



**Australian Government**

**Department of Health**

**MEDICAL SERVICES ADVISORY COMMITTEE**

**MSAC 1443 - Implantable loop recorders for diagnosis of atrial fibrillation in cryptogenic stroke**

**Applicant submitted protocol**

December 2016

## 1) Title of Application

Implantable loop recorders (ILR) for diagnosis of atrial fibrillation (AF) in cryptogenic stroke (CS).

## 2) Purpose of application

*Please indicate the rationale for the application and provide one abstract or systematic review that will provide background.*

This application requests two new MBS items for ILRs for use in patients with CS and suspected AF:

- Insertion of ILR device (equivalent to MBS item 38285 for the existing syncope indication)
- Follow-up consultation (equivalent to MBS item 11722 for the existing syncope indication)

### *Summary of application rationale*

Ischemic stroke is a major cause of prolonged disability in adults with significant cost burdens. Understanding the underlying cause of these strokes is important to optimise patient management, and in particular, to minimise the risk of further strokes. However, in approximately one third of this patient population, the underlying cause of stroke remains undetermined, despite multiple investigations. These patients are diagnosed with cryptogenic stroke (CS), i.e. ischaemic stroke of obscure or unknown origin.

Atrial fibrillation (AF) is a common cardiac arrhythmia which significantly increases a person's risk of stroke. Studies show that between 15-38% of patients with ischaemic stroke will have AF. The true proportion may be even higher because of difficulties in detecting asymptomatic and intermittent AF. Under-detected AF therefore remains problematic.

The implications of detecting AF in CS are significant because it alters the treatment strategy. The superiority of anticoagulation compared to antiplatelet therapy in reducing stroke recurrence in patients with AF is well established.

Several short-term and mid- to long-term monitoring strategies exist for detection of AF in patients. Because of the difficulty in detecting asymptomatic and intermittent AF by conventional tests (e.g. telemetry, 24-hour ambulatory Holter monitoring), and compliance issues of longer external monitoring, long-term continuous monitoring with an implantable loop recorder (ILR) is proposed to optimise AF detection and consequently improve stroke secondary prevention and patient outcomes.

Therefore, this application will propose that ILRs will detect AF as the underlying cause of stroke and thereby improve outcomes via improved management.

It should be noted that in alignment with feedback from the PASC, the term “cryptogenic” is considered an outdated term, the current accepted term is ESUS – Embolic Stroke of Undetermined Source. This new term, ESUS, will be used in place of cryptogenic stroke in the final submission.

Moreover, the DRAFT Clinical Guidelines for Stroke Management (2017)<sup>1</sup>, under 6.3 – Cardiac investigations, makes a Strong Recommendation – For patients with embolic stroke of uncertain source, longer term ECG monitoring (external or implantable) should be used (Afzal et al 2015[76]; Kamel et al 2013[82]).

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<sup>1</sup> <https://informme.org.au/Guidelines/2017-Draft-Guidelines/>

### *What is cryptogenic stroke?*

Identifying an underlying stroke mechanism is crucial in secondary prevention of ischaemic stroke (Yaghi & Elkind, 2014). However, in 25-40% of ischaemic strokes no stroke aetiology is identified (Andrade, Field & Khairy, 2015; Sacco et al., 1989; Petty et al., 1999; Kolominsky-Rabas et al., 2001; Lee et al., 2001; Liao et al., 2007; Li et al. 2015). The term used to describe these ischaemic strokes of unknown or obscure mechanism is cryptogenic stroke (CS) (Andrade, Field & Khairy, 2015). More specifically, CS is defined as cerebral infarction that, despite extensive evaluation, is not attributable to a definite source of cardioembolism, large artery atherosclerosis, or small vessel disease (lacunar infarct) (Andrade, Field & Khairy, 2015; Adams et al., 1993). The diagnosis of CS is therefore a diagnosis of exclusion based on thorough investigation for other potential aetiologies (Prabhakaran and Elkind, 2015). Other terms used in the literature to describe CS include cryptogenous stroke and infarcts of unknown, uncertain, or undetermined cause. Embolic stroke of undetermined source (ESUS) is also a related term which describes a subset of CS.

### *What is the underlying mechanism of cryptogenic stroke?*

Why the underlying mechanism of CS is not determined could be due to one of three reasons: the inciting mechanism for ischaemia is transitory or reversible; the investigations performed did not explore all possible aetiologies; or the cause remains truly unknown (Andrade, Field & Khairy, 2015). The Cryptogenic Stroke/ESUS International Working Group propose that CS may be caused by occult arterial sources of thromboembolism, paroxysmal atrial fibrillation (PAF), patent foramen ovale (PFO), or minor-risk cardiac structural abnormalities (Li et al., 2015, Hart et al., 2014; Ntaios et al., 2015; Amarenco et al., 2009).

### *Atrial fibrillation and stroke*

Atrial fibrillation (AF) is a common cardiac arrhythmia, and independent of other risk factors, confers a 5- to 6- fold increased risk of ischaemic stroke (Friberg et al., 2014; Romero & Wolf, 2013; Coppens et al., 2013; Wolf, Abbott & Kannel, 1991). A prevalence of 15-38% has been reported among patients with ischaemic stroke (Friberg et al., 2014; Asberg et al., 2010; Wolf, Abbott & Kannel, 1987; Thygesen et al., 2009; Hannon et al. 2010; Björck et al., 2013) however the true proportion may be even higher because of difficulties detecting intermittent, silent AF (Friberg et al., 2014; Engdahl et al., 2013; Doliwa Sobocinski et al., 2012; Shintani, Shiigai & Arinami, 1998). These intermittent episodes (PAF is defined as a disease of episodic clusters) combined with an unreliable symptom profile (there is poor correlation between symptoms and AF episodes) means under-detection remains problematic (Andrade, Field & Khairy, 2015; Page et al., 1994; Kottkamp et al., 2004; Piorkowski et al., 2005; Strickberger et al., 2005; Ziegler, Koehler & Mehra 2006; Cotter et al., 2013; Verma et al., 2013).

*What is the implication of detecting atrial fibrillation in cryptogenic stroke?*

The implications of detecting AF in CS are significant because it alters the treatment strategy. In the absence of AF, the standard treatment for secondary prevention of stroke is antiplatelet therapy. When AF is present, antiplatelet therapy is only minimally effective (22% reduction in risk vs. placebo), and anticoagulation is strongly recommended (39-63% reduction in risk of stroke vs. antiplatelet therapy) (Gladstone et al., 2014).

The CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> scoring system (see Appendix 1, Table 11), which predicts stroke risk in patients with AF and guides use of oral anticoagulant treatments, is widely used and has been recommended in key European and US guidelines (Camm et al., 2012; January et al., 2014; NICE, 2014). According to CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub>, a patient who has AF and has experienced a prior stroke or TIA receives a score of 2. This score could be higher once the other risk factors in the tool are considered, however regardless, this score places the patient in the 2 and above group who are recommended to receive oral anticoagulation therapy (OAC) by The European Society of Cardiology (ESC), the National Institute for Health and Care Excellence (NICE), and the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) (Camm et al., 2012; January et al., 2014; NICE, 2014). Notably, anticoagulation is strongly recommended regardless of whether the AF is paroxysmal or sustained, because the stroke risks are similar (Gladstone et al., 2014; Hohnloser et al., 2007; Hart et al., 2000; The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators, 1990), and patients with either type of atrial fibrillation benefit from anticoagulation (Gladstone et al., 2014; Hohnloser et al., 2007; Al-Khatib et al., 2013; Flaker et al., 2012).

Consequently, if AF remains undetected in patients who have had CS, secondary prevention therapy is often suboptimal (Andrade, Field & Khairy, 2015).

Regarding outcomes of patients with CS, Li et al. (2015) in their large population-based study found that compared with non-cardioembolic ischaemic stroke, a similar proportion of those with CS died or were dependent at 6 months (CS 23% vs. 27%; p=0.26). In addition, between CS and non-cardioembolic ischaemic stroke the 10-year risks of death, vascular death, or any recurrent stroke were also comparable. Finally, the risks of recurrent ischaemic stroke did not differ between stroke subtype (CS, small vessel disease, large vessel disease, and cardioembolic) (Li et al., 2015).

*What options are there to detect atrial fibrillation in patients with cryptogenic stroke? How do these compare?*

Options currently available in Australia for detecting AF in patients with CS include the short-term monitoring strategies of standard 12-lead electrocardiography (ECG), continuous cardiac rhythm monitoring with inpatient telemetry, and 24-hour ambulatory ECG (Holter) monitoring. A mid-term monitoring strategy which is available, but not publically funded, is use of event loop recorders (ELRs), which are external devices allowing up to 30 days of cardiac rhythm monitoring. A long-term monitoring strategy, and the subject of this application, is use of implantable loop recorders (ILR). The ILR is a subcutaneous device implanted in the left pectoral region that is capable of continuous uninterrupted arrhythmia monitoring (Andrade, Field & Khairy, 2015).

Table 1 lists these monitoring strategies and summarises their duration of monitoring. Figure 3 (page 13) further illustrates the monitoring duration for one-time and repetitive periodic external monitoring.

