NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation document

Zio XT for detecting cardiac arrhythmias

The National Institute for Health and Care Excellence (NICE) is producing guidance on using Zio XT for detecting cardiac arrhythmias in the NHS in England. The medical technologies advisory committee has considered the evidence submitted by the company and the views of expert advisers.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the public. This document should be read along with the evidence (see the committee papers).

The advisory committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and resource savings reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?

Note that this document is not NICE's final guidance on Zio XT for detecting cardiac arrhythmias. The recommendations in section 1 may change after consultation.

After consultation the committee will meet again to consider the evidence, this document and comments from the public consultation. After considering the comments, the committee will prepare its final recommendations which will be the basis for NICE's guidance on the use of the technology in the NHS in England. For further details, see the medical technologies evaluation programme process and methods guides.

The key dates for this guidance topic are:

Closing date for comments: 10 April 2020

Second committee meeting: 24 April 2020

Details of the advisory committee are given in section 5.

NICE medical technologies guidance addresses specific technologies notified to NICE by companies. The 'case for adoption' is based on the claimed advantages of introducing the specific technology compared with current management of the condition. This case is reviewed against the evidence submitted and expert advice.

If the case for adopting the technology is supported, the specific recommendations are not intended to limit use of other relevant technologies that may offer similar advantages. If the technology is recommended for use in research, the recommendations are not intended to preclude the use of the technology in the NHS but to identify further evidence which, after evaluation, could support a recommendation for wider adoption.

1 Recommendations

1.1 Zio XT shows promise for detecting cardiac arrythmias. However, there is not enough evidence on its diagnostic accuracy compared with standard care to support the case for routine adoption in the NHS.

1.2 Research is recommended to address uncertainties about the diagnostic accuracy and resource use associated with Zio XT compared with standard care. This research should determine the:

- relative diagnostic accuracy of Zio XT for detecting various types of arrhythmia compared with continuous ECG monitoring used as standard care in the NHS.
- resource use associated with Zio XT monitoring compared with standard care, in particular the number of outpatient visits and repeat tests needed.

Why the committee made these recommendations

Zio XT is a remote electrocardiogram (ECG) monitoring service used to detect cardiac arrhythmias. The service comprises a wearable single-lead ECG device, software that analyses ECG data, and a technical report.

Clinical evidence suggests that Zio XT may be more acceptable to people than current standard care in the NHS, so they're more likely to wear it for longer. It may

also improve diagnostic yield (how many people are diagnosed with cardiac arrhythmia using Zio XT) compared with standard care. However, there is little published evidence investigating its relative diagnostic accuracy (the ability of the test to correctly identify people with the condition) compared with standard care over comparable time periods. This means it is not clear if changes to treatment are an appropriate response to the patient's condition.

There is also little evidence to show its likely effect on resource use in the NHS.

Therefore further research is recommended.

2 The technology

Technology

2.1 Zio XT (iRhythm Technologies) is a remote cardiac monitoring service used to detect cardiac arrhythmias. It has 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 biosensor is placed on the person's left upper chest. It records a continuous beat-to-beat ECG for up to 14 days. The person can also press a button to register when they feel symptoms (patient-captured events). 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 ZEUS's algorithm, overseen by accredited cardiac physiologists. A technical report including arrhythmia episodes, wear and analysis time, and patient-captured events is sent to the prescribing healthcare professional for final analysis and interpretation. There are no patient

identifiers in or on the Zio biosensor, and data cannot be accessed if the Zio biosensor were to be physically intercepted.

Innovative aspects

2.2 Zio XT provides a continuous recording of ambulatory cardiac monitoring for up to 14 days. This is a longer monitoring period than continuous ECG monitors used in NHS standard care, such as a Holter monitor, which can be up to 7 days but is usually for 24 hours to 48 hours.

2.3 The wearer can go about their normal daily activities during monitoring, including showering or bathing, because the device is water resistant. Zio XT can be worn under clothing, so may be more discreet than Holter monitors, which are generally worn in a pouch around the waist or neck, or carried in a pocket.

