Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1387.2 – Optimizer® Smart Implantable Pulse Generator (IPG) – Cardiac Contractility Modulation (CCM) therapy for patients with Chronic Heart Failure

Applicant: **Impulse Dynamics and Life Systems**

Date of MSAC consideration: **MSAC 75th Meeting, 28-29 March 2019**

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

1. Purpose of application

An application for the resubmission of an implantable pulse generator (IPG) delivering Cardiac Contractility Modulation (CCM) therapy for patients with chronic heart failure was received from Impulse Dynamics Australia Pty Ltd 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 did not support public funding of cardiac contractility modulation (CCM) therapy (Optimizer® Smart Implantable Pulse Generator) for patients with chronic heart failure because of uncertain clinical and cost-effectiveness.

MSAC acknowledged that there may be an unmet clinical need in patients with heart failure associated with a narrow QRS duration and persistent symptoms despite optimal medical therapy. However, MSAC considered that, although more clinical outcomes data were provided in the resubmission, the clinical evidence base remains uncertain, particularly regarding the therapy's effect on improving morbidity and mortality. The size of the total likely eligible patient population and the rate of uptake of CCM devices are also uncertain. These uncertainties flowed on to uncertainties with the modelled economic evaluation.

MSAC re-emphasised that any future application should present evidence from a randomised controlled trial powered to detect long-term benefits in primary outcomes of heart failure hospitalisations and mortality.

MSAC recommended that the Department write to the Prostheses List Advisory Committee to notify it of the decision and the basis for this assessment.

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

MSAC recalled that the requested services are for the implantation, removal, replacement and interrogation of a CCM device for the treatment of patients with symptomatic heart failure who have failed to respond to optimal medical therapy (OMT). MSAC recalled that it has considered this application on two previous occasions (July 2015 and July 2016). On both occasions, MSAC did not support MBS funding because of uncertain clinical and cost-effectiveness. MSAC emphasised that any future application should present evidence from a randomised controlled trial demonstrating that CCM therapy leads to significant reductions in morbidity and mortality among the proposed population. Since the previous submission, results of the FIX-HF-5C trial (confirmatory trial following the original FIX-HF-5 trial) have been published. This and other new evidence were presented in the current resubmission.

MSAC noted that patients with a left ventricular ejection fraction (LVEF) of ≤ 35% with prolonged QRS duration are eligible for cardiac resynchronisation therapy (CRT). However, patients with reduced LVEF but normal QRS duration are not eligible for CRT. MSAC acknowledged the unmet clinical need. MSAC noted that the US Food and Drug Administration (FDA) had recently supported use of CCM therapy in CRT-ineligible patients. However, MSAC noted that the FDA considered only the risk–benefit profile of the therapy and not cost-effectiveness.

MSAC noted that the item descriptor was changed during the application process (in response to direction from MSAC) to include a number of exclusion criteria that applied to the clinical trial populations. However, MSAC noted that pre-existing atrial fibrillation (AF) is not listed as an exclusion criterion in the proposed item descriptors. Patients with (persistent or permanent) AF were excluded from FIX-HF-5(C) trials so it is unknown whether patients with AF will benefit from CCM; more evidence is required for this population.

MSAC noted that the application contained little information as to how often the device would need to be interrogated and by whom. The proposed item descriptors do not specify restrictions for specialists, facilities or institutions. However, MSAC noted that the Cardiac Implantable Electronic Devices guidelines from the Cardiac Society of Australia and New Zealand (CSANZ) may be applicable to devices used for CCM therapy. This has implications for the accreditation and monitoring of specialists who will provide these services. Decisions would need to be made about who is able to implant the device, their competence and how often they should be monitored. MSAC suggested that it would be useful to seek advice about this from CSANZ.

MSAC considered that the comparator used in this application – OMT – is appropriate given that there are no alternative treatment options for the patient population with normal QRS duration.

MSAC acknowledged that there have been no signals of any safety issue with the CCM device and the intervention appears to be safe. Device-related adverse effects appear to be rare. The implantation failure rate was about 1% in the largest trial (FIX-HF-5). However, MSAC considered that this may be an underestimate if the CCM device becomes more widely implemented.

MSAC considered that there is insufficient evidence to be certain of clinical effectiveness. MSAC noted that most outcomes assessed in the relevant trials for this application were surrogate outcomes related to exercise capacity and quality of life. MSAC noted that, although there appears to be improvement over 24 weeks in various surrogate outcomes (peak VO_2, Six-Minute Walk Test (6MWT) and Minnesota Living With Heart Failure

Questionnaire [MLWHFQ]), included studies are subject to moderate to high levels of bias due to small numbers and lack of blinding.

