Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1374.1 – Subcutaneous implantable cardioverter defibrillator therapy for prevention of sudden cardiac death

Applicant: **Boston Scientific Pty Ltd**

Date of MSAC consideration: **MSAC 81st Meeting, 31 March – 1 April 2021**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

A resubmission requesting Medicare Benefits Schedule (MBS) listing for the insertion of a subcutaneous implantable cardioverter defibrillator (S-ICD) lead (electrode) for the prevention of sudden cardiac death (SCD) was received from Boston Scientific by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC deferred its advice on the creation of a new MBS item for the insertion of an S-ICD lead for the prevention of SCD. MSAC considered the evidence demonstrated that S-ICD therapy had a different safety profile to the comparator transvenous ICD (TV-ICD) therapy. MSAC was inclined to accept that S-ICD had similar clinical effectiveness, but noted longer-term data remains lacking. MSAC anticipated there may be a subpopulation of patients with a high clinical need who would benefit from the device – however, considered that this subpopulation needs to be clearly defined in an MBS descriptor and that data for effectiveness in this subpopulation were lacking. MSAC also noted issues with the economic modelling that resulted in uncertain cost-effectiveness. MSAC considered that additional clinical data and revised economic analysis should be provided via ESC.

Consumer summary

This application from Boston Scientific Pty Ltd seeks to create a new Medicare Benefits Schedule (MBS) item for the insertion, removal or replacement of a subcutaneous implantable cardioverter defibrillator (S-ICD) lead to prevent an event known as sudden cardiac death (SCD). SCD is an unexpected death due to sudden loss of heart function. It is mainly caused by irregularity in the body's electrical signals that trigger the heart to beat normally.

Implantable cardioverter defibrillator (ICD) therapy uses a device to monitor a patient's heart function: if it detects irregularities in heartbeat, it will electrically shock (defibrillate) the heart to correct it. Irregular heartbeats can lead to the heart not pumping properly or not at all, which will result in death unless treated quickly. The device used for ICD therapy consists of two parts, an ICD generator and an ICD lead (electrode) that are both inserted into the chest. The ICD generator and lead detect the heart function. When required, the ICD generator creates the electric shock, which is delivered to the heart via the ICD lead.

There are two types of ICD therapies. One is called a transvenous ICD (TV-ICD), where the lead is inserted into the heart. The other type is called a subcutaneous ICD (S-ICD), where the lead is placed under the skin in the middle of the patient's chest.

The advantage of the S-ICD lead is that it is less invasive because it does not need to be put into the heart. This means there is less risk for infection and less risk for patients where it is difficult to reach the heart because of the shape of their blood vessels, or the shape of the heart itself. However, unlike TV-ICD, S-ICD cannot regulate the speed of the heartbeat. This means it cannot be used for pacing like a pacemaker to deliver constant electrical impulses to stimulate the heart and maintain constant heartbeats if the heart is pumping too slowly.

A side effect of all ICDs is that sometimes they can 'over sense' and deliver an electrical shock when it isn't required, called an 'inappropriate shock'. MSAC noted that patients can be left psychologically affected by these experiences and the trial results indicated that patients with S-ICD experienced more of these 'inappropriate shocks' than people with a TV-ICD.

The S-ICD procedure costs more than the TV-ICD procedure, and the S-ICD generator has a shorter battery life than the TV-ICD generator.

MSAC accepted that there appears to be a small group of patients, with a high need to avoid the risks associated with implanting a TV-ICD lead in the heart, who would benefit from the S-ICD. However, MSAC considered that more information is required from experts who use this technology to more clearly define which patients would benefit from S-ICD and to confirm the comparative effectiveness and cost-effectiveness of S-ICD for these patients.

MSAC's advice to the Commonwealth Minister for Health

MSAC deferred its advice on creating a new MBS item for insertion of a subcutaneous lead for S-ICD therapy for prevention of sudden cardiac death. This is because there was not enough evidence to be certain that S-ICD therapy is at least as clinically effective as a TV-ICD therapy and the economic impact was also uncertain. MSAC has asked the applicant to provide more data so that MSAC can make a decision in the future.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application is a resubmission requesting a new MBS item for the insertion, removal or replacement of S-ICD lead for the prevention of SCD. MSAC recalled that this application was previously considered by MSAC in November 2014 but was not supported for public funding because of uncertain comparative long-term safety and clinical effectiveness which translated into uncertain cost-effectiveness.

MSAC noted the proposed population is patients who require treatment of life-threatening ventricular arrhythmia and who do not require pacing therapy. MSAC noted that these patients are currently treated with TV-ICD therapy and that the claimed clinical need for S-ICD is in a subpopulation of the proposed population, e.g. patients who are eligible for TV-ICD (with no indication for pacing) who are reluctant to attempt or re-attempt TV-ICD due to the risks associated with TV-ICD lead insertion (e.g. difficult venous anatomy, a high risk of infection, paediatric). MSAC noted that the main source of evidence to support this resubmission, the PRAETORIAN[1] trial, excluded this subpopulation of patients but MSAC considered the PRAETORIAN trial results are likely to be generalisable to this subpopulation of patients.

MSAC noted that S-ICD therapy is currently provided in public hospitals to this subpopulation, generally young patients who do not require pacing and have no evidence of T wave over-sensing. MSAC noted local experience is that approximately 30% of patients undergo exercise stress testing to screen for T wave over-sensing as this can increase the chance of inappropriate shocks. MSAC considered that data on the utilisation of S-ICD from public hospitals should be sought. MSAC also noted that international Clinical Practice Guidelines[2] recommend S-ICD therapy in patients who meet criteria for an ICD who have inadequate vascular access or are at high risk for infection, and in whom pacing for bradycardia or VT termination or as part of CRT is neither needed nor anticipated. MSAC considered that the population in the proposed MBS item descriptor required revision to restrict the population to the subpopulation with high clinical need for S-ICD and should specify inclusion/exclusion criteria and align with recommendations of the MBS Review Taskforce[3]. MSAC also suggested the item could specify patients who have no anticipated need for pacing within the next 10 years.

MSAC noted that a separate item descriptor for removal of the S-ICD lead had not been proposed. MSAC noted that a separate item descriptor for removal of an TV-ICD lead is in recognition of the complexity and risks of the procedure to remove the TV-ICD lead that is implanted in the right ventricle, e.g. risk of cardiac perforation and need for cardiac surgical support, which do not apply to S-ICD. MSAC noted, in the pre-MSAC response, the applicant indicated their willingness to work with the Department to develop a revised item descriptor that is restricted to the high need clinical subpopulation and provides clarity regarding replacement procedures. MSAC recommended that clinical societies such as the Cardiac Society of Australia and New Zealand should be consulted during the revision of the MBS item descriptor.

MSAC noted the clinical evidence presented in the applicant developed assessment report (ADAR) consisted of one open-label non-inferiority randomised clinical trial (RCT;

[1] A PRospective, rAndomizEd Comparison of subcuTaneOous and tRansvenous ImplANtable Cardioverter Defibrillator Therapy (PRAETORIAN) - NCT01296022
[2] Al-Khatib SM, et al. (2017) Journal of the American College of Cardiology.72(14):e91–220
[3] MBS Review Taskforce: Final Report from the Cardiac Services Clinical Committee [CSCC], 2018

PRAETORIAN[4] trial). MSAC also noted that there were plans for future data (recurrent event analysis and quality of life) to be published from this trial and that all participants have been invited to participate in the PRAETORIAN XL study, an observational sub-study extending the follow-up and planning to report on in-appropriate shocks, lead-related complications and the development of an indication for pacing.

In regard to comparative safety, MSAC noted the ADAR claimed S-ICD has non-inferior safety compared to TV-ICD. However, MSAC noted there were wide confidence intervals for the primary outcome in the PRAETORIAN trial, so MSAC considered that either substantial benefit or harm could not be ruled out. In addition, some patients will require multiple replacements, but there were no data on safety of replacement procedures.

MSAC also noted that the pre-MSAC response provided further data, including a systematic review by Rordorf (2021)[5] which included 13 studies (1 randomised controlled trial (RCT) and 12 observational, N = 9073 patients). MSAC noted that the authors concluded that TV-ICD and S-ICD were overall comparable in terms of the composite of clinically relevant device-related complications and inappropriate shock in patients with an indication for ICD without the need for pacing. However, MSAC noted that the safety profile of S-ICD is different to TV-ICD. There were more lead-related complications with TV-ICD but more pocket related complications with S-ICD. Further, while the rate of inappropriate shocks appeared the same, there were more inappropriate shocks due to over-sensing with S-ICD. MSAC noted the inappropriate shocks due to over sensing as an important issue, noting that inappropriate shocks can traumatise very young people. MSAC noted new generations of the S-ICD device include a high-pass sensing filter (SMART Pass) that aims to reduce cardiac over-sensing. The pre-MSAC response presented a cohort study by Theuns (2018)[6] that concluded the SMART Pass filter reduced the rate of inappropriate shocks with S-ICD. MSAC noted that this was not a RCT but does suggest the SMART Pass reduces inappropriate shocks.