2.4 The Zio biosensor has no external leads or wires; this is intended to reduce noise artefacts in the data. Zio XT uses proprietary software to detect arrhythmic events in the ECG data and to create the report that is delivered to the healthcare professional. The intention is to reduce the time needed for NHS staff to analyse the continuous monitoring data.

Intended use

2.5 NICE's guideline on transient loss of consciousness ('blackouts') in over 16s and on managing atrial fibrillation recommend the best ways to detect arrhythmia. The NICE Pathway for heart rhythm conditions describes NICE recommendations on the care pathway for patients. NICE recommends a 12-lead ECG for the first assessment. If the ECG does not detect arrhythmia, and paroxysmal atrial fibrillation is suspected, ambulatory ECG monitoring is recommended using either Holter monitoring or cardiac event recorders, depending on symptoms and symptom frequency.

2.6 Zio XT is intended to replace or enhance current standard care (24-hour Holter monitoring or cardiac event recorder monitoring) for cardiac arrhythmia detection in people with palpitations, fainting (syncope) and

suspected cardiac arrhythmia. Zio XT is prescribed by a healthcare professional, most often a cardiologist or GP, in primary, secondary or tertiary care. It may also be prescribed by a stroke clinician or neurologist.

2.7 Full details on using Zio XT are in the instructions for use.

Costs

2.8 The cost of monitoring with Zio XT is £310 per patient (excluding VAT). This figure includes the cost of the biosensor and the cost of analysing and reporting the data.

For more details, see the website for Zio XT.

3 Evidence

Clinical evidence

The clinical evidence comprises 30 published studies

3.1 The clinical evidence comprises 17 published studies, which include 169,063 patients referred to ambulatory monitoring, and 13 abstracts:

- 1 UK-based randomised controlled trial (Kaura et al. 2019)
- 3 prospective within-subject comparative studies (Barrett et al. 2014, Eysenck et al. 2019, Rosenberg et al. 2013)
- 6 prospective non-comparative studies (Rho et al. 2018; 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)
- 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 external assessment centre (EAC) noted that some of the non-comparative studies may have overlapping populations because the data are retrospective. For full details of the clinical evidence, see section 3 of the assessment report, which is in the supporting documents for this guidance.

Four comparative studies are considered pivotal to the decision problem

3.2 Three of the 4 comparative studies compared 14-day Zio XT with a 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 (the Novacor R. Test; Eysenck et al. 2019). The size of the studies varied, with a total of 357 participants, including people with a recent stroke or transient ischaemic attack (TIA), people with pacemakers or diagnosed atrial fibrillation, and people with suspected arrhythmia. The EAC considered the multicentre UK randomised controlled trial to be the highest-quality study (Kaura et al. 2019). The EAC judged the other 3 comparative studies to be of adequate quality. The EAC did not do a meta-analysis because it considered the evidence to be too heterogeneous in terms of populations, methodology, comparators, and outcomes reported.

The UK-based randomised controlled trial has a high withdrawal rate because there was a high refusal rate for the Holter monitor

3.3 The randomised controlled trial compared the diagnostic yield of 14-day Zio XT with 24-hour Holter monitoring in 116 people with stroke or TIA. There was a high withdrawal rate from the Holter group because 20% of the randomised participants refused to use the 24-hour Holter monitor. This may have biased results. According to the study authors, the study was adequately powered for the primary outcome. An independent power analysis carried out by the EAC found that the randomised controlled trial was likely to be underpowered because of the high withdrawal rate. The study is underpowered for the secondary outcomes, which included anticoagulation use and mortality.

Evidence suggests that monitoring with Zio XT increases diagnostic yield

3.4 Three studies comparing arrhythmia detection rates for Zio XT with 24-hour Holter monitoring showed an increased diagnostic yield with Zio XT over total wear time. Results from Eysenck et al. (2019) indicated that Zio XT may be more accurate in detecting the presence or absence of atrial fibrillation 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).