MSAC noted that claims of clinical effectiveness in the applicant's pre-MSAC response hinged on pooled efficacy data from the FIX-HF-5C trial and a *post-hoc* subgroup analysis from the FIX-HF-5 trial. Secondary analysis of heart failure hospitalisations and mortality showed a 73% reduction in event rates (2.9% vs 10.8%, $P = 0.042$). However, MSAC considered this result highly uncertain given the high risk of bias associated with pooling results of the *post-hoc* subgroup with results of FIX-HF-5C trial, pooled sample size (n = 389) and the number needed to treat of 13 over 24 weeks. MSAC also considered it unlikely that such a large reduction in hospitalisations would arise from the small improvements seen in symptoms.

MSAC also noted that data presented in the resubmission extends only to 24 weeks for the FIX-HF-5C trial, 50 weeks for the FIX-HF-5 subgroup and 3 years for a European registry study. Clinical effectiveness data beyond 24 weeks duration are of low quality and at high risk of bias, and the effect (and durability) of CCM beyond 24 weeks is therefore uncertain.

MSAC noted the following key drivers of the economic model and issues associated with each of them:

- Time horizon of 40 years – in previous submissions, MSAC stated that time horizons of 30 years and 15 years resulted in over-extrapolation of 12 months of data. Although the resubmission now includes FIX-HF-5C data, it continues to rely on 12-month effectiveness data. MSAC considered that a more appropriate time horizon would be 5 years, given the prevailing mortality rate in the proposed population.
- Survival benefit – the model applies the same probability of death irrespective of New York Heart Association (NYHA) class. Monthly distribution of patients by NYHA class is based on a (poorly described) logistic regression model of 12 months of individual patient data from the FIX-HF-5 trial; other data may have been included but this could not be verified. Given the very low frequency of death in the trial (which was not statistically significant), MSAC considered this approach may not be valid. It is also inconsistent with the known association between NYHA class and mortality.
- Changes in NYHA class – NYHA class distributions over the first 12 months of the model are different for each arm and sensitive to baseline values. The NYHA class at 12 months is then fixed in the model for the remainder of the time horizon (i.e. the last-observation-carry-forward assumption). MSAC considered it clinically implausible that patients would stay in the same NYHA class for up to 40 years.
- Utility weights – the submission describes mapping MLWHFQ scores from FIX-HF-5(C) individual patient data to EuroQol-5D (EQ-5D) utility weights (using two published algorithms) to be applied in the model. However, the base case in the model uses utility weights sourced from the literature. MSAC noted that the literature-based weights appear more reliable and using these weights in the model favours CCM.

MSAC noted the ICER sensitivity analysis from the Critique showing that ICERs could be as high as $144,000 if the time horizon was shortened to 5 years and $139,000 if there was no survival benefit of CCM relative to OMT.

MSAC noted that there is uncertainty about the size of the total likely eligible patient population and the level of uptake of CCM because:

- estimates of the percentage of patients with reduced ejection fraction are applied twice in the population calculation;
- 'failed OMT' is not clearly defined;
- incident vs prevalent cases of heart failure are not appropriately accounted for; and
- uptake rates over Years 1–5 (2%, 8%, 12%, 16% and 20%) are not adequately justified; advice to the Assessment Group indicated that uptake might be up to 50% (which would increase the cost to the MBS to more than $140 million in Year 5).

MSAC also noted that some costs are underestimated. MSAC noted that the largest proportion of the cost for CCM therapy is the cost of the device. The applicant lists the price of the Optimizer® Smart device as $32,615 (which was included in the assessment). MSAC noted that an application has been made for the device to be listed on the Prostheses List (13 February 2019). If patients choose to undergo this procedure in the absence of MBS subsidy, there is potential for significant out-of-pocket costs to patients.

4. Background

This is the second resubmission of Application 1387. In the previous resubmission (Application 1387.1) the MSAC did not support public funding due to uncertain clinical and cost-effectiveness. MSAC considered that the key areas of uncertainty related to the impact of CCM therapy on long term morbidity and mortality and as a consequence, the cost-effectiveness of the intervention. MSAC emphasised that any future application should present evidence from a randomised controlled trial demonstrating that CCM therapy leads to significant reductions in morbidity and mortality amongst the proposed population (Public Summary Document (PSD) 1387.1 2016, p3). The FIX-HF-5C trial remained ongoing at the time of the first re-submission in 2016 but has since been completed.

