring in People Where Ambulatory ECG Monitoring is Required (NCT05560828)	1440	To analyse quantitative data (anticoagulant uptake and other changes to treatment related to the results from monitoring) collected from participating sites and complementary qualitative data on Zio XT utilisation from questionnaires.	December 2022
Extended Ambulatory Monitoring With iRhythm Zio XT Improves Care of Patients With Hypertrophic Cardiomyopathy (EXAMNE-HCM) (NCT04056715)	300	To evaluate if the use of Zio XT results in identifying a greater burden of tachyarrhythmia-NSVT compared to current ACCF/AHA guideline recommended 48-hour monitoring.	February 2022
Electrocardiogram-based Artificial Intelligence-assisted Detection of Heart Disease (ECG-AID) (NCT05442203)	1000	To evaluate two devices (Zio patch and ECG) that can predict who has or may develop atrial fibrillation or structural heart disease based on the results of an ECG.	September 2024

Abbreviations: ACCF, American College of Cardiology Foundation; AHA, American Heart Association; ECG, Electrocardiogram; NSVT, Non sustained ventricular tachycardia.

Summary

From the clinical evidence, the Zio XT patch is generally safe with no major adverse effects and has high patient wear times as it is easy to wear. Zio XT was found to provide similar diagnostic accuracy when compared to the Holter device. Zio XT improves diagnostic yield of CAs compared to the current standard of ambulatory ECG monitoring – the Holter device (6% to 32.5% versus 0% to 2.1%), though there were no significant differences when compared to other ECG monitoring devices. This improved diagnostic yield has led to changes in the clinical management of patients who used the Zio XT patch, mainly the introduction of anticoagulants to patients who were detected for CA during the monitoring period. However, there is no clear evidence if patients benefited from the change in the clinical management. There is some evidence that Zio XT was associated with shorter wait times to obtain results from the monitoring and also fewer hospital visits.

Based on the results of the NICE report, cost effectiveness of Zio XT hinges on the indication it was used for and whether repeat testing was done. Zio XT was found to be cost saving for patients in the cardiology model and cost incurring for patients in the stroke model. For the downstream stroke scenario, Zio XT was cost saving if no repeated testing was done. Across all scenarios and models, cost analysis findings point to an overall range of Zio XT being cost saving of £72.55 to cost incurring of £79.47.

A limitation of the evidence base is the lack of studies looking at the impact of Zio XT on patient outcomes. Finally, evidence on the cost effectiveness of using the Zio XT patch remains mixed. More studies might help bring clarity on Zio XT's clinical and cost efficacy.

VII. Estimated Costs

According to two studies in the NICE guidance, the price for the Zio XT in the UK ranges from £284 to £440 (S$459 to S$711)[a] per patient. Following consultation with NICE, the company lowered the cost from £310 to £265 (S$501 to SS$428)[a] per patient, inclusive Zio XT, analysis and data reporting.

VIII. Implementation Considerations

The use of this patch should not have a large impact on current healthcare practices with regards to ambulatory ECG monitoring, as the Zio XT functions very similarly to the Holter device. One slight difference would be the Zio XT patch has to be sent to the manufacturer for analysis of the ECG recording and to generate the report from the recording.[18] This might ease the workload of a healthcare institution, as the processing of the ECG recording from Holter devices is usually done inhouse.[14]

As Zio XT requires ECG recordings to be sent to either the manufacturer or a central server for processing, personal patient data may be exposed to an external party. Therefore, current clinical workflows need to be reassessed for any potential vulnerabilities for patient data to be compromised and safeguards have to be setup to minimise the risk of such events. In addition, before using the device, patients should be informed that personal data may be obtained during a recording, and proper consent obtained and documented to ensure transparency.

Zio XT uses AI to recognise CA events from the ECG recordings. As such, there is a need to ensure the AI conforms as much as possible to the Ministry of Health (MOH)'s Artificial Intelligence in Healthcare Guidelines (AIHGIe).[21] Relevant organisational approvals and proper documentation are required when introducing the device into the local healthcare ecosystem. This could include updating current clinical workflows, conducting risk assessment to predict potential failures of the device or AI software, ensuring the accuracy and performance of the AI, identifying and minimising any potential cybersecurity vulnerabilities, staff training for product familiarisation and also proper consent from patients to ensure transparency during usage of these devices. If introduced, long term monitoring and review of the devices is also required.