**Table 1** Type of monitoring of atrial fibrillation in patients with cryptogenic stroke

Type of monitoring	Duration of monitoring
12-lead ECG	NA
Inpatient continuous telemetry	3-5 d
Holter monitor	24 h - 7 d
ELR	30 d
ILR	36 mo

Source: adapted from Yaghi & Elkind (2014)

Abbreviations: ECG, electrocardiogram; NA, not applicable; ELR, external loop recorders; ILR, implantable loop recorders; d, days; mo, months; h, hours

The various monitoring strategies above all differ in effectiveness. In their systematic review and meta-analysis, Afzal et al. (2015) have compared the effectiveness of ILR versus wearable devices in identifying AF in patients with CS. A summary of the results of this systematic review is presented in Section 7 of this document.

#### *What happens if and when AF is detected in a patient with ILR?*

The ILR is used to provide the initial diagnosis of AF in patients, who can then move onto appropriate treatment management of their AF with OAC. After the diagnosis of AF the ILR no longer has an explicit role to play in the management of the patient. After AF diagnosis, the ILR device itself will remain in the patient for the 3 year lifespan of the device because it is safe and because it may provide some incidental information.

Following the documentation of an AF episode, the ILR continues to provide ongoing heart rhythm information that enables:

- 1) The physician (Cardiologist) to implement AF rate and rhythm control strategies as per clinical guidelines without the need for additional holter monitoring.
- 2) The identification of other cardiac arrhythmias which may require intervention (e.g. bradycardia, tachycardia, pauses)

Nonetheless, the subject of this assessment is the diagnosis of the first AF event. Subsequent treatment and management of the AF will be conducted independent the ILR.

The device will also be removed after three years in patients without an AF finding.

#### *Implantable loop recorder use in other indications*

ILRs are already listed on the MBS for the diagnosis of primary disorder in patients with recurrent unexplained syncope (item 38285).

#### *A note on terminology*

ILRs have several names in practice and in the literature which include:

- Insertable loop recorder (also abbreviated to ILR)
- Insertable cardiac monitor (ICM)
- Implantable cardiac event recorders
- Cardiac implantable electronic device (CIED) (this term is not exclusively applied to ILRs)

In order to ensure clarity, the same term, implantable loop recorder (ILR) will be used throughout this document.

### **3) Population and medical condition eligible for the proposed medical services**

#### *Provide a description of the medical condition (or disease) relevant to the service.*

There are two medical conditions that are relevant to this service (ILR): CS, the medical condition required by patients to be eligible for this service, and AF, the medical condition diagnosed by this service.

### *Cryptogenic stroke*

CS, the medical condition required by patients to be eligible for this service, is the term used to refer to strokes for which no definite cause can be identified (Yaghi & Elkind, 2014). However, clearly the term cryptogenic is only as good as the testing that has been done, i.e. how thorough investigations have been performed to determine a cause (Yaghi & Elkind, 2014). For example, a stroke may be considered cryptogenic because no cause is found after exhaustive testing, routine testing, or an incomplete evaluation (Yaghi & Elkind, 2014). Therefore, in defining the population with CS who would be eligible for this service, the minimal work-up required to make the diagnosis of CS should be well defined. Currently in Australia the following investigations would usually have been performed, with no cause for the stroke found, for a diagnosis of CS to be made (National Stroke Foundation, 2010; Campbell, 2015):

- Blood testing (which may include a prothrombotic screen)
- Brain imaging (MRI or CT)
- Carotid artery imaging (e.g. with contrast-enhanced magnetic resonance angiography [CE-MRA], doppler ultrasound, MRA, or CT angiography [CTA])
- Cardiac imaging (e.g. with echocardiography, transthoracic echocardiography [TTE], or transoesophageal echocardiography [TEO])
- Cardiac monitoring (e.g. 12-lead ECG, in-patient monitoring with telemetry for 24-48 hours, +/- an in-patient 24-hour Holter monitor)

### *Atrial fibrillation*

AF is the medical condition diagnosed by this service. AF increases with age occurring in 0.12 to 0.16% of those <49 years, 3.7 to 4.2% of those 60–70 years, and 10 to 17% of those ≥80 years (Zoni-Berisso et al., 2014). Due to a greater ability to treat chronic cardiac and noncardiac diseases, and the improved ability to suspect and diagnose AF, the overall prevalence of AF is also increasing, with the currently prevalence (2%) double that reported in the last decade (Zoni-Berisso et al., 2014). It is a heterogeneous disease in terms of its aetiology, pathophysiology, clinical presentation, natural history, and outcomes (Kirchhof et al., 2015; de Vos et al., 2010; de Vos et al., 2012). However, despite this heterogeneity, studies have consistently shown that a prior thromboembolic event is the single strongest risk factor for recurrent stroke in patients with AF (Sanna, Diener & Passman, 2014; “Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation”, 1994; Gage et al., 2001). In addition, the superiority of anticoagulation compared to antiplatelet therapy for secondary stroke prevention in patients with AF has been clearly demonstrated (Sanna, Diener & Passman, 2014; “Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation”, 1994).

*Define the proposed patient population that would benefit from the use of this service. This could include issues such as patient characteristics and /or specific circumstances that patients would have to satisfy in order to access the service.*

The proposed patient population that would benefit from the use of ILRs is as follows:

- For diagnosis of atrial fibrillation in patients with cryptogenic stroke where:
  - a diagnosis of cryptogenic stroke has been made based on results of the medical history, physical examination, brain and carotid imaging, cardiac imaging, surface ECG testing including 24-hour Holter monitoring, and other tests as indicated, and
  - atrial fibrillation is suspected

Expert clinician advice was sought (ANZ SFG, 2015) and informed the assessment on the minimum tests required for a patient with ischemic stroke in Australia to receive a diagnosis of cryptogenic stroke and be eligible for this intervention.

This proposed patient population is consistent with the pivotal trial evidence base from the CRYSTAL AF trial (Sanna et al., 2014). A framework for developing the item descriptor for this indication is provided by MBS item number 38285, ILR for the diagnosis of primary disorder in patients with recurrent unexplained syncope, which is detailed in Figure 1.

**Figure 1 MBS item 38285 - ILR in patients with recurrent unexplained syncope**

Category 3 - THERAPEUTIC PROCEDURES

38285	Group	T8 - SURGICAL OPERATIONS
	Subgroup	6 - CARDIO-THORACIC
	Subheading	1 - CARDIOLOGY PROCEDURES

IMPLANTABLE ECG LOOP RECORDER, insertion of, for diagnosis of primary disorder in patients with recurrent unexplained syncope where:

- a diagnosis has not been achieved through all other available cardiac investigations; and
- a neurogenic cause is not suspected; and
- it has been determined that the patient does not have structural heart disease associated with a high risk of sudden cardiac death.

including initial programming and testing, as an admitted patient in an approved hospital

[Multiple Services Rule](#)

(Anaes.)

Fee: \$192.90 Benefit: 75% = \$144.70 85% = \$164.00

(See para [T8.62](#) of explanatory notes to this Category)

[← Previous - Item 38275](#) [Next - Item 38286 →](#)

Source: <http://www.mbsonline.gov.au/>

*Indicate if there is evidence for the population who would benefit from this service i.e. international evidence including inclusion / exclusion criteria. If appropriate provide a table summarising the population considered in the evidence.*

The proposed population for ILR use in cryptogenic stroke is based on evidence from the CRYSTAL AF trial (Sanna et al., 2014; Sinha et al., 2010). This randomized, controlled study of 441 patients assessed whether long-term monitoring with an ILR is more effective than conventional follow-up (control) for detecting AF in patients with cryptogenic stroke.

In the CRYSTAL AF trial, 90.9% of patients randomised had a recent episode of cryptogenic ischemic stroke, and 9.1% of patients had a recent episode of cryptogenic symptomatic transient ischemic attack. However, the proposed patient population for this assessment does not include cryptogenic TIA.

The inclusion and exclusion criteria are detailed in Table 2 below.