MSAC also noted that in December 2020, the Therapeutic Goods Administration (TGA) issued a Class I hazard alert for the EMBLEM S-ICD subcutaneous electrode (Model 3501) regarding potential issues with electrode body fractures (i.e. a crack in the lead). MSAC noted that the product remains on the Australian Register of Therapeutic Goods (ARTG) (i.e. the hazard alert is not a full product recall), and that as per the hazard alert instructions, Boston Scientific has issued advice to healthcare professionals to be aware of this potential issue. Information issued to healthcare professionals included recommendations for the prompt identification of a potential electrode body fracture, as well as in evaluating the competing risks of alternative treatments for preventing SCD. MSAC advised that the Department follow up with the TGA to confirm resolution of this matter and request the applicant to provide any updated data/information that contributes to the resolution of this matter.

Overall, MSAC considered that S-ICD had a different safety profile to TV-ICD, that the non-inferior safety claim was not fully supported and that longer-term data on lead complications, all shocks and battery life is required.

In regard to comparative effectiveness, MSAC noted the ADAR's claim of non-inferior clinical effectiveness for preventing SCD. MSAC noted that the PRAETORIAN trial reported

[4] A PRospective, rAndomizEd Comparison of subcuTaneOous and tRansvenous ImplANtable Cardioverter Defibrillator Therapy (PRAETORIAN) - NCT01296022

[5] Rordorf R, et al. (2021) Heart Rhythm. 18(3):382–391, https://doi.org/10.1016/j.hrthm.2020.11.013

[6] Theuns D, et al (2018) Heart Rhythm. 15(10):1515-1522

that there was no difference in the deaths for all-cause or for SCD between S-ICD and TV-ICD. However, MSAC noted that these outcomes were secondary endpoints that were under-powered. MSAC also noted that more patients crossed-over from S-ICD to TV-ICD than vice versa, suggesting patients cross over to TV-ICD due to developing an indication for pacing. MSAC noted the pre-MSAC response presented a propensity score matched study using patients from the MIDAS TV-ICD study and EFFORTLESS S-ICD registry which indicated that there were no differences in physical or mental QoL up to 6 months (Pederson 2016[7]). Overall, MSAC considered that S-ICD probably has similar comparative clinical effectiveness to TV-ICD but that further data are required, in particular data on patient quality of life and long term data on the conversion to TV-ICD.

MSAC noted the ADAR presented a cost-minimisation analysis comparing S-ICD with TV-ICD, which was revised in the pre-ESC response to apply defibrillation testing (DFT) costs based on MBS item 38212 and DFT rates from the PRAETORIAN trial: 90.4% for S-ICD and 46.1% for TV-ICD. This showed a revised cost saving of $**redacted**. However, MSAC agreed with ESC that it was inappropriate that the model assumed a similar battery length between the S-ICD and TV-ICD and did not include any costs for battery replacement. MSAC noted that the sensitivity analysis in the Commentary tested different battery life assumptions, 6 years for S-ICD versus 10 years for TV-ICD, which indicated S-ICD was no-longer cost saving (i.e. cost of $**redacted** more than TV-ICD). Overall, MSAC considered the cost-effectiveness of S-ICD, in particular in the longer-term, was uncertain and that a revised cost-minimisation analysis was required that included: a 20-year time horizon, battery lifespans for both devices' current models, costs for exercise stress testing to screen for T wave over-sensing in patients being considered for S-ICD (assume rate should be 30%), ongoing conversion to TV-ICD based on registry data, and DFT and GA rates based on local experience.

MSAC noted that a market-share approach was used to estimate the budget impact of MBS listing of the S-ICD lead that assumes substitution of 10% of the TV-ICD market in Year 1 increasing to 20% in Year 3. MSAC noted that there are very few (if any) patients who are unable to receive TV-ICD and accepted that S-ICD would be a substitute in a subgroup of patients who are eligible for TV-ICD. MSAC noted that if the proportion of S-ICD patients who develop a pacing indication is larger than expected, there will be more crossovers to TV-ICDs, which will increase costs to private health insurers. Overall, MSAC considered the estimated impacts to the MBS and PL were uncertain.

MSAC advised that an ADAR submitted for reconsideration should focus on the issues raised by MSAC (Table 1) and could re-enter the MSAC pathway at the assessment stage (i.e. ADAR lodged for ESC consideration).

[7] Pederson SS, et al. (2016) American Journal of Cardiology. 118(4):520-526

Table 1 Items to be resolved before reconsideration.

Item	MSAC advice to applicant for addressing in a resubmission
MBS item descriptor	Revision of the MBS item descriptor to restrict the population to the subpopulation with high clinical need for S-ICD and should specify inclusion and exclusion criteria, and align with recommendations of the MBS Review Taskforce. Clinical society consultation should be sought on the inclusion and exclusion criteria to define the high need clinical subgroup to be included in the item descriptor.
Uncertain safety and effectiveness	Provide additional data: • PRAETORIAN trial data on Quality of life data (SF-36, Duke Activity Status Index questionnaires at 30 months) and all shocks. • Longer-term registry follow-up data on conversion to TV-ICD, battery life, shocks, and lead complications. • Public hospital data on current S-ICD utilisation.
Cost-minimisation analysis	Revise the economic analysis to include: • a 20 year time horizon • costs for exercise stress testing to screen for T wave over-sensing in patients being considered for S-ICD (assume rate should be 30%) • different battery lives (current models) • ongoing conversion to TV-ICD based on registry data • DFT and general anaesthesia rates based on local experience.
Recent TGA recall on S-ICD lead	Confirmation that TGA recall has been resolved and provide any updated data/information that contributes to the resolution of this matter

4. Background

This is the first resubmission for MSAC Application 1374, which sought assessment of the S-ICD therapy system and proposed the creation of a new MBS item for insertion of the S-ICD lead (electrode). MSAC considered Application 1374 in November 2014 (MSAC Application 1374 Public Summary Document [PSD]). At that time, MSAC did not support public funding for S-ICD because of uncertain comparative long-term safety and clinical effectiveness, which translated into uncertainty in the economic analysis. MSAC suggested the results from a large, prospective, multi-centre, randomised trial (PRAETORIAN) – which was underway at the time of MSAC consideration – may help to address the uncertainties.

An ADAR was resubmitted (MSAC Application 1374.1) following the publication of the findings from the PRAETORIAN trial (Knops et al. 2020[8]). The key issues raised in the MSAC Application 1374 PSD, and how these were addressed in the resubmission (MSAC 1374.1), are outlined in Table 2.

[8] Knops, RE et al. (2020) The New England Journal of Medicine, 383:526-536.

Table 2 Key concerns raised in 2014 Public Summary Document for Application 1374 and addressed in the resubmission

	Issue for MSAC	Resubmission conclusions [from ADAR Table ES-2]	Assessment Group comments
1	S-ICD therapy is an alternative option to TV-ICD for patients that do not require pacing therapy and in whom insertion of a TV-ICD is not ideal or feasible.		*Not resolved. The implication is that S-ICD is intended for a subpopulation with a high clinical need for an alternative to TV-ICD. The proposed descriptor is for a broader population and the clinical evidence is in a broader population (and possibly excludes the 'high needs' subpopulation).*
2	The evidence base for evaluation of the comparative safety and effectiveness for S-ICD was limited and based on small, non-randomised, unblinded studies with short-term follow-up and surrogate (largely technical) endpoints.	PRAETORIAN is a large (N=849) randomised non-inferiority trial comparing S-ICD and TV-ICD. At median follow-up of 49.1 months, there were no statistically significant differences between treatment arms for the composite primary endpoint (device related complications or inappropriate shocks), with 15.1% patients experiencing events in the S-ICD group and 15.7% in the TV-ICD group (HR = 0.99 [95% CI: 0.71, 1.39; p=0.95]). The non-inferiority margin was 1.45, indicating S-ICD is non-inferior to TV-ICD with respect to the primary endpoint (p=0.01).	*Resolved. An RCT is now available, although not all uncertainties have been resolved because the median duration of follow-up was only 49.1 months, which is insufficient to evaluate longer-term outcomes including revision, replacement and switching.*
3	This limited evidence raised a number of uncertainties such as: • levels of inappropriate shock (for short-term studies)	There was a slightly higher rate of inappropriate shocks for S-ICD (9.7%) compared to TV-ICD (7.3%); however, the rate was not statistically significant (HR = 1.43 (95% CI: 0.89, 2.30). The inappropriate shocks include 24 patients (5.6%) who experienced cardiac oversensing (including T-wave and P-wave oversensing and shock below the detection limit). It should be noted this result overestimates the true rate of inappropriate shocks due to the lack of SMART PASS technology, which was shown by Theuns (2018) to reduce the risk of first inappropriate shocks (HR=0.502) and all inappropriate shocks (HR=0.320). The low rate of inappropriate shocks with SMART PASS technology (one (0.1%) at 30 days) was demonstrated in the UNTOUCHED registry study (Boersma, 2019).	*Not satisfactorily resolved. There are residual concerns because the PRAETORIAN publication reported the first occurrence of an event (i.e., 'first' inappropriate shock), not 'all' inappropriate shocks (recurrent event analysis).* *The effectiveness of the SMART Pass filter in reducing inappropriate shocks has not been confirmed in an RCT.*
4	• effect of physical activity (especially contact sport)		*Not resolved.*
5	• potential for increased complications with S-ICDs vs TV-ICDs	There was a trend towards an improved rate of device related complications in the S-ICD arm (5.9%) compared to the TV-ICD arm (9.8%) (HR = 0.69 [95% CI: 0.44, 1.09]). S-ICD had lower rates of most device related complications including infection, pneumothorax, lead perforation, tamponade, lead repositioning and lead replacement. TV-ICD had lower rates of bleeding, fewer sensing issues and the development of pacing indications.	*Not satisfactorily resolved. A comparative analysis of complications is presented in the ADAR, although follow-up in the PRAETORIAN trial was too short to capture chronic complications.*
6	• effect of larger sized automatic defibrillator and position of subcutaneous lead on patient		*Not resolved.* *The issue was indirectly addressed in the ADAR in terms of QoL but was not*