Evidence suggests that patients found Zio XT acceptable and wore it for most of the scheduled days

3.5 Evidence from comparative studies suggests that most patients were happy to wear the Zio XT biosensor, 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. In Eysenck et al. (2019), the Zio XT biosensor was worn for longer than 3 other continuous cardiac monitors evaluated. In Barrett et al. (2014), 93.7% of participants found the biosensor comfortable to wear compared with 51.7% for the Holter monitor. A survey into patients from a UK cardiology clinic (Hall et al. 2019) found that Zio XT was significantly preferred to Holter monitoring in terms of shape, comfort, practicality and returning method.

The diagnostic accuracy of Zio XT and the impact of the technology on clinical outcomes are uncertain

3.6 The diagnostic accuracy of Zio XT compared with standard care was not clearly defined in any study. Barrett et al. (2014) and Rosenberg et al. (2013) carried out some analysis comparing a Holter monitor and Zio XT over the same 24-hour period with different results. Rosenberg et al. (2013) reported that there was significant agreement between Zio XT and the Holter monitor recordings over the same 24-hour period. However, Barrett et al. (2014) reported the Holter monitor detected 11 arrhythmia events that were not detected by Zio XT over a simultaneous 24-hour monitoring period. The authors stated that 2 were caused by Zio XT

algorithm misclassification, which was then corrected, and 7 were errors made by the company's report reviewer. A technical study by Hannun et al. (2019) reported good diagnostic performance for the deep neural network used as part of Zio XT compared with a committee of cardiologists. There is no evidence to show that an increased diagnostic yield with Zio XT improves clinical outcomes. The EAC considered that, without more information about diagnostic accuracy, it's not clear if the changes to treatment reported in the studies were an appropriate response to the patient's condition.

The evidence for Zio XT is broadly generalisable to NHS practice

3.7 Five studies were done in the UK and the EAC considered the evidence is generalisable to the NHS: 2 comparative studies (Kaura et al. 2019, Eysenck et al. 2018), 1 prospective non-comparative study (Reed et al. 2018), and 2 conference abstracts (Chandratheva et al. 2017 and Ghosh et al. 2018). The 2 remaining comparative studies were in the USA.

Cost evidence

The cost evidence comprises 5 published studies

3.8 Five published studies reported the economic impact of the technology:

- a UK budget impact analysis (Kaura et al. 2019)
- a UK study reporting technology costs using data from the REMAP-AF trial (Eysenck et al. 2019)
- a prospective matched cohort study reporting healthcare resource use (Steinhubl et al. 2018)
- 2 conference abstracts (Ghosh et al. 2018, Chandratheva et al. 2017).

Two studies reported that the technology was cost saving. Two reported it was not compared with other devices including Holter monitoring. Studies consistently reported that Zio XT is the most efficient in terms of avoiding delays between clinic and diagnosis confirmation.

The company presented 3 cost models showing that monitoring with Zio XT saves between £55 and £85 per patient over 1 year

3.9 The company created 3 de novo cost analyses comparing the 14-day Zio XT with blended strategies, based on a 24-hour Holter monitor or a cardiac event recorder, in different care pathways:

- The cardiology model (presented as a base case) considered people with symptomatic palpitations or syncope and assessed the costs associated with the diagnostic process only.
- The stroke model (presented as a base case) considered people who have had a stroke or TIA and assessed the costs associated with the diagnostic process only.
- The downstream stroke model was presented as a scenario analysis and extrapolated the economic consequences of the extra risk of recurrent stroke because of delayed or missed diagnosis of atrial fibrillation.

All models had a time horizon of 1 year. Overall, the company's models showed that using Zio XT saves between £55 and £85 per patient because of reductions in repeat testing, referrals or cardiology outpatient review, and events in stroke populations. For full details of the cost evidence, see section 4 of the EAC's assessment report in the supporting documents for this guidance.