**Table 2**      **CRYSTAL AF trial: inclusion and exclusion criteria**

<b>Inclusion and Exclusion criteria</b>
<p>1. Recent episode (&lt;60 days) of cryptogenic symptomatic TIA* or recent episode of cryptogenic ischemic stroke.</p> <ul style="list-style-type: none"><li>• A stroke/TIA is considered to be cryptogenic if no possible cause can be determined despite extensive workup according to the standard protocol of the participating centre.</li><li>• Before randomization, the following tests are minimally required as standard tests to establish the diagnosis of cryptogenic stroke:<ul style="list-style-type: none"><li>• MRI or CT</li><li>• 12-lead ECG for AF detection</li><li>• 24-h ECG monitoring for AF detection and PAC analysis (eg, Holter)</li><li>• TEE</li><li>• CTA or MRA of head and neck to rule out other causes of stroke pathologies</li></ul></li></ul>
<p>2. Patient or legally authorized representative is willing to sign patient consent form</p>
<p>3. Patient is ≥40 years old</p>
<b>Exclusion criteria</b>
<p>1. Patient has known aetiology of the TIA or stroke (based on neuro-/cardiac/vascular imaging), such as:</p> <ul style="list-style-type: none"><li>• Angiographic signs of large-artery atherosclerosis (MRA, CTA, or digital subtraction angiography) in the artery feeding the acute ischemic territory</li><li>• Radiographic appearance consistent with acute small-artery occlusion, with lesion <math>\geq 1</math> cm in diameter (DWI or CT).</li><li>• Evidence of a high-risk cardiac or aortic arch source of embolism (LV or LA thrombus or “smoke,” emboligenic valvular lesion or tumour, PFO with extant source of venous thromboembolism, aortic arch plaque <math>\geq 3</math> mm thick or with mobile components or any other high-risk lesion)</li><li>• History of spontaneous DVT</li><li>• Stroke of other determined cause such as presence of nonatherosclerotic vasculopathies, hypercoagulable states (must be tested in patients &lt;55 years old) and haematological disorders</li></ul>
<p>2. Patient has untreated hyperthyroidism.</p>
<p>3. Patients had myocardial infarction &lt;1 month before stroke/TIA.</p>

#### **Inclusion and Exclusion criteria**

4. Patient had coronary bypass grafting <1 month before stroke/TIA.
5. Patient has valvular disease requiring immediate surgical intervention.
6. Patient has documented history of AF or atrial flutter.
7. Patient has presence of a PFO, and PFO is/was an indication to start OAC in the patient according to the ESO guidelines.<sup>5</sup>
8. Patient has permanent indication for anticoagulation at enrolment.
9. Patient has permanent OAC contraindication.
10. Patient is already included in another clinical trial that will affect the objectives of this study.
11. Patient's life expectancy is <1 year.
12. Patient is pregnant.
13. Patient is indicated for implant with a pacemaker, ICD, CRT device, or an implantable hemodynamic monitoring system
14. Patient is not fit, or is unable or unwilling to follow the required procedures of the Clinical Investigation Plan.

Source: Sinha et al. 2010

Abbreviations: PAC, Premature atrial complex; TEE, transesophageal echocardiography; DWI, diffusion-weighted imaging; LV, left ventricular; LA, left atrial; OAC, oral anticoagulation; ESO, European Stroke Organisation; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; DVT, deep vein thrombosis

\* Only TIAs with the following documented characteristics can be included: visible lesion on MRI or CT that fits the symptoms of the TIA and at least one of the following symptoms - speech problems, weakness of arm or leg, or hemianopsia.

*Provide details on the expected utilisation, if the service is to be publicly funded.*

The age-standardised stroke incidence is 157 per 100,000 among male Australians, while this is 123 per 100,000 among female Australians (Thrift et al., 2009; taken from AIHW, 2013). These incidence rates translate to an estimated total national incidence of 34,068 in 2016 (ABS, 2012). It has been also reported that 79% of all stroke cases are ischaemic (National Stroke Foundation, 2014). The incidence to ischemic stroke is hence estimated to be 26,928 in 2016. Table 3 summarises the estimated incidence of CS in Australia for 2016.

**Table 3 Estimated incidence of cryptogenic stroke in Australia, 2016**

Parameter	Estimate	Source
Australian population, 2016	24,359,761	ABS, Population Projections, Series B
Stroke incidence (per 100,000)	157 / 123 for males / females	Thrift et al., 2009
Total incidence	34,068	Calculated
% ischaemic	79%	National Stroke Foundation 2014
Total ischaemic stroke incidence	26,928	Calculated
% cryptogenic	20-40%	Sanna et al., 2014
Total cryptogenic ischaemic stroke incidence	5,386-10,771	Calculated

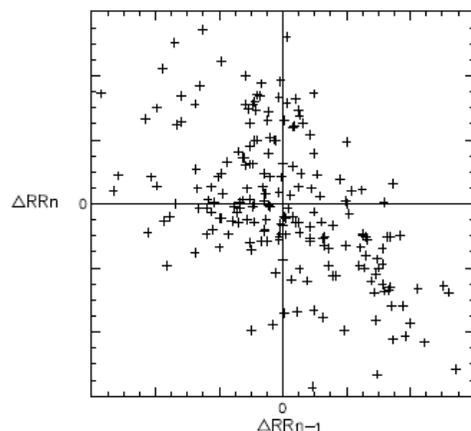
CS occurs in 20-40% of all ischaemic stroke cases (Sanna et al., 2014), which means that 5,386 – 10,771 cases can potentially become eligible for ILR under the proposed indication. The application will examine the applicability of these data inputs to the Australian context.

#### **4) Intervention/investigation – proposed medical service**

*Provide a description of the proposed medical service.*

ILRs monitor the electrical activity of the heart, continuously storing information as ECGs, and recording abnormal activity such as arrhythmia. This makes it a very useful diagnostic tool. The ILR is implanted under local anaesthesia; a small incision is made lateral to the sternum, creating a pocket for the ILR to be placed.

ILR detects the occurrence of AF episodes from variations in the ventricular rhythm. AF episodes are detected using an automatic algorithm based on the pattern of R-wave interval variability within 2-minute periods. The differences between consecutive R-wave intervals are plotted in a Lorenz plot. In the Lorenz plots the difference between 2 consecutive R-wave intervals ( $\Delta RR_n$ ) is plotted on the vertical axis (Figure 2). The preceding R-wave interval difference ( $\Delta RR_{n-1}$ ) is plotted on the horizontal axis. Pattern recognition is used to identify AF episodes; R-wave intervals during AF episodes are highly irregular and uncorrelated. Additionally, a P-wave presence algorithm looks for evidence of a P-wave between two R-waves.



**Figure 2 Lorenz plot of an AF episode**

There are no known contra-indications to the insertion of the ILR. Patients who receive ILR may safely undergo common procedures associated with atrial fibrillation and/or stroke. These include:

- MRI and CT scans
- External cardioversion or defibrillation
- Cardiac ablation
- Insertion of implantable pacemaker or cardioverter defibrillator

ILR continuously senses the patient's subcutaneous ECG, and analyses the timing of atrial and ventricular events to detect arrhythmias. The device stores episode data (arrhythmia type, date, start time, duration and ventricular rate) and ECGs for each episode type. Episode data for a maximum of 30 AF episodes is stored within the device at any given time. When the log is full, data from the most recent episode will overwrite the oldest stored episode data of that type. ILR reserves 27 min of ECG storage per day for automatically detected episodes. Two minutes of ECG is stored for each AF episode. When the available memory is full, a new ECG recording will overwrite the oldest stored ECG recording.

ILR communicates with the monitor e.g. the Medtronic MyCareLink monitor every evening and automatically transfers data stored within the device to the online network e.g. Carelink Network where it is stored and accessible to the patient's physician. The physician receives an alert when a patient's AF has been detected, after which the patients can be treated accordingly. Once the ILR has been inserted, no further resources are expended until such time where an AF has been detected and the physician has been alerted. That is, no proactive monitoring of the output of the ILR is necessary.

The timeframes for monitoring the patient is at the clinician's discretion. Generally, there is no additional monitoring once the patient has been diagnosed. However, the clinician may choose to continue to receive alerts to confirm their diagnosis.

Several ILRs or implantable cardiac event recorders are currently available on Part C of the Prosthesis List with a Minimum Benefit of \$3,900.00 (08.14.01 - Implantable Cardiac Event Recorders), as summarised in Table 4 below.

**Table 4** Implantable cardiac event recorders currently available on the Prosthesis List\*

Billing Code	Product name	Description	Manufacturer
<b>08.14.01 - Implantable Cardiac Event Recorders</b>			
MI141	Reveal LINQ	Insertable Cardiac Monitor	Medtronic
MC763	Reveal XT	Reveal XT Insertable Cardiac Monitor	Australasia Pty Ltd
MC768	Reveal DX	Insertable Cardiac Monitor	
SJ152	SJM Confirm Model DM2102	Implantable cardiac monitor with atrial fibrillation monitoring.	St Jude Medical Australia Pty Ltd
SJ159	SJM Confirm Model DM2100	Implantable cardiac monitor	
BT153	BioMonitor	Implantable cardiac monitor for continuous remote monitoring of patients with Atrial Fibrillation (AF) or unexplained syncope	Biotronik Australia Pty Ltd

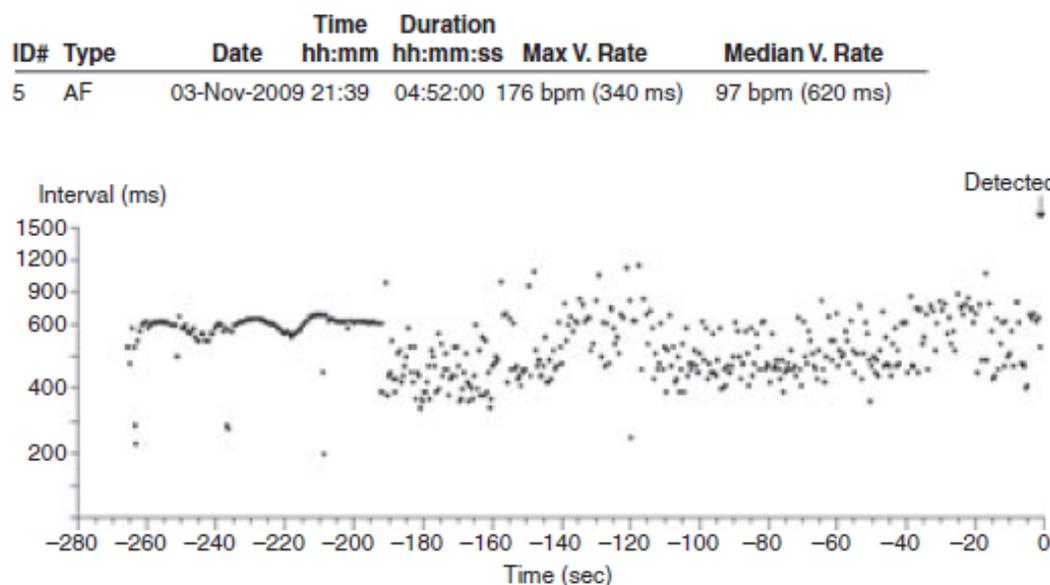
Source: DOH (2015b)

\*Note: A search, (*imped\* or implant\* or insert\**) and (*monitor\* or record\* or \*graph*), in the Australian Register of Therapeutic Goods (ARTG) did not identify any other relevant registered devices.