	Issue for MSAC	Resubmission conclusions [from ADAR Table ES-2]	Assessment Group comments
	experience and discomfort levels.		*explicitly addressed. It is noted that current (3rd) generation devices are less bulky (20% thinner) than 1st generation devices.*
7	• potential for T-wave oversensing with S-ICDs		*Not satisfactorily resolved. This issue was not explicitly addressed in the ADAR, but T-wave oversensing is one of the most frequent causes of inappropriate shocks. Patient screening for suitability for S-ICD can identify (and exclude) patients with the potential for T-wave oversensing.*
8	• rates of lead migration/ dislodgement	Lead repositioning occurred in 0.5% of patients in the S-ICD study arm and 1.7% of patients in the TV-ICD study arm (HR = 0.28 [95% CI: 0.06, 1.36]). Lead replacement was required in 0.7% of patients in the S-ICD study arm and 2.1% of patients in the TV-ICD study arm (HR = 0.33 [95% CI: 0.09, 1.21]).	*Not satisfactorily resolved. The duration of follow-up in the PRAETORIAN trial was insufficient to fully assess lead-related complications.*
9	• use of surrogate efficacy endpoints (technical performance and safety of ICD) in the absence of patient-relevant outcomes such as SCD and overall death	During the course of the trial, 83 (16.4%) patients in the S-ICD arm and 68 (13.1%) in the TV-ICD arm died (HR = 1.23; 95% CI: 0.89, 1.70). Of these, 52 (12.2%) patients in the S-ICD arm and 46 (10.9%) in the TV-ICD arm died of cardiovascular causes.	*Resolved. The primary efficacy outcomes specified in the PICO (ratified by PASC in 2014) were technical outcomes. The ADAR focuses on patient-relevant safety and efficacy outcomes reported in the PRAETORIAN trial.*
10	• no HRQoL outcomes were provided.	A comparison between QoL measured with the Short-Form Health Survey in the EFFORTLESS registry and a matched cohort of patients with TV-ICD was undertaken. Patients with an S-ICD did not differ significantly on physical (p=0.8157) and mental QoL scores (p=0.9080) across baseline, 3, and 6 months after implantation in adjusted analyses.	*Not satisfactorily resolved. 12-month QoL data from the EFFORTLESS registry and a matched cohort (MIDAS study) were published in 2019 but not included in the ADAR. These data have been extracted and included in the commentary.* *QoL data from PRAETORIAN have not yet been published.*
11	Not convinced that the claim of S-ICD non-inferiority had been proven in terms of comparative safety and effectiveness. The long-term safety of S-ICD was particularly uncertain due to the limited follow-up in the studies presented. The results from a large prospective, multi-centre, RCT (PRAETORIAN) due for completion in June 2018 may help to address the uncertainties.		*Not fully resolved. PRAETORIAN is a non-inferiority trial that directly compares S-ICD with TV-ICD, although longer-term follow up is warranted and is ongoing. Further publications from PRAETORIAN are expected (e.g., recurrent event analysis; QoL). An extension study to 8 years' follow-up (PRAETORIAN XL observational sub-study) is expected to be completed in 2024.*
12	Questioned the ability of the current data set to address the assumption of non-inferior safety and clinical effectiveness and therefore considered that this uncertainty flowed on to the economic evaluation as the CMA was presented based on an assumption of non-inferiority between the two ICD devices.		*Not fully resolved. The inputs in the CMA are largely sourced from the PRAETORIAN non-inferiority trial. Any uncertainty in the clinical claim of non-inferiority will flow on to the CMA.*
13	It was noted that this estimation [of total health care costs] was reliant on the accuracy of the number of eligible patients and uptake of S-ICD in Australia.		*Not satisfactorily resolved. The ADAR assumes substitution of a proportion of TV-ICD use with S-ICD but does not acknowledge the potential for growth in the market.*
14	The assumptions for similar resource use for S-ICD compared to TV-ICD may not be reasonable as S-ICD lead insertion is relatively straightforward and would take half		*Not satisfactorily resolved. The ADAR proposes a fee for S-ICD lead insertion that is the same as the fee for TV-ICD lead insertion, based solely on procedure time.*

	Issue for MSAC	Resubmission conclusions [from ADAR Table ES-2]	Assessment Group comments
	the time of TV-ICD. Therefore, the fee reduction may be too small in recognition of the simpler and shorter procedure time of S-ICD relative to TV-ICD procedures.		
15	Sensitivity analyses on the uncertainties identified indicated that fewer cost savings for MBS would occur for listing S-ICD therapy if there was increased market growth, greater switching from S-ICD to TV-ICD and x-ray costs were included.		*Not fully resolved. The financial analysis in the ADAR includes x-ray costs but does not include sensitivity analyses around increased market growth or greater switching to S-ICD.*
16	Other factors also had the potential to impact on the economic modelling and increase financial uncertainty around this intervention such as: • outcome data limited to under five years		*Not resolved. The median follow-up in the PRAETORIAN trial is less than 5 years. Refer to Issue 2.*
17	• overestimated proposed fee for S-ICD lead placement		*Not satisfactorily resolved. Refer to Issue 14*
18	• underestimation of patients that will develop pacing requirements after S-ICD insertion		*Not satisfactorily resolved. This relates to insufficient duration of follow-up. Refer to Issue 2 and Issue 16.*
19	• reduced battery life due to higher defibrillation threshold.		*Not fully resolved. There are residual concerns around the assumption of similar battery life for S-ICDs and TV-ICDs, based on expert advice and manufacturer warranty periods.*
	Other concerns raised in the PSD		
20	The lack of subgroup analysis of younger patients who represent an additional population if MBS listed. [PSD p.5]		*Not resolved. Not addressed in the ADAR.*
21	All RRs were close to or less than 1.0 and in favour of S-ICD and none were statistically significant. MIDs for these outcomes were not considered. [PSD p.6]		*Not fully resolved. The non-inferiority margin was reported in the ADAR for the primary outcome of the PRAETORIAN trial but MIDs for other outcomes were not discussed or defined.*
22	The application provided no pre-modelling studies for the CMA. The applicability of the included studies to the Australian population may be a concern, due to the lack of Australian study data. [PSD p.8]		*Not resolved. No translation issues were addressed in the ADAR. The applicability of the PRAETORIAN trial was not addressed despite it having no Australian study sites.*
23	The appropriateness of not including detailed patient inclusion criteria in the proposed MBS item descriptor for S-ICD lead service provision (in contrast to TV-ICD MBS item descriptors). [PSD p.10]		*Not satisfactorily resolved. The proposed descriptor is consistent with the 2014 Protocol for Application 1374 but a rationale for omitting the indication for ICD therapy is not provided in the ADAR.*

Source: Adapted from Table 9, p29 of the commentary; based on the PSD for Application 1374 and Table ES-2, p.16 (also reproduced as Table A-2, p.29) of the ADAR, with commentary assessment in italics
Abbreviations: ADAR=Applicant developed assessment report; CI=confidence interval; CMA= cost-minimisation analysis; HESP=Health Expert Standing Panel; HRQoL=health-related quality of life; ICD=implantable cardioverter defibrillator; MBS=Medicare Benefits Schedule; MID=minimally important difference; PSD=Public Summary Document; QoL=quality of life; RCT=randomised controlled trial; RR=relative risk; SCD=sudden cardiac death; S-ICD=subcutaneous implantable cardioverter defibrillator; TV-ICD=transvenous implantable cardioverter defibrillator

5. Prerequisites to implementation of any funding advice

The S-ICD system components (automatic defibrillator, subcutaneous lead and programmer) are listed on the Australian Register of Therapeutic Goods (ARTG; Table 3). The ARTG includes 2nd generation (EMBLEM™ S-ICD model A209) and 3rd generation (EMBLEM™

MRI S-ICD model A219) devices. The 1st generation SQ-RX® S-ICD device is no longer included on the ARTG.

The EMBLEM™ MRI S-ICD (Model A219) is listed on the Prostheses List (PL) with a benefit of $28,398. No leads that can be used with the S-ICD are currently listed on the PL. The resubmission stated the applicant intends to **redacted**.

The ADAR stated implantation of an S-ICD device is clinically similar to the insertion of a TV-ICD in terms of staffing, and required infrastructure. As such, the necessary capabilities to perform S-ICD implantation are already established at the relevant clinics and institutions.