[a] Based on the Monetary Authority of Singapore exchange rate as of 17 January 2023: £1=S$1.6150. Figures were rounded to the nearest dollar.

IX. Concurrent Developments

Examples of novel ambulatory ECG monitoring devices are provided. The Cardiostat[22] and the Spyder are worn as patches on the chest of the patient. The QardioCore[23] is worn as a belt around the lower chest, just above the abdomen. Spyder[24] is a locally created ambulatory ECG monitor that allows for real time monitoring.

Table 6: Concurrent developments similar to Zio XT

Device	Brief Description	Approval Status
Cardiostat™	Cardiostat™ is a single-lead ECG patch that is worn on the chest. It is light, showerproof and can record ECG for up to 14 days.	Not FDA approved yet.
QardioCore	QardioCore is a patchless, wireless Holter monitor that is splash and rain resistant. In addition to ECG, it can monitor other parameters like skin temperature, heart rate, heart rate variability, respiratory rate and activity tracking.	FDA approved.
Spyder	An ambulatory ECG monitoring patch worn on the chest that can record up to 30 days. ECG data can be uploaded to cloud storage for healthcare staff to monitor patient ECG in real time.	HSA and CE approved. Not FDA approved yet.
Abbreviations: CE, Conformitè Europëenne; ECG, Electrocardiogram; FDA, United States Food and Drugs Administration; HSA, Health Sciences Authority.		

X. Additional Information

The NICE HTA guidance recommends the Zio XT as an option for people with suspected CA who would benefit from ambulatory ECG monitoring for periods longer than 24 hours – only if NHS organisations collect information on resource use associated with use of Zio XT, and on long-term clinical outcomes for people using Zio XT.

In other guidelines that recommend the use of ambulatory ECG monitoring for the detection of CA, there is no direct mention of Zio XT. The European Society of Cardiology (ESC) guidelines on management of patients with ventricular arrhythmias recommend ambulatory ECG to detect and diagnose arrhythmias.[25] The American Heart Association (AHA), American College of Cardiology (ACC) and Heart Rhythm Society (HRS) guidelines for management of patients with ventricular arrhythmias recommend the use of ambulatory ECG monitoring to evaluate symptoms (palpitations, presyncope or syncope).[26]

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Appendix

Appendix A: Irregular ECGs identified by Zio XT

Table A1: List of Identifiable Arrhythmias by Zio XT

S/N	Type of CA
1	Atrial fibrillation
2	Atrial flutter
3	Atrioventricular block (AVB)
4	Bigeminy
5	Ectopic atrial rhythm (EAR)
6	Idioventricular rhythm (IVR)
7	Junctional rhythm
8	Noise
9	Sinus rhythm
10	Supraventricular tachycardia (SVT)
11	Trigeminy
12	Ventricular tachycardia
13	Wenckebach

Adapted from Hannun et al. (2019)[27]

Abbreviations: AF, Atrial fibrillation; AFL, Atrial flutter; AVB, Atrioventricular block; CA, Cardiac Arrhythmia; EAR, Ectopic atrial rhythm; IVR, Idioventricular rhythm; S/N, Serial number; SVT, Supraventricular tachycardia; VT, Ventricular tachycardia

Appendix B: Evidence Base

Table B1: Summary of Evidence Base

Type of Study	Number of Studies
NICE HTA Guidance	
Randomised controlled trial	1
Prospective, within-subject comparative	3
Prospective, non-comparative	6
Retrospective, non-comparative	7
Abstract	17
Other Evidence Base	
Randomised controlled trial	1
Prospective, comparative	3
Prospective, non-comparative	1
Retrospective,non-comparative	1

Note:

1. Inclusion criteria
    a. Studies that fulfil the PICO criteria listed in Table 1.
2. Exclusion criteria
    a. Studies only available in abstract form.
    b. Duplicate studies.

Table B2: Information on the included studies.