*If the service is for investigative purposes, describe the technical specification of the health technology and any reference or “evidentiary” standard that has been established.*

ILRs are implanted subcutaneously and monitor the heart continuously, registering beat-to-beat variability by measurement of the R-R intervals<sup>2</sup>, for up to 3 years (Christensen et al., 2014; Hindricks et al., 2010; Eitel et al., 2011). When irregular R-R-intervals are detected, the ILRs store 2 minutes of ECG and information regarding the time occurring and amount detected (Christensen et al., 2014). ILRs are programmed to detect AF which is defined as irregular R-R intervals and no visible p-waves<sup>3</sup> on correlating one-lead ECG transmissions (Christensen et al., 2014). Figure 3 shows an example of a transmission from an ILR where the regular R-R intervals in sinus rhythm to the scatter in AF is illustrated.

**Figure 3 R-R intervals of a transmission from an ILR**



Source: Christensen et al., 2014

<sup>2</sup> R-R intervals are the time between QRS complexes as measured in electrocardiography. They are used to calculate a person’s heart rate.

<sup>3</sup> P-waves are detected in electrocardiography and represent atrial depolarization, which results in atrial contraction. An absence of p-waves, in addition to irregular R-R intervals, are well-established key electrocardiographic characteristics of atrial fibrillation.

In their study to quantify the performance of the first ILR with dedicated AF detection capabilities, the Reveal XT (Medtronic), Hindricks et al. (2010) selected patients with already implanted ILRs and also monitoring them with a special Holter device. This Holter device stored simultaneous and continuous 46-hour recordings of the subcutaneous ECG, sensing and arrhythmia classification markers, and timestamps uploaded from the ILR, as well as a 2-channel surface ECG recording. Of 206 Holter recordings suitable for analysis, 76 (37%) contained at least 1 episode of core laboratory classified AF. From this data, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the ILR for identifying patients with any AF were 96.1%, 85.4%, 79.3%, and 97.4%, respectively (Hindricks et al., 2010).

*Indicate whether the service includes a registered trademark with characteristics that distinguish it from any other similar health technology.*

Not applicable

*Indicate the proposed setting in which the proposed medical service will be delivered and include detail for each of the following as relevant: inpatient private hospital, inpatient public hospital, outpatient clinic, emergency department, consulting rooms, day surgery centre, residential aged care facility, patient's home, laboratory. Where the proposed medical service will be provided in more than one setting, describe the rationale related to each.*

It is proposed that the ILR will be administered in settings detailed in Table 5. In each case, the patient would be referred by the neurologist looking after their CS to a cardiologist or other specialist trained in ILR insertion who would be responsible for inserting the ILR, following up the results, and communicating this to the referring neurologist. The specialist inserting the ILR could also be the neurologist who is managing the patient's CS.

**Table 5 Proposed delivery setting of implantable loop recorders in cryptogenic stroke**

Setting	Rationale
In-patient hospital	Following admission with a stroke, and the absence of a cause found on investigations including 24-hour inpatient telemetry, the patient with cryptogenic stroke would have the ILR inserted before discharge.
Inpatient day surgery centre	After discharge from hospital with the diagnosis of cryptogenic stroke, the patient may receive further investigations as an out-patient such as a 24-hour Holter monitor. In cases where the stroke was still classified as cryptogenic after these investigations, the patient would have the ILR inserted in the day surgery setting.

*Describe how the service is delivered in the clinical setting. This could include details such as frequency of use (per year), duration of use, limitations or restrictions on the medical service or provider, referral arrangements, professional experience required (e.g.: qualifications, training, accreditation etc.), healthcare resources, access issues (e.g.: demographics, facilities, equipment, location etc.).*

ILRs are likely to be inserted during the index hospitalisation for the CS or upon readmission for the express purpose of inserting the device.

ILRs are already being inserted for the diagnosis of primary disorder in patients with recurrent unexplained syncope (see Figure 1). Currently those inserting the device are electrophysiologists, interventional and general cardiologists, cardiothoracic surgeons, and general surgeons. Details on training requirements in order to insert and follow-up ILRs are provided in The Cardiac Society of Australia and New Zealand (CSANZ) document 'Guidelines for sub-specialty training in cardiac implantable electronic devices: selection, implantation and follow-up'. This document is provided in Appendix 2.

Insertion is performed using local anaesthetic. A video demonstrating the insertion of the Reveal LINQ ILR can be viewed [here](#). ILRs have an implanted lifespan of 3 years. Therefore, once inserted, the device could be explanted after 3 years or earlier if required. There is already an MBS item (38286) for removal of ILRs which is not patient population specific therefore can be used in this setting.

**5) Co-dependent information (if not a co-dependent application go to Section 6)**

*Please provide detail of the co-dependent nature of this service as applicable.*

Details of the co-dependent medical device, ILRs, for this service are provided in Table 6.

**Table 6 Co-dependent medical device information**

Source: DOH (2015b)

**DRAFT**

Product Category	Assessment Body	Product Group	Billing Code	Min Benefit	Sponsor	Product Name	Description	Size	ARTG	Last Updated
08 Cardiac	08.14 Implantable Cardiac Event Recorders	08.14.01 - Implantable Cardiac Event Recorders	MC763	\$ 3,900.00	Medtronic Australasia Pty Ltd	Reveal XT	Reveal XT Insertable Cardiac Monitor	61 x 19 x 8 mm with a volume of 9cc	149903	February 2012
08 Cardiac	08.14 Implantable Cardiac Event Recorders	08.14.01 - Implantable Cardiac Event Recorders	MC768	\$ 3,900.00	Medtronic Australasia Pty Ltd	Reveal DX	Insertable Cardiac Monitor	61 x 19 x 8 mm with a volume of 9cc	149904	February 2012
08 Cardiac	08.14 Implantable Cardiac Event Recorders	08.14.01 - Implantable Cardiac Event Recorders	SJ152	\$ 3,900.00	St Jude Medical Australia Pty Ltd	SJM Confirm Model DM2102	Implantable cardiac monitor with atrial fibrillation monitoring.	6.5cc, 12g	160466, 160756	February 2012
08 Cardiac	08.14 Implantable Cardiac Event Recorders	08.14.01 - Implantable Cardiac Event Recorders	SJ159	\$ 3,900.00	St Jude Medical Australia Pty Ltd	SJM Confirm Model DM2100	Implantable cardiac monitor	6.5cc, 12g	160466, 160755	February 2012
08 Cardiac	08.14 Implantable Cardiac Event Recorders	08.14.01 - Implantable Cardiac Event Recorders	BT153	\$ 3,900.00	Biotronik Australia Pty Ltd	BioMonitor	Implantable cardiac monitor for continuous remote monitoring of patients with Atrial Fibrillation (AF) or unexplained syncope	53.3m m x 42.7m m x 7.1mm, 26 grams	215074	February 2015
08 Cardiac	08.14 Implantable Cardiac Event Recorders	08.14.01 - Implantable Cardiac Event Recorders	MI141	\$ 3,900.00	Medtronic Australasia Pty Ltd	Reveal LINQ	Insertable Cardiac Monitor	45 x 7 x 3.5mm, 1.18cc	218791	February 2014

6) Comparator – clinical claim for the proposed medical service

*Please provide details of how the proposed service is expected to be used, for example is it to replace or substitute a current practice; in addition to, or to augment current practice.*

*Atrial fibrillation monitoring options available in Australia for patients with cryptogenic stroke*

As previously mentioned, several short-term and mid-term monitoring strategies exist for detection of AF in patients with CS. Ambulatory ECG devices available in Australia, and their relevant MBS items, are listed in Table 7. Note ILRs have been added in italics for comparison with the other devices, however the current MBS item for implantation is for use in recurrent unexplained syncope only.