Table 3 S-ICD automatic defibrillators and associated leads and components listed on the ARTG

ARTG no. Start date	GMDN/ Product Category	Unique Product Identifier	Sponsor
286705 14/03/2017	35852 / Medical Device AIMD	EMBLEM™ MRI S-ICD A219 - Defibrillator, implantable, automatic	Boston Scientific Pty Ltd
260382 29/09/2015	35852 / Medical Device AIMD	EMBLEM™ S-ICD Pulse Generator Model A209 - Defibrillator, implantable, automatic	Boston Scientific Pty Ltd
291908 24/07/2017	35853 / Medical Device Class III	EMBLEM™ S-ICD Subcutaneous Electrode Model 3501 - Lead, defibrillator, implantable	Boston Scientific Pty Ltd
260384 29/09/2015	35853 / Medical Device Class III	EMBLEM™ S-ICD Subcutaneous Electrode Model 3401 - Lead, defibrillator, implantable	Boston Scientific Pty Ltd
260383 29/09/2015	47205 / Medical Device Class III	EMBLEM™ S-ICD Programmer Model 3200 - Cardiac pulse generator programmer	Boston Scientific Pty Ltd

Source: Table 11, p38 of the commentary, taken from the ARTG website (https://www.tga.gov.au/australian-register-therapeutic-goods), accessed 06 January 2021
Abbreviations: AIMD=Active implantable medical device; ARTG no.=Australian Register of Therapeutic Goods number; GMDN=Global medical device nomenclature; S-ICD=subcutaneous implantable cardioverter defibrillator
Note: The two devices that were included in the Final Protocol for Application 1374 (ARTG no. 219499 and 219500) are 1st generation models that are no longer included on the ARTG.

6. Proposal for public funding

A new MBS item is proposed for insertion, removal and replacement of subcutaneous leads for the S-ICD system. Separate MBS items already exist for services relating to insertion of an automatic defibrillator for primary prevention of SCD (MBS item 38387) and for secondary prevention of SCD (MBS item 38393).

The proposed MBS item descriptor and fee is provided in Table 4.

Table 4 Proposed MBS item descriptor

Category 3 – THERAPEUTIC PROCEDURES
SUBCUTANEOUS DEFIBRILLATOR LEAD, insertion, removal or replacement of, for prevention of sudden cardiac death in patients who do not have symptomatic bradycardia, incessant ventricular tachycardia, or spontaneous, frequently occurring ventricular tachycardia that is reliably terminated with antitachycardia pacing. Multiple ~~Services~~ *Operations* Rule (Anaes.) (Assist.)
MBS Fee: $1,085.55

Source: Table 3, pxiv of the commentary; based on Table A-4, p35 of the ADAR, with commentary amendment in italics and strikethrough

The proposed wording is identical to the wording in the final protocol for application 1374 (May 2014).

The Commentary noted that the submission intends for S-ICD to be used for primary and secondary prevention of SCD. However, the proposed descriptor does not contain the same detailed criteria for ICD therapy that is specified in the MBS items for TV-ICD lead insertion and allows for use in a broader population than were eligible for the PRAETORIAN trial. MSAC considered that the descriptor should include detailed patient inclusion and exclusion criteria. However, MSAC advised that clinical societies should be consulted on the population, noting that the 'high clinical need' for this device is much more likely in a narrower population to that proposed in the descriptor.

The resubmission proposed the same MBS service fee as for TV-ICD lead insertion under MBS item 38384 and 38390. The resubmission acknowledged that there are some differences between transvenous and subcutaneous lead placement, but they do not expect that these would result in appreciable differences in resource use or procedure time.

The pre-MSAC response advised the applicant is willing to work with the Department to develop a restriction that is clinically appropriate and consistent with the clinical evidence. This may involve restricting the eligible population to those aged ≥18 years and those who pass screening based on surface ECG waveform analysis. In addition, an explanatory note (similar to TN.8.66) may be needed to clarify eligibility expectations for replacement procedures.

MSAC agreed with ESC's consideration that it may be reasonable to accept the reports of similar procedure time for S-ICD and TV-ICD lead insertion (including from PRAETORIAN) in justifying the MBS fee, despite the potential for TV-ICD lead insertion to be more complex. MSAC noted the proposed item includes insertion and removal/replacement of S-ICD leads. This is in contrast to the current funding arrangement for TV-ICD, whereby a separate MBS item for lead removal (MBS item 38358) with a higher fee exists due to the complexity of the removal procedure.

7. Summary of public consultation feedback/consumer Issues

See MSAC Application 1374 PSD for consumer feedback previously received. No additional consumer feedback was received regarding the resubmission of MSAC Application 1374.1.

8. Proposed intervention's place in clinical management

The clinical management algorithm and the proposed place of S-ICD remains consistent with the previous submission (see MSAC Application 1374 PSD).

9. Comparator

Consistent with the previous submission, the main comparator to S-ICD therapy in the current resubmission was single or dual-chamber TV-ICD therapy (see MSAC Application 1374 PSD).

The Commentary noted that the resubmission claimed there are several patient groups with a high clinical need for S-ICD, particularly patients in whom insertion of TV-ICD leads is contraindicated, who may never receive TV-ICD (it is not a viable treatment option), have failed TV-ICD implantation, or have had a TV-ICD removed. These patients may receive medical management (or cardiac catheter ablation) as an alternative. However, MSAC considered TV-ICD was the appropriate main comparator for S-ICD.

10. Comparative safety

One publication by Knops et al. 2020[9], reporting results of the PRAETORIAN trial, was the only trial identified comparing the safety and effectiveness of S-ICD with TV-ICD. The PRAETORIAN trial is a randomised, open-label, non-inferiority trial that included 849 subjects with an indication for an ICD but no indication for pacing, from 39 study sites in the US and Europe. The median duration of follow-up in the primary publication was 49.1 months.

The Commentary noted that future publications from PRAETORIAN are also expected to address recurrent event analysis (the primary publication interrogates 'first' events only) and QoL (assessed using the SF-36 questionnaire and the Duke Activity Status Index [DASI]). In addition, all subjects in PRAETORIAN have been invited to join the PRAETORIAN XL observational sub-study, which is an extension of the trial for an additional 48 months to obtain further information regarding inappropriate shocks, lead-related complications, and development of an indication for pacing.

The results of PRAETORIAN demonstrated no statistically significant differences between treatment arms for the composite primary endpoint comprising device related complications and inappropriate shocks (hazard ratio (HR) = 0.99 [95% CI: 0.71, 1.39; p=0.95]; Table 5). The non-inferiority margin for the HR was 1.45, indicating S-ICD was non-inferior to TV-ICD with respect to the primary endpoint (p=0.01). However, inappropriate shocks were numerically more common with S-ICDs versus TV-ICD. Conversely, device-related complications were numerically less frequent in S-ICD patients. Also, numerically more infections were observed in TV-ICD versus S-ICD patients, whereas bleeding and subsequent pacing indications were more common with S-ICDs. None of these differences were statistically significant and event rates for individual complications were low.

[9] Knops, RE et al. (2020) The New England Journal of Medicine, 383:526-536.

Table 5 Results of device-related complications and inappropriate shocks in the PRAETORIAN trial

Outcome	Risk of bias	S-ICD *n (%)* N=426	TV-ICD *n (%)* N=423	HR/OR [95% CI] [a]	*RD* *[95% CI]* [a]
Composite primary outcome	Low	68 (16.0%) [b]	68 (16.1%) [b]	*HR* 0.99 [0.71, 1.39] [b] *OR 0.99 [0.69, 1.43]*	*0.00 [-0.05, 0.05]*
Device related complications	Low	31 (7.3%) [b]	44 (10.4%) [b]	*HR* 0.69 [0.44, 1.09] *OR 0.68 [0.42, 1.09]*	*-0.03 [-0.07, 0.01]*
Infection		4 (0.9%)	8 (1.9%)	0.~~50~~*49* [0.15, 1.6~~65~~]	*-0.01 [-0.03, 0.01]*
Bleeding		8 (1.9%)	2 (0.5%)	4.03 [0.85, 19.08]	*0.01 [0.00, 0.03]*
Thrombotic event		1 (0.2%)	2 (0.5%)	0.50 [0.04, 5.48]	*0.00 [-0.01, 0.01]*
Pneumothorax		0 (0%)	4 (0.9%)	0.11 [0.01, 2.04]	*-0.01 [-0.02, 0.00]*
Lead perforation		0 (0%)	4 (0.9%)	0.11 [0.01, 2.04]	*-0.01 [-0.02, 0.00]*
Tamponade		0 (0%)	2 (0.5%)	0.20 [0.01, 4.13]	*0.00 [-0.01, 0.00]*
Lead repositioning		2 (0.5%)	7 (1.7%)	0.28 [0.06, 1.36]	*-0.01 [-0.03, 0.00]*
Lead replacement		3 (0.7%)	9 (2.1%)	0.33 [0.09, 1.21]	*-0.01 [-0.03, 0.00]*
Device malfunction		4 (0.9%)	6 (1.4%)	0.66 [0.18, 2.35]	*0.00 [-0.02, 0.01]*
Sensing issues		4 (0.9%)	0 (0%)	9.02 [0.48, 168.08]	*0.01 [0.00, 0.02]*
Pacing indication		5 (1.2%)	1 (0.2%)	5.01 [0.58, 43.08]	*0.01 [0.00, 0.02]*
Implantation failure		0 (0%)	3 (0.7%)	0.14 [0.01, 2.74]	*-0.01 [-0.02, 0.00]*
Defibrillation test failure		3 (0.7%)	0 (0%)	7.00 [0.36, 135.93]	*0.01 [0.00, 0.02]*
Pain or discomfort		2 (0.5%)	3 (0.7%)	0.66 [0.11, 3.97]	*0.00 [-0.01, 0.01]*
Inappropriate shock	Low	41 (9.6%) [b]	29 (6.9%) [b]	*HR* 1.43 [0.89, 2.30] *OR 1.45 [0.88, 2.38]*	*0.03 [-0.01, 0.06]*
Atrial fibrillation or supraventricular tachycardia		11 (2.6%)	27 (6.4%)	**0.39 [0.19, 0.79]**	*-0.04 [-0.07, -0.01]*
Cardiac oversensing		24 (5.6%)	2 (0.5%)	**12.57 [2.95, 53.52]**	*0.05 [0.03, 0.07]*
Noncardiac oversensing		8 (1.9%)	0 (0%)	17.20 [0.99, 299.00]	*0.02 [0.01, 0.03]*