The EAC's changes to the models make monitoring with Zio XT cost incurring

3.10 The EAC revised the base-case (cardiology and stroke) models to address some potential limitations:

- the proportion of patients having repeat Holter tests after 24-hour Holter monitoring was changed to 27%
- NHS reference costs were used for Holter monitoring rather than Patient Level Information and Costing System (PLICS) data
- the cost of an outpatient visit before discharge was included for all tests.

The EAC revised the downstream stroke model to:

- include the cost of anticoagulants (and their side effects)
- lower the estimated stroke risk
- include repeated diagnostic test costs.

The EAC considered the downstream stroke cost model the most informative. After these revisions, the EAC concluded that Zio XT is unlikely to be cost saving when compared with current practice. Zio XT became cost incurring by:

- £0.82 per patient per year in the cardiology model
- £70.81 per patient per year in the stroke model
- £20.83 per patient per year in the downstream stroke model.

Scenario analyses suggest that cost saving is influenced by the number of repeat tests and outpatient follow-up visits

3.11 The EAC did a scenario analysis to explore the impact of repeat monitoring after a negative test. Zio XT was cost incurring when all monitoring was repeated after a negative test. When monitoring with a 24-hour Holter or a 7-day cardiac event recorder was repeated after a negative first test, but Zio XT was not repeated, the technology was cost saving. The EAC also explored the impact of excluding follow-up outpatient visits after monitoring for some or all tests. It also modified the model structure to include the sensitivity and specificity parameters of the tests. For full details, see the addendum to the EAC's assessment report in the supporting documents for this guidance.

4 Committee discussion

Clinical-effectiveness overview

Zio XT is an innovative technology which shows promise for ambulatory monitoring

4.1 The clinical experts who had experience of using Zio XT explained that it offers continuous monitoring over 14 days and is well accepted by patients. Experts commented on how easy it is to fit and the improved patient acceptability, adding that people are more likely to wear Zio XT for longer. The committee agreed that Zio XT is an innovative design and there is a plausible clinical benefit.

The evidence shows that Zio XT can improve diagnostic yield and patient acceptability

4.2 Evidence shows that Zio XT can increase patient wear time. Three of the 4 comparative studies showed improved diagnostic yield over total wear time compared with 24-hour Holter monitoring. Eysenck et al. (2019) reported a longer wear time for Zio XT compared with the R-test (a cardiac event recorder). The clinical experts agreed that it was plausible that monitoring with Zio XT could increase diagnostic yield, primarily because Zio XT is worn for 14 days, which is much longer than the Holter monitor. The clinical experts also advised that Zio XT has usability advantages for patients: it is more convenient and discreet to use than a Holter monitor and the Zio biosensor stays on better. The committee concluded that Zio XT increases diagnostic yield for detection of cardiac arrythmias compared with 24-hour Holter monitoring.

The committee considers Zio XT to be a diagnostic service for detecting cardiac arrhythmia

4.3 The committee questioned whether Zio XT is a diagnostic service. The company said that the Zio XT algorithm highlights areas of concern on the ECG trace, then a company-based cardiac physiologist reviews and confirms the arrhythmia type. A report including a sample of the ECG

trace is generated for the referring healthcare professional. The company said that the technology is a decision support tool that provides a report allowing the referring healthcare professional to make a diagnosis. The company also said that full disclosure of ECG traces is available on request. The committee considered that, although the referring healthcare professional may override the arrythmia event summary in the Zio XT report, the initial diagnosis is made by the company's cardiac physiologist on the basis of events detected by the algorithm in Zio XT. The committee therefore concluded Zio XT to be a diagnostic service and so information on diagnostic accuracy is needed to fully assess the clinical benefit of Zio XT.

Outcome measures

Diagnostic accuracy is an important outcome that is not directly assessed against standard care

4.4 The available evidence does not provide reliable estimates of diagnostic sensitivity or specificity. Although Hannun et al. (2019) showed that Zio XT's ZEUS algorithm was able to classify a broad range of distinct arrhythmias and performed with a similar accuracy to cardiologists, the study was not carried out in a clinical setting. Also, Zio XT's ECG recordings are captured using a single-lead biosensor while Holter monitors use 3 leads. Experts said that although 3-lead ECG recordings may be better at detecting certain types of arrythmia, most clinical decisions can be made from 1 lead. The committee concluded that further research would be needed to confirm Zio XT's diagnostic accuracy in detecting cardiac arrhythmia compared with Holter monitoring.