**Table 7 Ambulatory ECG devices and relevant MBS items**

Device	Period of recording	Trigger	Data upload	Relevant MBS item
Continuous recording device (early Holter devices without full disclosure)	Up to 24 hours	Not Triggered (Continuous)	On return of device to clinic	11708
Continuous recording device (Holter devices with full disclosure)	Up to 24 hours	Not Triggered (Continuous)	On return of device to clinic	11709
External loop recorder or event loop recorder (ELR)	Pre-post event	Largely patient triggered but some devices are auto triggered	Periodically by patient OR telemetry	11710
Event recorder (handheld)	Post event	Patient triggered	Periodically by patient	11711
Real-time cardiac telemetry (e.g. V-Patch)	Pre-post event	Auto-triggered (can also be patient triggered)	Telemetry	11708
<i>Implantable loop recorder (ILR)*</i>	<i>Pre-post event</i>	<i>Auto-triggered (can also be patient triggered)</i>	<i>Telemetry</i>	<i>38285, for implantation and 11722 for reading at follow-up consultation</i>

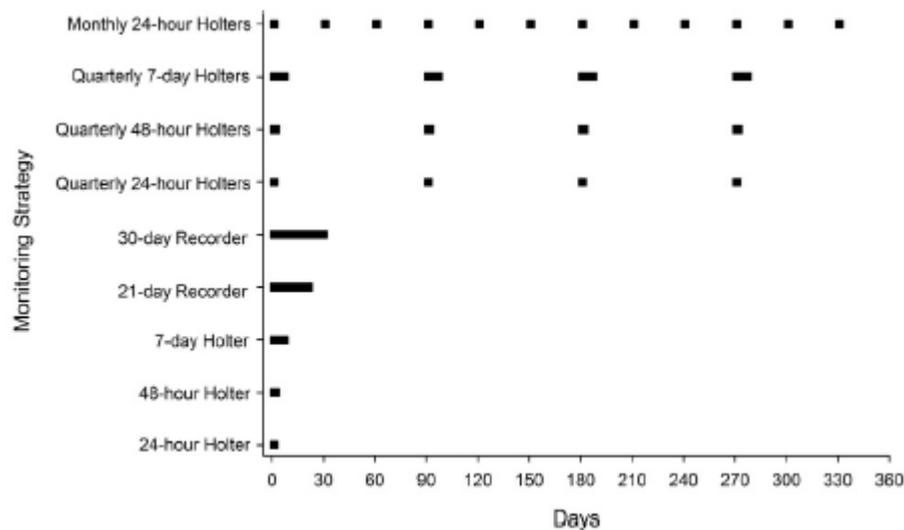
Source: DOH (2015a)

Abbreviations: AECG, ambulatory electrocardiography, MBS, Medical Benefits Schedule

\*Note: ILRs have been added in italics for comparison with the other devices, however the current MBS item for implantation is for use in recurrent unexplained syncope only.

The above mentioned monitoring strategies can be for one-time use or for repetitive external monitoring. Figure 4 provides an illustration of how these various devices might be used (Choe et al., 2015). Note, ILRs, which would monitor continuously for 3 years, are not represented in this figure.

**Figure 4 Simulation of strategies for one-time and repetitive periodic external monitoring**



Source: Choe et al., 2015

*Comparator used in key clinical trial*

In the pivotal CRYSTAL AF trial (Sanna et al., 2014) long-term monitoring with an ILR was compared to conventional follow-up (control) for detecting AF in patients with CS. Patients in this control group underwent assessment at scheduled and unscheduled visits, with ECG monitoring performed at the discretion of the site investigator.

*Comparators based on current practice*

Based on expert opinion (ANZ SFG, 2015) current practice for further investigation of a patient diagnosed with CS is either no further investigation or a 24-hour Holter monitor.

30-day monitoring was not considered a comparator as this is rarely performed in current practice. The reasons that these are not used often are because they are not publicly funded, and there can be issues with patient compliance. It has been demonstrated that patient compliance diminishes as the monitoring duration

increases due to concerns regarding skin irritation and the inconvenience associated with performing activities of daily living (Choe et al., 2015; Vasamreddy et al., 2006; Kamel et al., 2013).

#### *Proposed comparators for submission*

Considering the monitoring options available in Australia, the key trial data, and current practice, it is proposed that the comparator for ILRs is standard of care (no further investigation or 24-hour Holter monitor). Using the comparator standard of care, ILRs will replace current clinical practice. The pivotal CRYSTAL AF trial (Sanna et al., 2014) provides comparative data for long-term monitoring with an ILR was compared to conventional follow-up (control) for detecting AF in patients with CS.

#### **7) Expected health outcomes relating to the medical service**

*Identify the expected patient-relevant health outcomes if the service is recommended for public funding, including primary effectiveness (improvement in function, relief of pain) and secondary effectiveness (length of hospital stays, time to return to daily activities).*

#### *Outcomes assessed in key clinical trial*

In the pivotal CRYSTAL AF trial (Sanna et al., 2014) the following outcomes were measured:

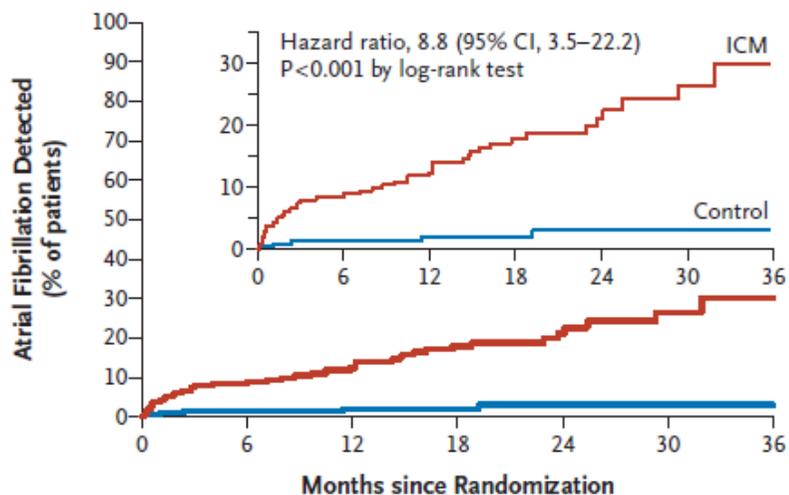
- Primary outcome
  - Time to first documented event of AF by 6 months of continuous rhythm monitoring versus stand arrhythmia diagnostics
- Secondary outcomes
  - Time to first documented AF by 12 months of continuous rhythm monitoring versus standard arrhythmia diagnostics
  - Incidence of recurrent stroke or TIA in both arms
  - Change and reasons for change in use of oral anticoagulation and of antiarrhythmic drugs over time in both arms
  - Quality of life in both arms
  - Economic and clinical disease burden and the care pathways in both arms (hospitalisations, medication use, stroke, death).
  - Role of the Patient Assistant device in the time to AF diagnosis in subjects implanted with the Reveal XT.

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Results from key clinical trial

Results from the primary outcome (time to first documented event of AF by 6 months) and a secondary outcome (time to first documented AF by 12 months) are summarised in Figure 5. This graph also provides longer term data up to 36 months (Sanna et al., 2014). This was not a defined outcome but is considered relevant to include given that the device is capable of monitoring for up to 3-years.

**Figure 5 Time to first detection of atrial fibrillation to 36 months**



**No. at Risk**

Control	220	194	167	114	72	36	7
ICM	221	191	173	102	57	29	8

Abbreviations: ICM, insertable cardiac monitor.(synonym for ILR, see Section 2)

Source: Sanna et al., 2014

By 6, 12 and 36 months respectively, AF had been detected in 8.9% of patients in the ILR group (19 patients) versus 1.4% of patients in the control group (3 patients) (HR 6.4; 95% CI 1.9-21.7; p<0.001), 12.4% (29 patients) versus 2.0% (4 patients) (HR 7.3; 95% CI 2.6-20.8; p<0.001), and 30.0% (42 patients) versus 3.0% (5 patients) (HR 8.8; 95% CI 3.5-22.2; p<0.001).

The incidence of recurrent stroke or TIA, a secondary outcome, was reported as 5.2% (11 patients) in the ILR group compared to 8.6% (18 patients) in the control group during the first 6 months after randomisation, and 7.1% (ILR; 15 patients) compared to 9.1% (control; 19 patients) during the first 12 months.

Another secondary outcome, the rate of use of oral anticoagulants was reported as 10.1% in the ILR group versus 4.6% in the control group at 6 months ( $p = 0.04$ ) and 14.7% versus 6.0% at 12 months ( $p = 0.007$ ). By 12 months, 97.0% of patients in whom atrial fibrillation had been detected were receiving oral anticoagulants (Sanna et al., 2014).