Source: Table 14, p 63 of the commentary based on Table B-10, p.56 of the ADAR, with commentary amendments in italics
Abbreviations: CI=confidence interval; HR=hazard ratio; OR=odds ratio; *RD=risk difference;* S-ICD=subcutaneous implantable cardioverter defibrillator; TV-ICD=transvenous implantable cardioverter defibrillator
Note: Statistically significant results are shown in bold.
a OR *and RD* were calculated for the purpose of the ADAR in Attachment D. Knops 2020 reported HR for the following outcomes: composite primary outcome; overall device-related complication rate; and overall inappropriate shock rate.
b These percentages were calculated for the purpose of the ADAR based on n/N. The percentages reported in Knops et al. (2020) (Table 2, p.533) refer to 4-year cumulative incidences based on Kaplan–Meier estimates in time-to-first-event analyses. Multiple end points could occur in one patient; only the first end point was included in the estimation of the cumulative incidence.

The Commentary noted that the confidence intervals for the primary outcome were wide so the data cannot rule out either substantial benefit or substantial harm with S-ICD. If the high-pass sensing filter (SMART Pass) that is available in the current generation S-ICDs is confirmed in randomised trials to reduce inappropriate shocks without compromising the detection of ventricular arrhythmias (VAs) or time to therapy, then the risk-benefit profile for S-ICDs may be more favourable. However, no RCTs are available yet to confirm this. The primary outcome data also related to only the first occurrence of an event (i.e., 'first' inappropriate shock). No data are yet available from PRAETORIAN for 'all' inappropriate shocks (recurrent event analysis). The Commentary considered that the median follow-up of 49 months was insufficient to fully assess device-related complications. It is likely that over a longer period of follow-up, device-related complications will increase for both types of ICD (e.g., the development of a pacing indication in S-ICD patients and lead-related complications in TV-ICD patients). Since some patients are prone to undergo multiple automatic defibrillator replacements during their lifetime, especially younger patients who

will have a longer life expectancy, data regarding the safety of replacement procedures would be informative.

11. Comparative effectiveness

All efficacy outcomes in PRAETORIAN were considered secondary endpoints. The trial was not powered for efficacy outcomes (such as mortality), and non-inferiority margins were not pre-specified. The total number of deaths from any cause was numerically higher in the S-ICD group (83 patients) than the TV-ICD group (68 patients) but the number of deaths due to SCD was identical (18 patients from each group). There were no statistically significant differences between study groups in terms of death from other cardiovascular causes, major cardiac events, hospitalisations, or crossovers (Table 6). However, there were numerically more crossover of patients from the S-ICD group to TV-ICD group than the reverse due to those patients developing the need for bradycardia pacing or antitachycardia pacing (ATP).

Table 6 Results of efficacy endpoints (secondary outcomes) in the PRAETORIAN trial

Outcome	Risk of bias	S-ICD n (%) N=426	TV-ICD n (%) N=423	HR/OR [95% CI] [a]	RD [95% CI] [a]
Death from any cause	NA	83 (19.5) [b]	68 (16.1) [b]	HR 1.23 [0.89, 1.70] OR 1.26 [0.89, 1.80]	0.03 [-0.02, 0.09]
Sudden cardiac death [c]	NA	18 (4.2)	18 (4.3)	0.99 [0.51, 1.94]	0.00 [-0.03, 0.03]
Death from other cardiovascular causes	NA	34 (8.0)	28 (6.6)	1.22 [0.73, 2.06]	0.01 [-0.02, 0.05]
Appropriate shock therapy	NA	83 (19.5) [b]	57 (13.5) [b]	**HR 1.52 [1.08, 2.12] OR 1.55 [1.08, 2.24]**	0.06 [0.01, 0.11]
Major adverse cardiac event	NA	64 (15.0) [b]	80 (18.9) [b]	HR 0.80 [0.57, 1.11] OR 0.76 [0.53, 1.09]	-0.04 [-0.09, 0.01]
Hospitalisation for heart failure	NA	79 (18.5) [b]	74 (17.5) [b]	HR 1.08 [0.79, 1.49] OR 1.07 [0.76, 1.52]	0.01 [-0.04, 0.06]
Crossover to other study device	NA	18 (4.2) [b]	11 (2.6) [b]	HR 1.64 [0.77, 3.47] OR 1.65 [0.77, 3.54]	0.02 [-0.01, 0.04]

Source: Table 4, ppXXII of commentary (Derived from Table B-11, p.59 of the ADAR and the Attachment D Excel workbook)
Abbreviations: CI=confidence interval; HR=hazard ratio; NA=not assessed (in ADAR); OR=odds ratio; RD=risk difference; S-ICD=subcutaneous implantable cardioverter defibrillator; TV-ICD=transvenous implantable cardioverter defibrillator
Note: Statistically significant results are shown in bold.
a HR was reported in Knops et al. (2020). OR and RD were calculated for the purpose of the ADAR (Attachment D Excel workbook).
b These percentages were calculated for the purpose of the ADAR based on n/N.
c Includes death from unexplained causes.

The Commentary noted a higher cumulative incidence of appropriate shocks was found for S-ICD than with TV-ICD, which was mainly explained by the inability of S-ICD to deliver ATP. Eleven first 'appropriate' shocks were delivered in the S-ICD group for a VT below the tachycardia zone. These therapies are not 'inappropriate' in a strict sense but may be considered unnecessary from a clinical perspective. If these events were counted towards the primary endpoint as 'inappropriate' shocks, then it is possible that PRAETORIAN may have missed its non-inferiority boundary.

Clinical claim

On the basis of the benefits and harms reported in the evidence base for patients with an indication for defibrillator therapy but with no indication for pacing, the resubmission proposes that, relative to TV-ICD, S-ICD has non-inferior safety with respect to device-related complications and inappropriate shocks, and non-inferior effectiveness with respect to the incidence of SCDs.

The Commentary considered this clinical claim based on evidence from the PRAETORIAN trial to be reasonable because (i) device-related complications are trending towards being lower for S-ICD than TV-ICD, (ii) the incidence of inappropriate shocks is anticipated to be lower in practice than in PRAETORIAN because of the availability of more modern devices and improvements in programming, and (iii) the incidence of SCDs was similar across the two groups in PRAETORIAN. Nevertheless, the trial was not powered for efficacy outcomes and a higher significant risk of 'appropriate' shocks and a trend toward an increase in non-cardiovascular deaths were encountered in the S-ICD group, leaving some uncertainties regarding the true equivalence of the two technologies. Long-term follow-up is therefore warranted and is ongoing.

The resubmission also claimed that while the clinical claim is one of non-inferiority, "it is reasonable to predict many patients in the subgroups described earlier will benefit from an MBS listing of S-ICD via reduced infection risk and/or improved quality of life (QoL)". MSAC considered that this claim was not substantiated by the data presented in the original application and resubmission.

Translation issues

There were no Australian study sites in any of the studies included in the resubmission.

The Commentary noted that the resubmission did not address the applicability of the evidence base to the target population eligible for ICD implantation services on the MBS, despite this being a concern raised in the PSD for the previous application (MSAC Application 1374 PSD, pp.8, 12). The resubmission did not provide any evidence to support the use of S-ICD in younger patients (including children and adolescents) who could potentially benefit from a subcutaneous rather than transvenous leads. Further, patients who were not suitable for TV-ICD implantation, according to the discretion of the physician, were not screened for enrolment in PRAETORIAN. As a consequence, patients in whom S-ICD may be particularly useful (e.g., cases where insertion of transvenous leads is particularly challenging or contraindicated) may not be represented in the trial.

12. Economic evaluation

A cost-minimisation analysis (CMA) was presented comparing S-ICD with TV-ICD which is appropriate for a clinical claim of non-inferior safety and efficacy (Table 7). The costs captured in the CMA included those for the primary procedure (MBS services, prostheses and hospitalisation costs) and follow-up costs, including those associated with device-related complications and consequent crossover from S-ICD to TV-ICD.