Author (Year)	Type of Study	Interventions	Number of Participants	Summary of Results
NICE (2020)[18]	HTA guidance report	Zio XT; Holter; CAM; e-patch, Novacor R-Test, cardiac pacemakers,	169,063 (30 studies)	• Evidence base shows that Zio XT increases diagnostic yield • Zio XT was generally accepted by patients and had high device wear time • The limitation of the evidence base would be insufficient evidence on diagnostic accuracy of Zio XT and its effect on clinical outcomes
Khan et al.(2020)[11]	Non-comparative feasibility study	Zio XT	467	• It is feasible to implement Zio XT for ambulatory ECG monitoring in a stroke clinic
Gladstone et al. (2021)[12]	Randomised Clinical trial	Zio XT, Standard clinical care	856	• The use of Zio XT was well tolerated, increased the detection rate for AF and was associated with initiation of anticoagulant therapy
Gupta et al. (2022)[13]	Comparative matched study	Zio XT, Holter, Event monitor	330	• Zio XT and 30-day monitor were superior to Holter for detection of new AF but not different from each other

				• Zio XT had higher frequency of NSVT compared to both Holter and event monitor
Lang et al. (2022)[14]	Retrospective Holter data with prospective comparative study	Zio XT, Holter	218	• Time taken to start ECG monitoring and number of hospital visits were lower for Zio XT
Rooney et al. (2019)[15]	Prospective cohort study (non-comparative)	Zio XT (2 weeks and 4 weeks)	2616	• Zio XT monitoring for 4 weeks had 78% more subclinical AF compared to 2 weeks of Zio XT monitoring
Gutierrez et al. (2020)[16]	Retrospective cohort comparative study	Zio XT, cardiac pacemakers	125	• Cardiac pacemaker cohort (44.7%) had larger proportion of NSVT compared to Zio XT cohort (32.5%)
Abbreviations: AF, Atrial fibrillation; ECG, Electrocardiogram; HTA, Health technology assessment; NICE, National Institute for Health and Care Excellence; NSVT, Non-sustained ventricular tachycardia.				

Table B3: Summary of NICE HTA Guidance Evidence

Key Evidence	Summary of Evidence
Diagnostic Accuracy	• Zio XT found to be more accurate than Novacor R Test (external event/loop monitor) but less accurate than pacemaker in detecting the presence or absence of atrial fibrillation. • Zio XT had a 99% sensitivity, 100% specificity, 98% positive predictive value, 98% negative predictive value compared to decision of clinical investigator as gold standard. • Simultaneous 24-hour monitoring period had mixed results. One found the Holter detected more CA events than Zio XT. Another found Holter and Zio XT detected the same events and had significant agreement. • No significant difference in accuracy between Zio XT and Holter monitoring.
Diagnostic Yield and Time to Event	• The diagnostic yield for arrhythmia is generally higher for Zio XT compared to Holter monitoring, due to the extended monitoring period. • Overall, about 46-70% of arrhythmias detected occur within 48-hours, with the variation being attributed to the heterogeneity of the monitored population.
Clinical Pathway Outcomes	• Multiple studies observed higher proportion of patients who used Zio XT were given medication or had medication switched. • However, there is no clear evidence if patients benefitted from the change in the clinical pathways.
Patient Experience and Wear Time	• Mean wear time was 10.8 to 12.8 days (out of 14 days) for the comparative studies. • The Zio XT was also worn longer compared to 3 other continuous cardiac monitors. • Multiple studies found the Zio XT easy and comfortable to use compared to the Holter.
Cost-effectiveness	• A de novo cost analysis was done comparing Zio XT to the Holter device and event monitor. • Three models (Cardiology, Stroke, Downstream Stroke) were tested with two scenarios (no repeat testing, with or without repeat testing). • Across all models and scenarios, Zio XT ranged from cost saving of £72.55 to cost incurring of £79.47, depending on the model and scenario.