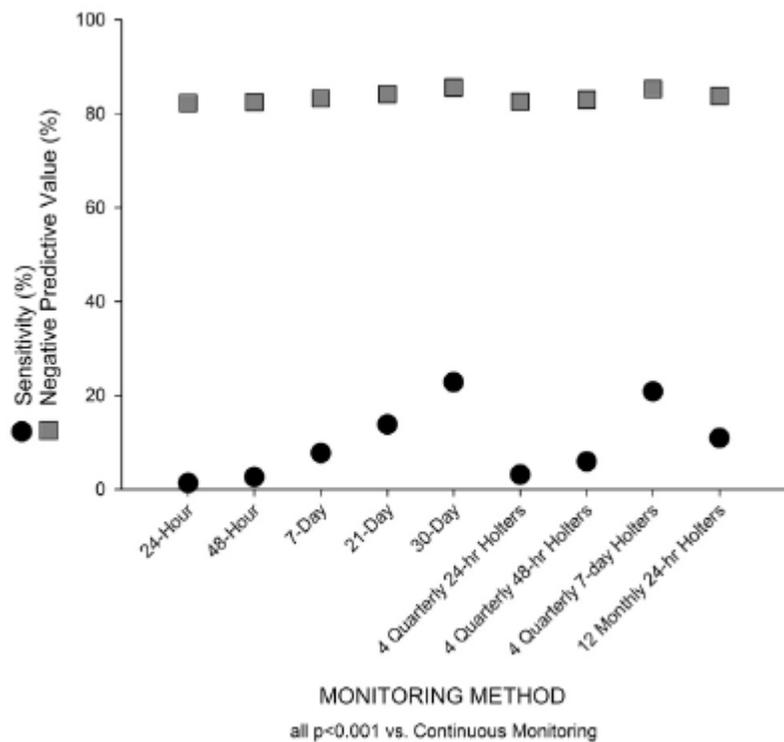
#### *Relevance of clinical trial outcomes to current practice*

The outcomes assessed in the CRYSTAL AF trial (Sanna et al., 2014) are relevant because they reflect the decision making process in current clinical practice. Specifically, if AF is detected in a patient with CS, then it is recommended that oral anticoagulation is initiated.

*Comparison between monitoring options of atrial fibrillation detection outcome*

Choe et al. (2015) assessed the sensitivity and NPV of various external monitoring strategies for AF detection in a population with CS. To do this they simulated intermittent monitoring strategies and compared this to continuous rhythm monitoring with an ILR using data from the CRYSTAL AF trial (Sanna et al., 2014). The results are presented in Figure 6.

**Figure 6 Sensitivity and NPV of one-time and repetitive periodic external monitoring for AF detection**



Source: Choe et al., 2015

As previously mentioned, in their systematic review and meta-analysis, Afzal et al. (2015) have compared the effectiveness of ILR versus wearable devices in identifying AF in patients with CS. Three randomised trials (RCTs) and 13 observational studies were identified. There was significantly ( $p < 0.05$ ) higher AF detection with ILR (23.3%, CI 13.83-32.29) compared to wearable devices (13.6%, CI 7.91-19.32).

*Describe any potential risks to the patient.*

*Safety data from key clinical trial*

In the CRYSTAL AF trial (Sanna et al., 2014) where ILRs (REVEAL XT, Medtronic) were compared with standard of care for detecting AF in patients with CS, 5 of the 208 inserted ILRs (2.4%) were removed due to infection at the insertion site or pocket erosion. The three most common adverse events associated with the ILR were infection (3 patients; 1.4%), pain (3 patients, 1.4%) and irritation or inflammation at the insertion site (4 patients, 1.9%). The ILR remained inserted in 98.1% and 96.6% of patients at 6 and 12 months respectively.

*In the REVEAL LINQ Usability trial (Pürerfellner et al., 2015), 9 of the 30 enrolled patients who had a REVEAL LINQ device implanted experienced adverse events during one month of follow-up (10 adverse events in total) There were 4 procedure-related events: implantation site pain (n=2) and wound infection (n=2). Two serious adverse events were reported in 3 patients (2 AF events in 1 patient, and 1 palpitation event in 1 patient), however none of these events were procedure or system related. Specify the type of economic evaluation.*

A modelled cost-effectiveness analysis will be presented. The proposed structure of this modelled analysis is described in Section 11 (Decision analytic).

**8) Fee for the proposed medical service**

*Explain the type of funding proposed for this service.*

It is expected that the funding type for these two services would follow the precedent of the syncope MBS items, specifically:

- Insertion of ILR device: equivalent to MBS item 38285 for the existing syncope indication which is category 3 (therapeutic procedures)
- Follow-up consultation: equivalent to MBS item 11722 for the existing syncope indication which is category 2 (diagnostic procedures and investigations).

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*Please indicate the direct cost of any equipment or resources that are used with the service relevant to this application, as appropriate.*

ILRs such as Reveal LINQ™ (Medtronic) are currently listed on Part C of the Prosthesis List with a Minimum Benefit of \$3,900.00 (08.14.01 - Implantable Cardiac Event Recorders; see Table 4). Several other brands and manufacturers exist on the list; all implantable cardiac event recorders are associated with the Minimum Benefit amount of \$3,900.00.

*Provide details of the proposed fee.*

The requested MBS fee for insertion, initial programming and testing for the proposed indication is same as that currently approved for the syncope indication (MBS item 38285; \$192.90). Similarly, a follow-up consultation (for re-programming of device, retrieval of stored data, analysis, interpretation and report) for the proposed indication is performed in a similar manner to the syncope indication (MBS item 11722; \$34.75), and the requested benefit for this service is also set at the current level.

The above approach is justified and appropriate because, while they relate to very different indications, the extent and type of expertise / procedural complexity and duration are likely to be similar between the proposed indication and the existing syncope indication.

#### **9) Clinical Management Algorithm - clinical place for the proposed intervention**

*Provide a clinical management algorithm (e.g.: flowchart) explaining the current approach (see (6) Comparator section) to management and any downstream services (aftercare) of the eligible population/s in the absence of public funding for the service proposed preferably with reference to existing clinical practice guidelines.*

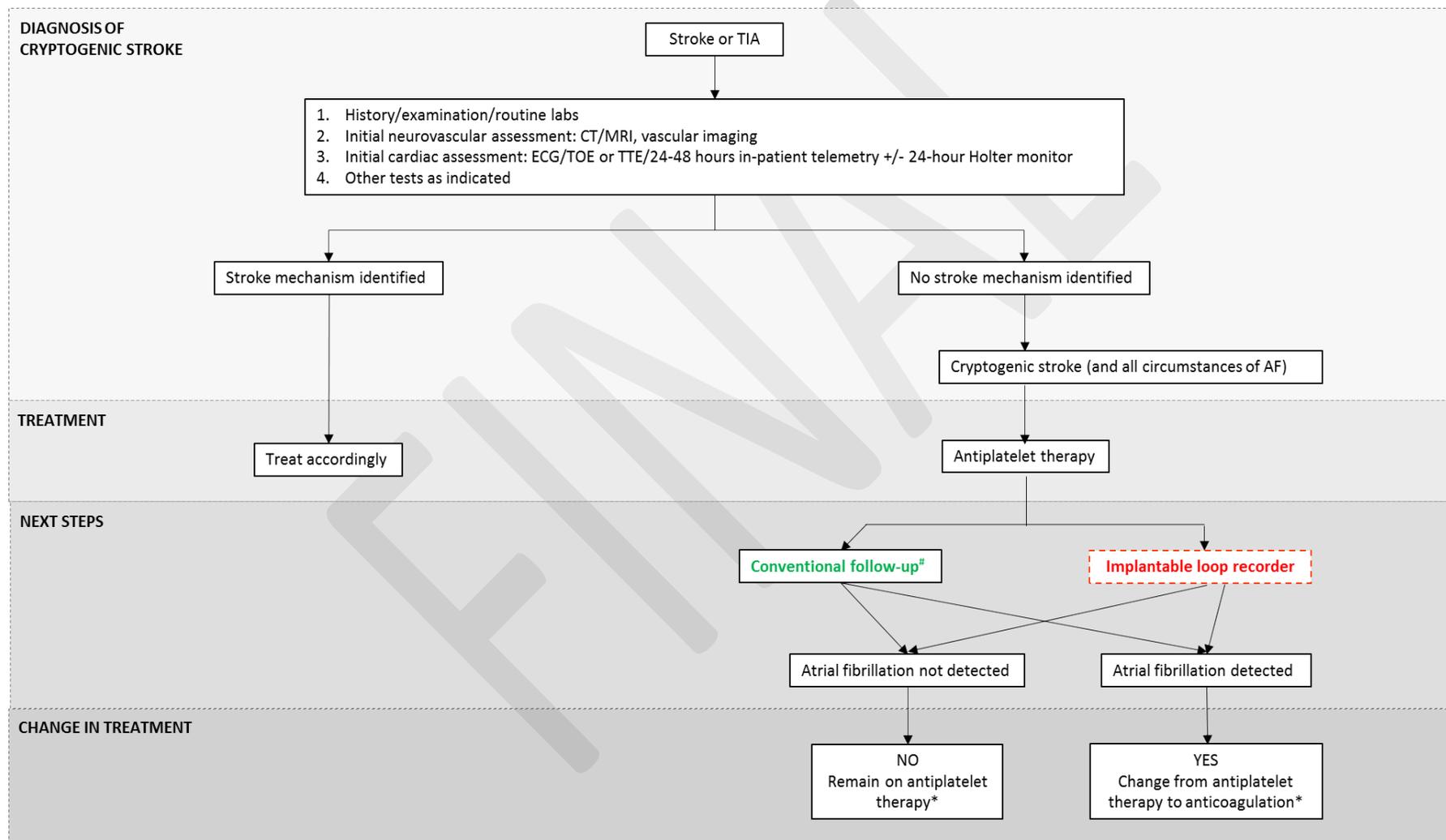
*Provide a clinical management algorithm (e.g.: flowchart) explaining the expected management and any downstream services (aftercare) of the eligible population/s if public funding is recommended for the service proposed.*

A clinical management algorithm for investigation of stroke mechanism including cryptogenic stroke which reflects current practice is illustrated in Figure 6. This figure also includes the proposed place of ILRs (red text) if public funding is recommended, and demonstrates the proposed comparator to ILRs (green text).