Table 7 Summary of the economic evaluation

Perspective	Health care
Comparator	TV-ICD
Type of economic evaluation	CMA
Sources of evidence	Primarily PRAETORIAN trial (Knops et al. 2020)
Time horizon	Device crossover in both directions captured to 5 years
Outcomes	Not applicable (safety and efficacy outcomes considered non-inferior in ADAR)
Costs considered	Medical services, prostheses, hospitalisation and safety costs (device-related complications, including crossovers to alternative device)
Software packages used	Microsoft Excel

Source: Table D-1, p.73 of the ADAR, with commentary additions

Abbreviations: ADAR=Applicant developed assessment report; CMA=cost-minimisation analysis; TV-ICD=transvenous implantable cardioverter defibrillator

Key assumptions, primarily drawn from the PRAETORIAN trial, included:

- rates of general anaesthesia during the implantation procedure
- rates of device-related complications (requiring hospitalisations)
- rates of crossover to the alternative device and the timing of crossover.

The Commentary highlighted several limitations and uncertainties to the submission's model:

- exclusion of some costs from the CMA (e.g., ECG screening pre-implant to assess oversensing; assistance during the insertion procedure; management of inappropriate shocks)
- the assumption that follow-up testing of the implanted defibrillator is performed in only 3.6% of patients and is similar for S-ICD and TV-ICD
- allocation of hospital costs given the short median length of stay in the PRAETORIAN trial (with these then applied to device-related complications, which are higher for TV-ICD versus S-ICD)
- the assumption that general anaesthesia is used in only 48.8% of S-ICD procedures and 3.1% of TV-ICD procedures
- estimates of battery longevity, which are assumed equivalent despite information suggesting that TV-ICD may have a longer battery life
- the impact of battery longevity and the risks associated with device replacement over the longer term (i.e., beyond 5 years)
- the assumption that battery replacement is always performed as an outpatient procedure and therefore incurs no hospitalisation costs
- chronic complications and crossover from S-ICD to TV-ICD beyond five years of follow-up.

The resubmission estimated that S-ICD would provide cost savings of $**redacted** relative to TV-ICD in the CMA base case. The cost saving was a result of lower prostheses and medical service costs during the primary procedure, which are somewhat offset by higher safety costs due to increased crossover from S-ICD to TV-ICD and cardiac resynchronisation therapy defibrillator (CRT-D). When the costs are recalculated assuming 100% follow-up testing for S-ICD patients (who require defibrillation testing (DFT)) instead of 3.6%, and application of an alternative MBS item for ICD testing, S-ICD is no longer cost-saving relative to TV-ICD. A comparison of costs adjusted in the commentary is presented in Table 8.

MSAC noted that key assumptions made in the economic model are derived from the PRAETORIAN trial. MSAC noted that younger patients, whom were not a population included in the trial, would require more replacements over their lifetime. Due to S-ICD having a shorter battery lifespan (5-6 years according to literature) compared to TV-ICD (12-14 years), younger patients will be subject to even more replacements if given S-ICD as opposed to TV-ICD.

Table 8 Comparison of total health care costs associated with S-ICD and TV-ICD procedures

Input costs	S-ICD	TV-ICD	Difference
Primary procedure costs	~~$46,671~~ *$47,300*	~~$47,563~~ *$47,581*	~~-$892~~ *-$282*
Medical service costs	~~*$1,476*~~ *$2,104*	~~*$1,633*~~ *$1,651*	~~*-$157*~~ *$453*
Prostheses costs	*$34,392*	*$35,127*	*-$735*
Hospitalisation costs	*$10,803*	*$10,803*	*$0*
Safety costs	~~$1,773~~ *$1,766*	~~$1,370~~ *$1,374*	~~$403~~ *$391*
Device-related complication costs	*$637*	*$1,059*	*-$421*
Crossover costs	~~*$1,136*~~ *$1,128*	~~*$311*~~ *$316*	~~*$825*~~ *$813*
Total costs	~~**$48,444**~~ ***$49,065***	~~**$48,933**~~ ***$48,956***	~~**-$489**~~ ***$110***

Source: Table 6, pxxiii of the commentary; based on Table D-18, p.87 of the ADAR, with commentary amendments in italics and strikethrough
Abbreviations: S-ICD=subcutaneous implantable cardioverter defibrillator; TV-ICD=transvenous implantable cardioverter defibrillator

No sensitivity analyses were provided in the resubmission. The Commentary conducted some limited sensitivity analyses in which all but two of the analyses, the CMA showed higher costs for S-ICD relative to TV-ICD (Table 9).

Table 9 Comparison of total health care costs associated with S-ICD and TV-ICD procedures

Analysis	S-ICD	TV-ICD	Difference
Base case (Table 31)	~~**$48,444**~~ ***$49,065***	~~**$48,933**~~ ***$48,956***	~~**-$489**~~ ***$110***
Including a physician assistant (1/5 of total operation fees)	*$49,445*	*$49,210*	*$236*
100% general anaesthesia for S-ICD	*$49,114*	*$48,956*	*$158*
90.4% follow-up ICD testing for S-ICD and 46.1% for TV-ICD (taken from Knops et al. 2020)	*$49,012*	*$49,224*	*-$212*
Minimum TV-ICD prosthesis cost ($28,398) [a]	*$49,057*	*$48,221*	*$836*
Maximum TV-ICD prosthesis cost ($29,750)	*$49,072*	*$49,573*	*-$500*
6 years expected battery life for S-ICD, 10 years for TV-ICD	*$49,035*	*$48,962*	*$73*

Source: Table 32, p96 of the commentary
a This device has reduced functionality (e.g., no wireless monitoring) p 77 of the ADAR.
Abbreviations: S-ICD=subcutaneous implantable cardioverter defibrillator; TV-ICD=transvenous implantable cardioverter defibrillator
Note: Rounding errors may apply. See spreadsheet "SICD_Section E"xlsx for complete calculations.

The pre-ESC response acknowledged the Department's advice that MBS item 38213 is not eligible to be used for DFT, and that the DFT rate of 3.6% applied to both S-ICD and TV-ICD in the submission, may not be appropriate. Therefore, the pre-ESC response provided a revised analysis that applied DFT costs based on MBS item 38212 and DFT rates from the PRAETORIAN trial, 90.4% for S-ICD and 46.1% for TV-ICD (Table 10).

Table 10: Revised cost-minimisation analysis applying MBS item 38212 for DFT testing

Row		S-ICD	TV-ICD	Difference	Source / calculation
	DFT				
A	% of patients tested	90.4%	46.1%		PRAETORIAN (Knops 2020)
B	Cost of DFT	$1,279.43	$652.45		A * MBS item 38212 (MOR, x 100%)
C	Lead placement	$595	$835		Proposed; MBS item 38384/38390 (MOR, x50% with DFT, x100% without DFT)
D	Implant of generator	$81.34	$114.21		MBS item 38387/38393 (MOR, x25% with DFT, x50% without DFT)
E	Fluoroscopy guidance of lead	-	$262.80		MBS item 61109
F	Chest x-ray with fluoroscopic screening	$61.65	-		MBS item 58506
G	Anaesthesia service costs	$175.43	$131.72		MSAC ADAR 1374.1 (Table D-4)
I	**Total medical service costs**	**$2,192.73**	**$1,996.51**	**$196**	**B+C+D+E+F+G**
J	**Prostheses costs**	**$34,392**	**$35,127**	**-$735**	**MSAC ADAR 1374.1 (Table D-18)**
K	**Hospitalisation costs**	**$10,803**	**$10,803**	**$0**	**MSAC ADAR 1374.1 (Table D-18)**
L	**Safety costs**	**$1,782**	**$1,375**	**$408**	**Recalculated assuming 90.4% of S-ICD and 46.1% of TV-ICD patients receive MBS item 38212 for DFT.**
M	**Total costs**	**$49,170**	**$49,301**	**-$131**	**I+J+K+L**

Source: Table 1, p6 of the pre-ESC response.
Abbreviations: ADAR=Applicant Developed Assessment Report; DFT=defibrillation testing; MBS=Medicare Benefits Schedule; MSAC=Medical Services Advisory Committee; S-ICD=subcutaneous implantable cardioverter defibrillator; TV-ICD=transvenous implantable cardioverter defibrillator

MSAC considered that an extended CMA should be performed including at least a 20 year time horizon (rather than 10 year). MSAC considered that the base case should also include a comparison of battery lifespans for both devices' current models, ongoing conversion to TV-ICD using registry data, along with DFT and general anaesthesia rates based on local experience.

13. Financial/budgetary impacts

A market share approach was applied in estimating the financial implications to the MBS of introducing S-ICD for primary and secondary prevention of SCD. The ICD market was projected based on the historical MBS use of TV-ICD lead insertion services (MBS items 38384 and 38390). The resubmission assumed that S-ICD use will derive from substitution of existing TV-ICD use and is not expected to grow the market since it is proposed for a subset (75%) of TV-ICD eligible patients. Uptake of S-ICD was assumed to start with 10% of the existing TV-ICD market in Year 1, increasing to 20% in Year 3 and remaining constant thereafter. The proportion of S-ICD patients expected to crossover to TV-ICD was taken from the PRAETORIAN trial.

The estimated number of patients receiving S-ICD and the number of services for S-ICD lead insertion/removal is shown in Table 11.