Appendix C: Relevant Zio XT Study Data

Table C1: Diagnostic Yield Comparison

Study	Comparator	Number of Participants	Main Observation	Diagnostic Yield, n (%)		P value
				Zio XT	Comparator	
NICE HTA Guidance Report[18]						
Barrett et al. (2014)	24-hour Holter	146	CA events detected over total wear time	96 (NR)	61 (NR)	<0.001
			CA events detected over at 24 hours	52 (NR)	61 (NR)	0.013
Kaura et al. (2019)	24-hour Holter	116	Patients with detected PAF ≥ 30s at 90 days	7 (16.3)	1 (2.1)	NR
		90	Patients with detected PAF ≥ 30s at 28 days	6 (14.0)	1 (2.1)	NR
Rosenberg et al. (2013)	24-hour Holter	74	Patients with AF events	43 (NR)	25 (NR)	<0.0001
Reed et al. (2018)	No comparator	86	90-day diagnostic yield for symptomatic significant arrhythmia	NR (10.5)	NA	NA
Rho et al. (2019)	CAM	30	Number of CA events recorded	86.7±0.6 (NR)	121.7±2.1 (NR)	<0.001
Other Evidence Base						
Gladstone et al. (2021)[12]	Routine clinical follow-up plus a pulse check and heart auscultation at baseline and 6 months	856	6-months diagnostic yield for AF	NR (5.3)	NR (0.5)	NR
Gupta et al. (2021)[13]	24-hour Holter and 30-day event monitor	330	Diagnostic yield of AF≥30s	NR (6)	24-hour Holter: NR (0) 30-day event monitor: NR (3)	Zio XT vs 24-hour Holter: 0.04 Zio XT vs 30-day event monitor: 0.07
Gutierrez et al. (2020)[16]	Cardiac Pacemakers	125	Patients with NSVT events	13 (32.5)	38 (44.7)	NR

Rooney et al. (2019)[15]	None	386	Patients with subclinical AF	2 Weeks: 9 (2.3) 4 Weeks: 16 (4.1)	NA	NA

Abbreviations: AF, Atrial fibrillation; CA, Cardiac arrhythmia; CAM, Carnation ambulatory monitoring; HTA, health technology assessment; NA, Not applicable; NICE, National Institute for Health and Care Excellence; NR, Not reported; NSVT, Non sustained ventricular tachycardia; PAF, Paroxysmal atrial fibrillation.

Table C2: Device Wear Time

Study		**Patient Wear Time (Days)**	
	Comparator	**Zio XT**	**Comparator**
NICE HTA Guidance Report[18]			
Barrett et al. (2014) *Median, (Range)*	24-hour Holter	11.1 (0.9 to 14.0)	1.0 (0.9 to 1.0)
Eyesneck et al. (2019) *Mean, (Range)*	Novacor R-Test	12.8 (11.9 to 14.2)	9.3 (7.4 to 11.2)
Kaura et al. (2019) *Mean ± SD*	24-hour Holter	11.7 ± 3.7	NR
Rosenberg et al. (2013) *Mean ± SD*	Holter	10.8 ± 2.8	NR
Go et al. (2018) *Median (Analysable), (IQR)*	None	14 (11 to 14)	NA
Heckbert et al. (2018) *Median, (IQR)*	None	13.8 (13.2 to 14.0)	NA
Reed et al. (2018) *Median, (IQR)*	None	13.6 (11.8 to 14.0)	NA
Schreiber et al. (2014) *Median*	None	6.9	NA
Schultz et al. (2019) *Mean ± SD*	None	9.5 ± 4.1	NA
Solomon et al. (2016) *Mean ± SD*	None	9.6 ± 4.0	NA
Tung et al. (2015) *Mean (Analysable Percent), Median (IQR), Percentage*	None	10.9 (98.7), 13.0 (7.2 to 14.0), >10days: 66.9%	NA
Turakhia et al. (2013) *Mean ± SD*	None	7.6 ± 3.6	NA
Agarwal et al. (2015) *Mean ± SD*	None	13.0 ± 2.3	NA
Norby et al. (2015) *Mean (Analysable)*	None	12.5	NA
Sattar et al. (2012) *Mean (95% CI)*	None	6.1 (5.8 to 6.4)	NA.
Turakhia et al. (2012) *Mean ± SD*	None	7.1 ± 3.3	NA
Other Evidence Base			
Gladstone et al. (2021)[12] *Median, (IQR)*	Routine clinical follow-up plus a pulse check and heart auscultation at baseline and 6 months	27.4 (18.4 to 28.0)*	NR
Lang et al. (2022)[14] *Median*	24-hour Holter	13.9	NR
Khan et al,(2020)[11] *Mean, Median*	None	12.1, 13.8	NA

Rooney et al. (2019)[15] *Percentage*	None	≥7 days: 91.6% ≥10 days: 86.7% ≥12 days: 81.7%	NA
*Monitoring period is 28 days Abbreviations: CAM, Carnation ambulatory monitoring; CI, Confidence interval; HTA, health technology assessment; IQR, Inter quartile range; NA, Not applicable; NICE, National Institute for Health and Care Excellence; NR, Not reported; SD, Standard deviation. NA;			