The ILR is used to provide the initial diagnosis of AF in patients, who can then move onto appropriate treatment management of their AF with OAC. After the diagnosis of AF the ILR no longer has an explicit role to play in the management of the patient. After AF diagnosis, the ILR device itself will remain in the patient for the 3 year lifespan of the device because it is safe and because it may provide some incidental information. Nonetheless, the subject of this assessment is the diagnosis of the first AF event. Subsequent treatment and management of the AF will be conducted independent of the ILR.

The device will also be removed after three years in patients without an AF finding.

**Figure 7 Clinical management algorithm for investigation of stroke mechanism: current practice and clinical place for ILRs**



<sup>#</sup>No further investigation or conventional follow-up (which can include one or more investigative test; See Section 3) \* Treatment unless contraindicated

Red text: proposed place of medical service (ILRs); Green text: proposed comparator for ILRs

Abbreviations: ECG, electrocardiogram; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiogram

FUNDA

## 10) Regulatory Information

*Please provide details of the regulatory status. Noting that regulatory listing must be finalised before MSAC consideration.*

Regulatory information of ILRs approved in Australia is summarised in Table 8.

**Table 8 Regulatory information of ILRs approved in Australia**

ARTG no.	Sponsor	Start date	Product name	Intended purpose
218791	Medtronic Australasia Pty Ltd	23/12/2013	Reveal LINQ	The Reveal LINQ ICM is an insertable automatically-activated and patient-activated monitoring system that records subcutaneous ECG.
215074	Biotronik Australia Pty Ltd	24/9/2013	BioMonitor	BioMonitor is an implantable cardiac monitor for monitoring of heart rhythm. Its primary purpose is to provide early detection and diagnosis of symptoms of arrhythmias. BioMonitor does not have a pacing function.
160756	St Jude Medical Australia Pty Ltd	2/4/2009	SJM Confirm ICM Model DM2102	The SJM Confirm ICM is indicated for the monitoring and diagnostic evaluation of patients who experience unexplained symptoms such as: dizziness, palpitations, chest pain, syncope, and shortness of breath, as well as patients who are at risk for other cardiac arrhythmias. The SJM Confirm, Model DM2102 is also indicated for patients who have been previously diagnosed with atrial fibrillation or who are susceptible to developing atrial fibrillation.
See below <sup>#</sup>	St Jude Medical Australia Pty Ltd	See below <sup>#</sup>	SJM Confirm ICM Model DM2100	See below <sup>#</sup>
149902	Medtronic Australasia Pty Ltd	6/2/2008	Reveal XT	The Reveal XT Model 9529 insertable cardiac monitors are implantable patient-activated and automatically-activated monitoring systems that records subcutaneous ECG. The Reveal XT Model 9529 is designed to automatically record the occurrence of arrhythmias in a patient. Arrhythmia may be classified as atrial tachyarrhythmia/atrial fibrillation (AT/AF), bradyarrhythmia, asystole, or (fast) ventricular tachyarrhythmia.
149904	Medtronic Australasia Pty Ltd	6/2/2008	Reveal DX	The Reveal DX model 9528 insertable cardiac monitors are implantable patient-activated and automatically-activated monitoring systems that records subcutaneous ECG. The Reveal DX Model 9528 is designed to automatically record the occurrence of arrhythmia in a patient. Arrhythmia may be classified as bradyarrhythmia, asystole, or (fast) ventricular tachyarrhythmia. In addition, the Reveal DX can be activated by the patient to record cardiac rhythm during symptomatic episodes.

Source: [Therapeutic Goods Association](#)

<sup>#</sup>ARTG details could not be found for this product.

Abbreviations: no., number

## 11) Decision analytic

*Provide a summary of the PICO as well as the health care resource of the comparison/s that will be assessed, define the research questions and inform the analysis of evidence for consideration by MSAC (as outlined in Table 9).*

### *Summary of the PPICO*

The proposed patient population for this medical service is patients with CS and suspected AF. Given that CS is a diagnosis of exclusion, the minimal work-up required to make the diagnosis of CS should be well defined. Therefore, it is appropriate to add the 'P' of 'prior-tests' to the PICO summary. These prior tests apply to the proposed service and the comparator. This summary of PPICO to define the research questions is detailed in Table 9.

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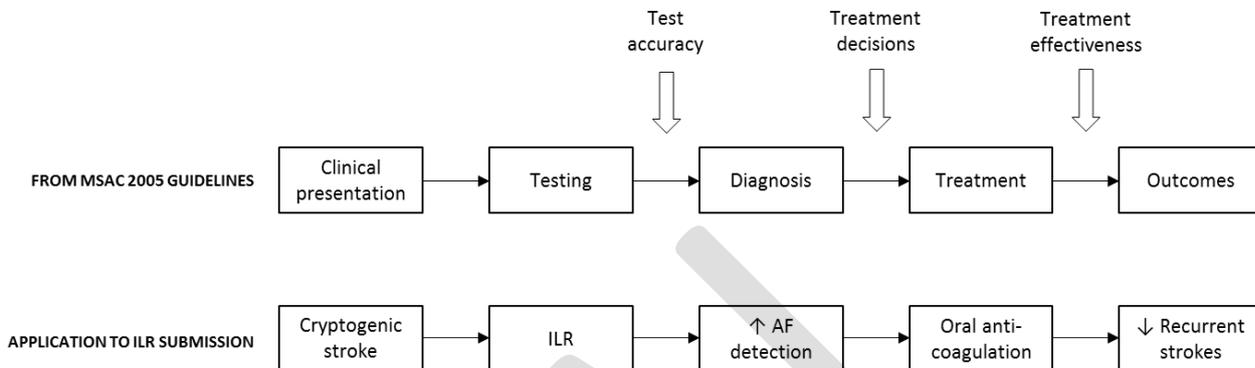
**Table 9 Summary of PPICO to define research question**

PPICO	Comments
<p>Prior-tests</p> <ul style="list-style-type: none"> <li>• A diagnosis of cryptogenic stroke has been made based on results of:               <ul style="list-style-type: none"> <li>- The medical history</li> <li>- Physical examination</li> <li>- Brain and carotid imaging</li> <li>- Cardiac imaging</li> <li>- Surface ECG testing which may include 24-hour Holter monitoring</li> <li>- Other tests as indicated</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• A framework for developing this indication is provided by MBS item number 38285, ILR for the diagnosis of primary disorder in patients with recurrent unexplained syncope.</li> </ul>
<p>Patients</p> <ul style="list-style-type: none"> <li>• For diagnosis of atrial fibrillation in patients with cryptogenic stroke where atrial fibrillation is suspected and recent (&lt;90 days) episode of stroke</li> </ul>	<ul style="list-style-type: none"> <li>• This proposed patient population is consistent with the pivotal trial evidence base from the CRYSTAL AF trial (Sanna et al., 2014)</li> </ul>
<p>Investigation</p> <ul style="list-style-type: none"> <li>• Implantable loop recorders (ILRs)</li> </ul>	<ul style="list-style-type: none"> <li>• Several ILRs are currently available on Part C of the Prosthesis List with a Minimum Benefit of \$3,900.00 (08.14.01 - Implantable Cardiac Event Recorders),</li> </ul>
<p>Comparator</p> <ul style="list-style-type: none"> <li>• Conventional follow-up (no further investigation or 24-hour Holter monitor)</li> </ul>	<ul style="list-style-type: none"> <li>• The application will assess the applicability of the key trial comparator arm (conventional follow-up) to the Australian setting. That is, whether the trial circumstances if use and patient population reflects current Australian clinical practice.</li> </ul>
<p>Outcomes</p> <ul style="list-style-type: none"> <li>• Primary outcome from key clinical trial               <ul style="list-style-type: none"> <li>○ AF detection rates</li> </ul> </li> <li>• Secondary patient-relevant health outcomes               <ul style="list-style-type: none"> <li>○ Change in clinical management (anticoagulation vs. antiplatelet therapy)</li> <li>○ Incidence of recurrent stroke</li> <li>○ Life years (LYs) quality-adjusted life years (QALYs) (modelled using the linked evidence approach)</li> </ul> </li> <li>• Diagnostic accuracy outcomes (for detection of AF)               <ul style="list-style-type: none"> <li>○ Sensitivity, specificity, negative and positive predictive values</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• The outcomes assessed in the key trial (CRYSTAL AF) are relevant because they reflect the decision making process in current clinical practice. Specifically, if AF is detected in a patient with CS, then it is recommended that oral anticoagulation is initiated</li> </ul>

### Overview of proposed approach

The approach taken in the submission will therefore be a linked evidence approach as per 2005 MSAC Guidelines (MSAC, 2005). This approach and its application to this submission is illustrated in Figure 8.