Table 11 Total number of patients and services for S-ICD

	2021 Year 1	2022 Year 2	2023 Year 3	2024 Year 4	2025 Year 5
Total number of patients receiving S-ICD	158	237	315	315	315
Total S-ICD lead placement/ removal services	159	239	320	322	323

Source: Table 7, pxxv of the commentary, based onTable E-7, p.93 of the ADAR, with commentary additions
Abbreviations: S-ICD=subcutaneous implantable cardioverter defibrillator

The Commentary noted that there is the potential for the number of eligible patients to be greater than or less than these estimates, as some of the underlying assumptions are subject to uncertainty. The estimate of patients with an indication for ICD therapy but without an indication for pacing was not based on Australian data. Additionally, PRAETORIAN did not enrol any Australian sites and the resubmission did not address this. 'Suitability' for S-ICD was not taken into account; some patients who are considered for S-ICD therapy will fail the patient screening tool provided by the manufacturer. Furthermore, if there is currently a pool of patients who are unsuitable for TV-ICD (e.g., due to structural abnormalities or difficult venous anatomy) or who are reluctant to attempt (or re-attempt) ICD therapy with a transvenous system (e.g., patients who are younger or have comorbidities or who have undergone previous ICD explant), then uptake of S-ICDs could be faster and grow larger than predicted in the resubmission. Uptake of S-ICD therapy could also increase if a modular approach (i.e., an 'add-on' leadless pacing option) becomes available in the future; however, this is unlikely to happen in the 5-year time horizon of the financial analysis.

The resubmission claimed the proposed listing will decrease TV-ICD services secondary to substitution for S-ICD, affecting relevant MBS items associated with TV-ICD, including fluoroscopic imaging.

The financial implications to the MBS resulting from the proposed listing of S-ICD are summarised in Table 12.

The Commentary noted that while the resubmission showed a net cost saving, this is subject to some uncertainty and may not be the case if there is growth in the ICD market due to S-ICD availability, as opposed to substitution only. Recalculation of the costs associated with follow-up ICD testing results in a net impact to the MBS of $64,800 in Year 1 rising to $139,948 in Year 5.

Table 12 Total costs to the MBS associated with S-ICD

Row		2021 Year 1	2022 Year 2	2023 Year 3	2024 Year 4	2025 Year 5	Source / calculation
-	**Cost of proposed new S-ICD service**	-	-	-	-	-	-
A	Total cost	$171,821	$259,440	$347,260	$349,068	$350,475	ADAR Table 35
B	-to MBS	$128,872	$193,909	$259,546	$260,898	$261,949	ADAR Table 35
C	-to patients [a]	$42,949	$65,531	$87,714	$88,170	$88,526	ADAR Table 35
-	**Impact on other MBS services**	-	-	-	-	-	-
D	Total cost	~~-$194,236~~ - *$86,727*	~~-$290,144~~ - *$128,920*	~~-$384,843~~ - *$169,944*	~~-$382,122~~ - *$167,312*	~~-$380,005~~ - *$165,264*	ADAR Table 49
E	-to MBS	~~-$144,706~~ - *$64,072*	~~-$216,151~~ - *$95,230*	~~-$286,690~~ - *$125,511*	~~-$284,648~~ - *$123,537*	~~-$283,061~~ - *$122,001*	ADAR Table 49
F	-to patients [a]	~~-$49,530~~ - *$22,655*	~~-$73,993~~ - *$33,690*	~~-$98,154~~ - *$44,433*	~~-$97,473~~ - *$43,775*	~~-$96,944~~ - *$43,263*	ADAR Table 49
-	**Net impact**	-	-	-	-	-	-
G	Total cost	~~-$22,415~~ *$85,094*	~~-$30,704~~ *$130,520*	~~-$37,583~~ *$177,316*	~~-$33,053~~ *$181,757*	~~-$29,530~~ *$185,211*	A+D
H	-to MBS	~~-$15,834~~ *$64,800*	~~-$22,243~~ *$98,678*	~~-$27,143~~ *$134,035*	~~-$23,750~~ *$137,361*	~~-$21,111~~ *$139,948*	B+E
I	-to patients [a]	~~-$6,581~~ *$20,294*	~~-$8,462~~ *$31,841*	~~-$10,440~~ *$43,281*	~~-$9,303~~ *$44,396*	~~-$8,419~~ *$45,263*	C+F

Source: Table 8, pxxvi of the commentary, based on Table E-3, p.92 of the ADAR, with commentary additions in italics and strikethrough
Abbreviations: MBS=Medicare Benefits Schedule; S-ICD=subcutaneous implantable cardioverter defibrillator
a The total cost over five years is provided by applying 75% of the schedule fee to the MBS and the remaining 25% "to patients".
Rounding errors may apply. See ADAR attachment (spreadsheet "SICD_Section E"xlsx) for complete calculations

The Commentary noted that the proposed MBS listing will impact on the use of S-ICDs on the PL, as there is unlikely to be substantial use of these devices in the private setting at present. The resubmission projects that substitution will result in a net benefit to private health insurers, which is driven by a less expensive S-ICD automatic defibrillator compared with the mean for single chamber TV-ICDs on the PL. The appropriateness of using a mean cost for TV-ICDs is uncertain and depends on relative use of different single chamber devices on the PL, with consideration of the groupings that are likely to be substituted for the S-ICD device. If battery life is shorter for S-ICDs than for TV-ICDs, the total cost to the PL may be higher over the longer term as replacements are needed more frequently. Also, if the proportion of S-ICD patients who develop a pacing indication is larger than expected, then there will be more crossovers to TV-ICDs, and this will increase costs to private health insurers.

The Commentary considered the greatest source of uncertainty is whether the proposed MBS listing will grow the ICD market. This is possible if there are currently patients who are unsuitable or contraindicated TV-ICD, or who are reluctant to attempt (or re-attempt) TV-ICD but would consider S-ICD therapy.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Issues previously raised by MSAC	The PRAETORIAN trial appears to address some of the issues previously raised by MSAC however, a number of issues remain.
Limited RCT evidence, of uncertain validity; ADAR is based on one trial	The PRAETORIAN trial has risk of: • selection bias (patients were not screened, groups were not evenly balanced at the start) • detection bias (adjudicators were not blinded) • attrition bias (large loss to follow up) • performance bias (results were not an ITT analysis) • industry bias (the RCT was funded by the applicant).
Non-inferior safety of S-ICD is not fully supported by the available evidence	Safety is uncertain. The trial primary outcome seems underpowered with a wide confidence interval that does not exclude benefit or harm.
Safety profile is not comparable between the two devices; difficult to measure without HRQoL data	The PRAETORIAN trial claimed S-ICD has a non-inferior safety profile, but it is comparing events of different "value". There were more shocks with the S-ICD system, and more bleeding in the PRAETORIAN trial. However, the TV-ICD had more lead-related complications including infection, perforations and lead breakage.
Lack of long-term data	Lead complications increase over time. The battery longevity issues for S-ICD have not been seen yet with the 4-year study follow up. The PRAETORIAN-XL observational study is yet to produce data. The ATLAS S-ICD trial, which initiated enrolment in 2017, will also compare single-chamber TV-ICDs with S-ICDs (NCT02881255).
Item descriptor provides greater eligibility than trial population	The proposed MBS item descriptor is broader than the patient population included in the PRAETORIAN trial. The MBS descriptor should contain more detailed inclusion and exclusion criteria. An explanatory note (similar to TN.8.66) may be needed to clarify eligibility expectations for replacement procedures.
High clinical need population was not included in the PRAETORIAN trial	The ADAR claimed this device would benefit patients with high clinical need including younger patients, patients at risk of infection or patients with complex venous anatomy; however, these groups were not included in PRAETORIAN trial.
Proposed rebate fee for S-ICD is the same as TV-ICD	Previous MSAC feedback was that the proposed fee was too high, compared with TV-ICD. However, ESC considered that the procedure times for S-ICD and TV-ICD may in fact be similar and justifying the fee based on similar procedure time may be appropriate.
Uncertainty regarding additional costs related to the procedure	The ADAR lacked information on the costs (and how these are included/covered) for additional accessories and/or services required for the procedure, for example: programmer, tunnelling tool, general anaesthesia requirement, etc.
ICD market growth	It is possible that the availability of an item on the MBS for the S-ICD lead (with electrode) could lead to overall market growth in ICDs, which would affect the cost-savings claim of the proposed device.

ESC discussion

ESC noted that this application was a resubmission seeking Medicare Benefits Schedule (MBS) listing for the insertion, removal and replacement of subcutaneous leads (with electrode) that are part of a subcutaneous implantable cardioverter defibrillator (S-ICD) therapy system for the prevention of sudden cardiac death (SCD). The Medical Services Advisory Committee (MSAC) has previously considered this application (MSAC Application 1374) in November 2014. MSAC did not support public funding for S-ICD leads because of uncertain comparative long-term safety and clinical effectiveness, which translated into uncertainty in the economic analysis. MSAC suggested the results from a large, prospective, multi-centre, randomised trial (PRAETORIAN) – which was underway at the time of MSAC consideration – may help to address the uncertainties. ESC noted the findings from the PRAETORIAN trial have now been published (Knops et al. 2020) and that while this trial appears to address some of the issues previously raised by MSAC, a number of issues still remain.

ESC noted feedback from the consumer representative that consumer organisations reported positive patient experiences with the subcutaneous devices. Organisations emphasised patient choice, and that some patients may prefer a subcutaneous device.