Other patient benefits or issues

Shaving of bodily hair is common to both Zio XT and Holter monitoring and is unlikely to restrict access for patients

4.5 Applying the Zio XT biosensor may require body hair to be shaved. Some religions forbid cutting or shaving body hair. The clinical experts advised that shaving is needed for both Zio XT and Holter monitoring. They

believed this would not restrict access for particular groups of people and said that, in their experience, most people agree to shave when using the Zio XT biosensor.

NHS considerations overview

Information on whether Zio XT meets necessary technical standards is not available

4.6 The algorithm used to analyse the data in Zio XT is based on a deep neural network (a computational model made up of multiple processing layers). The committee was not presented with information on whether Zio XT meets the Department of Health and Social Care's code of conduct for data-driven health and care technology in the NHS. NHSX has published a proposed NHS digital health technologies standard for digital technologies in the NHS, which is currently in consultation. NICE is commissioning some work to assess Zio XT's compliance with digital standards and to explore the use of artificial intelligence in the technology.

Zio XT is scalable but there are concerns about the impact on NHS resource

4.7 Clinical experts highlighted that there is currently a shortage of cardiac physiologists in the NHS, and that more widespread adoption of Zio XT in the NHS may further affect the recruitment of cardiac physiologists if they leave the NHS to work for the service. But they also said that reducing the burden on cardiac physiologists in the NHS of analysing ECG reports should be considered a benefit of Zio XT. The company said that it has the capability to scale up its service to the UK, and that it would adapt a successful model used in the USA. The company confirmed that the turnaround time for reports (4 days maximum but usually 24 hours) would not change. The committee was reassured that Zio XT is potentially scalable across the NHS but it was less certain about the impact on the NHS cardiac physiologist workforce.

Cost modelling overview

The EAC's updated model is acceptable but uncertainties remain

4.8 The committee accepted the EAC's model but considered that, because of the uncertainties about the diagnostic accuracy of Zio XT, it was difficult to draw firm conclusions about any cost benefits. The committee concluded that further evidence on its diagnostic accuracy is needed to show if Zio XT is cost saving compared with standard care.

Further information about resource use would be valuable

4.9 In its base-case analysis, the external assessment centre (EAC) assumed that all monitoring tests would be followed up with an outpatient visit. Clinical advice was that outpatient visits are not usually needed after a negative result from Zio XT, and that practice varies. In scenarios in which follow-up outpatient appointments were included for standard care but not for Zio XT, Zio XT was cost saving across all 3 of the EAC's revised models. The committee also noted that the number of repeat tests and assumptions associated with them affect the cost modelling results. The committee concluded that further information about the resource implications of using Zio XT would be valuable to inform the cost modelling.

Further research

Further research is needed to address uncertainties about the diagnostic accuracy and resource use associated with Zio XT

4.10 The committee concluded that further research is needed to address uncertainties about the diagnostic accuracy and resource use associated with Zio XT, compared with standard care using Holter monitoring or cardiac event recorder monitoring. This research should assess the diagnostic accuracy of Zio XT in detecting different types of arrhythmia compared with standard care over the same time period. Information on how Zio XT influences clinical decision making and the impact it has on

resource use, in particular on the number of repeat tests and outpatient follow-up appointments, would be valuable to help inform cost modelling.

5 Committee members and NICE project team

Committee members

This topic was considered by NICE's medical technology advisory committee which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of the medical technology advisory committee, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each medical technologies guidance topic is assigned to a team consisting of 1 or more technical analysts (who act as technical leads for the topic), a technical adviser and a project manager.

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Technical analyst

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Jessica Linville-Boud, Victoria Fitton
Project manager

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