**Figure 8 Proposed linked evidence approach for submission**



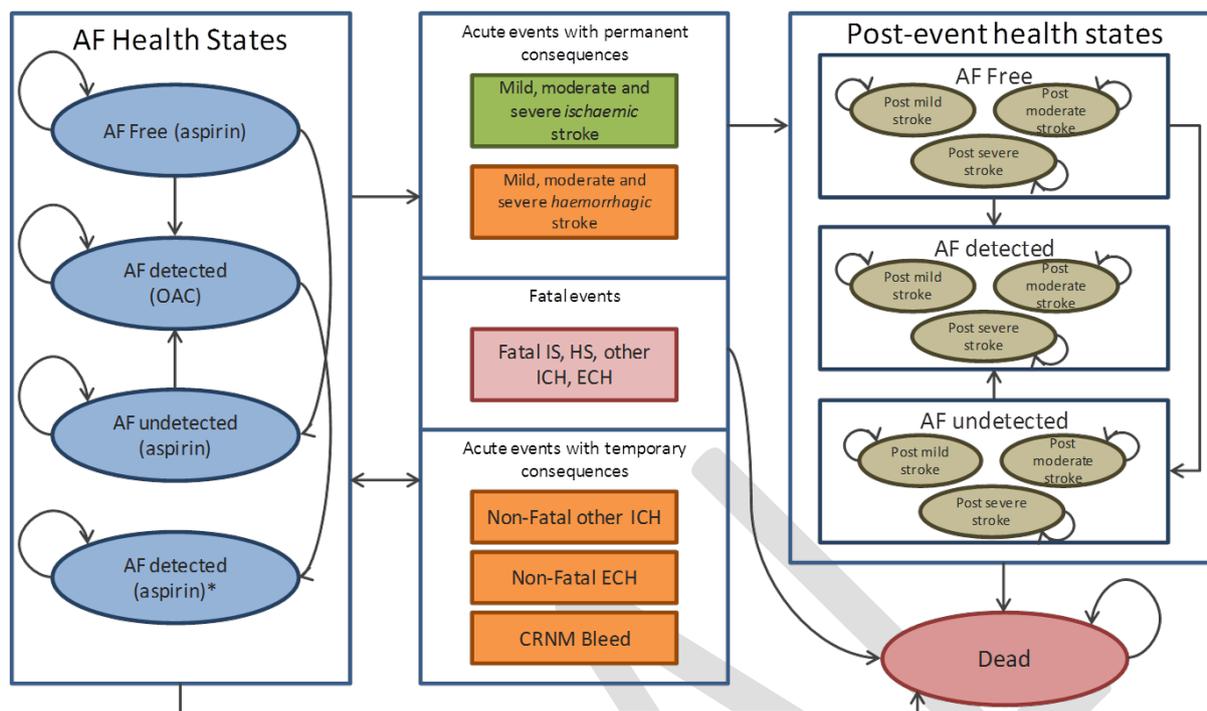
Adapted from: MSAC, 2005

### Proposed economic evaluation

A linked evidence approach will be taken to derive patient-relevant outcomes in terms of life years and quality-adjusted life years (QALYs). The fundamental elements to be captured by the employed approach are presented in Figure 8 above.

The underlying premise of the economic model is that the use of ILRs among cryptogenic strokes will lead to an effective and safe use of anticoagulation treatments (e.g., warfarin and newer oral anticoagulation therapies such as dabigatran) among patients with AF, which in turn reduces the risk of recurrent stroke. That is, ILRs offer an improved identification of patients with AF who would benefit from the use of anticoagulation therapies, facilitating the effectiveness and safety of secondary stroke prevention. The model also captures possible AEs caused by anticoagulation treatments (i.e., bleeds). The overview of the modelling approach planned for the submission is presented in 9 below. The model will also have a time horizon of life of the patient, as the improved clinical outcomes as a result from the new management pathway post ILR implantation continue to benefit the patient after the device's battery depletes.

**Figure 9 Overview of the modelling approach planned for the submission\***



\*Note: The modelling approach has not been finalised yet at this stage, and the presented figure is indicative only.

## 12) Healthcare resources

*Using Table 10 provide a list of the health care resources whose utilisation is likely to be impacted should the proposed intervention be made available as requested whether the utilisation of the resource will be impacted due to differences in outcomes or due to availability of the proposed intervention itself.*

As set out above, the extent and type of expertise / procedural complexity and duration in relation to provision of the proposed service (including device implantation and patient follow-up) are likely to be similar between the proposed indication and the existing syncope indication (MBS item 38285).

*Further details of resource use will be identified during the assessment phase of this application.*

## 13) Questions for public funding

*Please list questions relating to the safety, effectiveness and cost-effectiveness of the service / intervention relevant to this application.*

Questions related to ILR use in patients with CS that are relevant to this application include:

- Have all potential cost-savings been identified?
- Have all the resources been identified?
- What tests are necessary for the diagnosis of CS?
- Is the proposed population appropriate?
- What investigations are used in conventional follow-up of CS?

**Table 10 List of resources to be considered in the economic analysis**

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
<b>Resources provided to identify eligible population - these are the same for the proposed service and the comparator</b>										
Brain imaging (e.g. CT, MRI)	Private or Public Hospital	Radiology clinic/department	100%	Generally one-off	CT: 56001 \$195.05 MRI: 63064 \$403.20					
12-lead ECG for AF detection	Private or Public Hospital	Stroke service	100%		11700: \$31.25					
Ambulatory ECG monitoring (eg, Holter)	Private or Public Hospital, cardiologist / neurologist	Stroke service	100%		11708-11711: \$28.30 - \$167.45 (see Table 7)					
Brain and carotid imaging (e.g. CTA, MRA, TTE, TEO)	Private or Public Hospital	Radiology clinic/department	100%		CTA: 57350 \$510.00 MRA: 63101 \$492.80 TTE: 55114 \$230.65 TEO: 55125 \$137.75					
Blood tests	Private or Public Hospital	Stroke service	100%		Blood tests and coagulation studies: 65129 and/or 65070 \$35.50/\$16.95					
<b>Resources provided to deliver proposed intervention (See Section 4 above for more information)</b>										
Inplantation	Cardiologist, electrophysiologists etc	Private or Public Hospital, Day surgery (see Table 5)	100%		\$192.90 (proposed)					
Local anaesthesia	Anaesthetist		100%		20400: \$59.40.00					
Theatre / bed cost and general consumables: e.g. dressings	Private or Public Hospital		100%							
Follow-up consultation	Cardiologist	Private or Public Hospital, Doctor's office.	100%		\$34.75 (proposed)					

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
<b>Resources provided in association with proposed intervention</b>										
Management of adverse events (e.g., infection, pain, irritation, inflammation)	GP / cardiologist	GP / Doctor's office	Less than 2% (see "Describe any potential risks to the patient" above)		Level A consultation: \$16.95 \$34.75 (proposed; if provided as a part of follow-up consultation)					
Explantation	Private or Public Hospital	Private or Public Hospital, Day surgery (see Table 5)	100%		38286: \$173.75					
<b>Resources provided to deliver SOC</b>										
Ambulatory ECG monitoring (eg, Holter)	Private or Public Hospital, cardiologist / neurologist	Private or Public Hospital, Doctor's office.	Ad hoc		11708-11711: \$28.30 - \$167.45 (see Table 7)					
<b>Resources provided in association with SOC</b>										
Follow up consultations	Cardiologist	Private or Public Hospital, Doctor's office.	Ad hoc		53: \$21.00 54: \$38.00					
<b>Resources used to manage patients diagnosed with AF using the proposed intervention or the comparator SOC<sup>1</sup></b>										
Anticoagulation therapy	Specialist / GPs	Outpatient / PBS	High (unless contraindicated) with AF positive	Long-term			PBS: Dabigatran at \$91.77 / month (example)			

\* Include costs relating to both the standard and extended safety net.

Abbreviations: AE, adverse event; AF, arterial fibrillation; CT, computed tomography; CTA, computed tomography angiogram; ECG, electro cardiogram; ED, emergency department; ILR, implantable loop recorder; MRI, magnetic resonance imaging; MRA, magnetic resonance angiogram; SOC, standard of care; GA, general anaesthesia; TTE, transthoracic echocardiography; TEO, transoesophageal echocardiography.

<sup>1</sup> All identified AF cases receive the same care regardless the mode of diagnosis (i.e., ILR or SoC). More AF cases will be identified via ILR.

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## Appendix 1: The CHA<sub>2</sub>DS<sub>2</sub>-VASc stroke risk tool

**Table 11** The CHA<sub>2</sub>DS<sub>2</sub>-VASc stroke risk tool

	<b>Condition</b>	<b>Points</b>
C	Congestive heart failure (or Left ventricular systolic dysfunction)	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A <sub>2</sub>	Age ≥75 years	2
D	Diabetes Mellitus	1
S <sub>2</sub>	Prior Stroke or TIA or thromboembolism	2
V	Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (i.e. female sex)	1

Source: Lip et al. (2010), Friberg et al. (2013), Olesen et al. (2011)

## Appendix 2: Training requirements for insertion and follow-up ILRs

Attached PDF: The Cardiac Society of Australia and New Zealand (CSANZ) (2013) Guidelines for sub-specialty training in cardiac implantable electronic devices: selection, implantation and follow-up.



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