ESC noted that the S-ICD has been designed as an alternative to the traditional defibrillator for prevention of SCD, transvenous ICD (TV-ICD). ESC considered the differences between the S-ICD and TV-ICD systems. It was noted that a benefit of the S-ICD system is that it does not require vascular access but that the S-ICD system cannot provide pacing, can only be used for defibrillation, has a shorter battery life and can result in more inappropriate shocks. ESC noted that the applicant has proposed that S-ICD will substitute TV-ICD in a subpopulation of patients without a pacing indication. However, ESC was concerned that some patients may not initially require pacing and could be considered suitable for an S-ICD but may develop the need for pacing at a later stage, which would require replacement of the S-ICD with a TV-ICD. ESC noted that it is very difficult to determine which patients will require pacing at a later stage.

ESC considered there was a mis-match between the proposed MBS population, the population included in the key supporting trial (PRAETORIAN trial) and populations described in the Applicant Developed Assessment Report (ADAR) as having a high clinical need for S-ICD that avoids the risks associated with transvenous lead implantation. ESC considered the MBS descriptor population was broader than the population defined in the PRAETORIAN trial; noting some trial exclusions are not currently in the descriptor. ESC advised further detail in the descriptor or an explanatory note would be required to address this. Further, ESC noted that the ADAR claimed there is a high clinical need for S-ICD for younger patients (children and adolescents), patients at high risk of infection or patients with complex venous anatomy; however, ESC noted there were no data to support this claim as these groups were not included in the PRAETORIAN trial.

ESC also noted that a single MBS item for insertion, removal and replacement of leads was proposed, which is not consistent with current MBS items for TV-ICD lead insertion (i.e. a separate item exists for the removal of a transvenous lead). ESC was uncertain whether, for replacement procedures, the proposed MBS item will be claimed once or twice during a single procedure to remove and replace a subcutaneous lead.

ESC discussed whether the proposed rebate fee should be lower. ESC recalled that for the previous submission (MSAC 1374), the applicant proposed fee was based on the fee for TV-ICD lead insertion less 10% in acknowledgment of the difference in procedure duration; and

that MSAC had noted TV-ICD lead insertion was more technically complicated and would take longer compared to S-ICD lead insertion. However, ESC noted that the resubmission has proposed the same MBS fee for S-ICD as TV-ICD lead insertion (i.e. does not include 10% reduction). The justification provided for the fee was based on claimed similar resources and procedure time but did not address difference in procedure complexity. ESC noted that although TV-ICD lead insertion may be more technically complex, the procedure times may be similar as clinical experience with the S-ICD leads has led to additional suturing of S-ICD leads to prevent potential lead fracture. ESC considered that justifying the fee based on similar procedure time may be appropriate.

ESC noted that clinical evidence was limited, based on one non-inferiority trial (PRAETORIAN trial), and did not include any other data (i.e. observational studies/registries such as the EFFORTLESS S-ICD registry and the UNTOUCHED cohort study). ESC noted the primary endpoint in the PRAETORIAN trial was a composite safety endpoint of device-related complications and inappropriate shocks (i.e. did not include efficacy) and that the primary endpoint was initially superiority but was changed to non-inferiority during the trial. ESC noted that the hazards ratio (HR) used for the non-inferiority claim was 1.45, which meant that the S-ICD could be up to 45% worse and still be considered non-inferior. ESC disagreed with the ADAR's assessment that the PRAETAORIAN trial had a low risk of bias, noting there was high risk of selection bias, likely risk of selective outcome reporting bias and uncertain risk of detection and performance bias due to the trial design. ESC also noted there was uncertain risk of attrition bias due to patients lost to follow up (n=27 following randomisation and n=38 after implantation) and deaths (n=126).

In regard to comparative safety, ESC noted that the results of the PRAETORIAN trial reported there was no difference between S-ICD compared to TV-ICD with respect to the primary composite endpoint (hazard ratio [HR] = 0.99, CI 0.71–1.39). When analysing the components of the primary endpoint, ESC noted that the safety profile was different for S-ICD and TV-ICD as there were:

- more lead complications in the TV-ICD group (9.8% vs 5.9% for S-ICD)
- more inappropriate shocks in the S-ICD group (9.7% vs 7.3% for TV-ICD)
- more overall deaths in S-ICD group (but equal sudden cardiac deaths in both groups).

ESC also noted that 49% of patients required general anaesthesia for S-ICD implantation compared to 3% for TV-ICD. In addition, 18 patients with S-IC crossed over to TV-ICD compared to 11 patients with TV-ICD crossing over to S-ICD. ESC was concerned with the lack of long-term data and considered the 49-month average follow-up duration may be too short to see revision and replacement procedures, assess re-implementation risk, or consider patients who need to crossover to a TV-ICD due to pacing requirements. ESC noted there are ongoing trials that may provide longer term data (e.g. PRAETORIAN-XL trial, ATLAS S-ICD trial[10]). ESC noted that newer generations of S-ICD devices include a high-pass filter that is claimed to reduce T wave over-sensing, and thus inappropriate shocks. However, ESC considered the efficacy of the high-pass filter, to reduce inappropriate shocks, was unknown as there were no RCT data to support this claim.

In regard to comparative efficacy, ESC noted the hazard curve for all-cause mortality from the PRAETORIAN trial, and that the TV-ICD population appeared to be sicker but fared better after 4 years of follow up. The all-cause deaths for S-ICD was 19.5% compared to 16.1% for the TV-ICD study arm (HR = 1.23; 95% CI, 0.89–1.70) but that the rate of SCD was equal between S-ICD and TV-ICD. However, these endpoints were under-powered.

[10] Avoid Transvenous Leads in Appropriate Subjects (ATLAS S-ICD) - NCT02881255

Overall, ESC considered the claim of non-inferior safety and efficacy of S-ICD compared to TV-ICD was not supported.

ESC noted the ADAR presented a cost-minimisation analysis comparing S-ICD with TV-ICD, with a 5-year time horizon and based on estimates from the PRAETORIAN trial. ESC considered that if the non-inferiority claim is accepted for effectiveness and safety, then the battery life becomes a significant issue for the economic analysis (and budget impact), as the battery for the S-ICD defibrillator are likely to need replacement more frequently than the lead. ESC noted the average battery life for the S-ICD is 7–8 years (5–6 years is reported in the literature), compared with the TV-ICD average battery life of 12–14 years. ESC considered it inappropriate that the model assumed a similar battery length between the S-ICD and TV-ICD and did not include any costs for battery replacement. ESC also considered that the difference in battery life could be significant if the device is used in younger patients.

ESC noted that the PRAETORIAN baseline demographics are similar to an Australian and New Zealand population-wide study assessing complication rates for cardiovascular implantable devices identified by the commentary (Ranasinghe et al. 2019[11]). ESC agreed with the pre-ESC response that although the applicability of the general anaesthesia rates from the PRAETORIAN trial to Australian clinical practice is uncertain, the assumed rates of general anaesthesia (48% and 3% for TV-ICD and S-ICD, respectively) based on the PRAETORIAN trial may be conservative and in this instance appropriate.

ESC noted the model also assumed that the device set-up, programming and defibrillation testing (DFT) was included. ESC noted that the rate of DFT applied in the model was 3.6% for both S-ICD and TV-ICD based on historical MBS item utilisation for TV-ICD. However, the PRAETORIAN trial reported DFT was conducted for ~90% of S-ICD patients and ~46% of TV-ICD patients. ESC also noted that in contrast to the PRAETORIAN trial, DFT is not routinely performed following TV-ICD insertion in Australian clinical practice. ESC considered a rate of 3.6% DFT for TV-ICD in the model may be appropriate but that the rate of 3.6% DFT for S-ICD to be inappropriate. In addition, the Department confirmed that the DFT MBS item used in the ADAR model was incorrect (should be MBS item 38212 - $1,415.30, not MBS item 38213 - $421.50). ESC noted the revised analysis by the commentary, to correct the rate of DFT for S-ICD patients (to 100% as per manufacturer instructions) and the fee for DFT, resulted in higher cost for the S-ICD (changed from a cost difference of $**redacted** to $**redacted**.

ESC noted sensitivity analyses by the commentary showed a key driver was the cost of the device and the cost of the TV-ICD device. ESC noted that the ADAR did not address other costs such as the tunnelling tool and programming device, leading to uncertainty as to how the costs would be covered.

ESC noted that a market-share approach was used to estimate the budget impact that assumes substitution of the current market. However, ESC noted that suitability was not considered, and did not factor that some patients may fail the manufacturer's screening, when estimating eligibility for S-ICD. ESC noted the revised financial estimates indicate S-ICD will have a net impact to the MBS of $64,800 in the first year increasing to $139,948 by year 5. ESC noted the claim that S-ICD will generate cost savings for the MBS and PL (less expensive device) compared with TV-ICD. However, ESC considered that there is potential for inclusion of S-ICD lead insertion on the MBS to grow the ICD market, due to S-ICD use in

[11] Ranasinghe et al (2019). *Annals of Internal Medicine*. 171:309.

patients who have complex venous anatomy or who are reluctant to attempt (or reattempt) TV-ICD. ESC considered the assertion that S-ICD will be cost saving is uncertain.

15. Other significant factors

Nil.

16. Applicant comments on MSAC's Public Summary Document

The applicant had no comment.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website