The CCM device considered by the MSAC in July 2016 was the Optimizer® IV; however, the current resubmission has been extended to include the Optimizer® Smart device.

5. Prerequisites to implementation of any funding advice

The current resubmission provided the components of the Australian Register of Therapeutic Goods (ARTG) listings pertinent to the Optimizer® Smart system (ARTG listings: 293356, 303677, 303373, 29335 and 301341). In addition, the components of the previously assessed Optimizer® IV system are registered on the ARTG (see PSD 1387.1 July 2016).

6. Proposal for public funding

The proposed MBS item descriptor is summarised in Table 1, which was based on the descriptors presented in the PICO in conjunction with MSAC feedback from the first resubmission. The items relate to the insertion, removal or replacement of the CCM IPG (A); two bipolar leads (Optimizer® Smart) (B); three bipolar leads (Optimizer® Smart or IV) (C); and the interrogation of the CCM system (D). These have been assigned unique identifiers (in red) to reference them in this paper.

Table 1 Proposed MBS item descriptor.

Category 3 - THERAPEUTIC PROCEDURES
MBS Item number XXXXX A Permanent Cardiac Contractility Modulation (CCM) Implantable Pulse Generator (IPG) device insertion, removal or replacement of, for a patient with all of the following: Patient MUST: Have symptomatic heart failure due to systolic left ventricular dysfunction despite failed Optimal Medical Therapy Be classified as NYHA Class III Be aged ≥18 years old Have a QRS duration <120ms Have a LVEF ≥25% and ≤45% and Patient MUST NOT: Have a mechanical tricuspid valve Have a PR interval >375 ms Have clinically significant ambient ectopy Have a potentially correctible cause of heart failure, such as valvular heart disease or congenital heart disease **Fee**: $255.45 **Benefit**: 75% = $191.60
MBS Item number XXXXX B The permanent insertion, removal or replacement of two bipolar leads (two leads in the right ventricle). All leads are connected to the Cardiac Contractility Modulation (CCM) Implantable Pulse Generator (IPG). **Fee**: $837.35 **Benefit**: 75% = $628.05
MBS Item number XXXXX C The permanent insertion, removal or replacement of three bipolar leads (two leads in the right ventricle and one in the right atrium). All leads are connected to the Cardiac Contractility Modulation (CCM) Implantable Pulse Generator (IPG). **Fee**: $1036.05 **Benefit**: 75% = $777.05
MBS Item number XXXXX D Interrogation of the Cardiac Contractility Modulation (CCM) Implantable Pulse Generator (IPG) device for the following: Interrogate the IPG device parameters as currently programmed Modify the IPG device parameters Read ECG signals from patient and display for analysis Retrieve statistics accumulated by the IPG device as it operates Log the activity of the IPG device Store standard programs for future use Program the IPG device to safe parameter values in emergency situations. **Fee**: $69.75 **Benefit**: 75% = $52.35 85% = $59.30

The item descriptor proposed in the current resubmission was revised based on the exclusion criteria of the pivotal trials. This was in response to the MSAC which was concerned there remained a large number of exclusion criteria applied to the clinical trial populations by the applicant, which had not been incorporated into the descriptor (PSD 1387.1 2016, p3).

As per Application 1387.1, the implantation procedure must be performed by a Fellow of the Royal Australasian College of Physicians (FRACP) with specialty training in cardiology. This could include physicians with specialist training in electrophysiology or interventional cardiology. It is proposed that the insertion of the Optimizer® Smart device will be delivered in either an inpatient private or public hospital setting and requires one overnight hospital stay.

7. Summary of Public Consultation Feedback/Consumer Issues

The current resubmission provided clinical endorsement of CCM therapy from individual cardiologists; this was supportive of funding for CCM therapy noting improvements in quality of life, symptoms and LVEF in patients with heart failure. There was no public consultation feedback.

8. Proposed intervention's place in clinical management

The clinical treatment algorithm and the proposed place of CCM therapy (outlined in red) is shown in Figure 1. The current resubmission states that CCM therapy is currently the only treatment option for approximately 70% of HF patients with advanced HF symptoms who are inadequately controlled on OMT and have normal QRS duration. These patients are ineligible for cardiac resynchronisation therapy (CRT) as CRT is indicated for symptomatic HF patients with QRS duration of ≥120 ms. CCM would be delivered in addition to OMT.

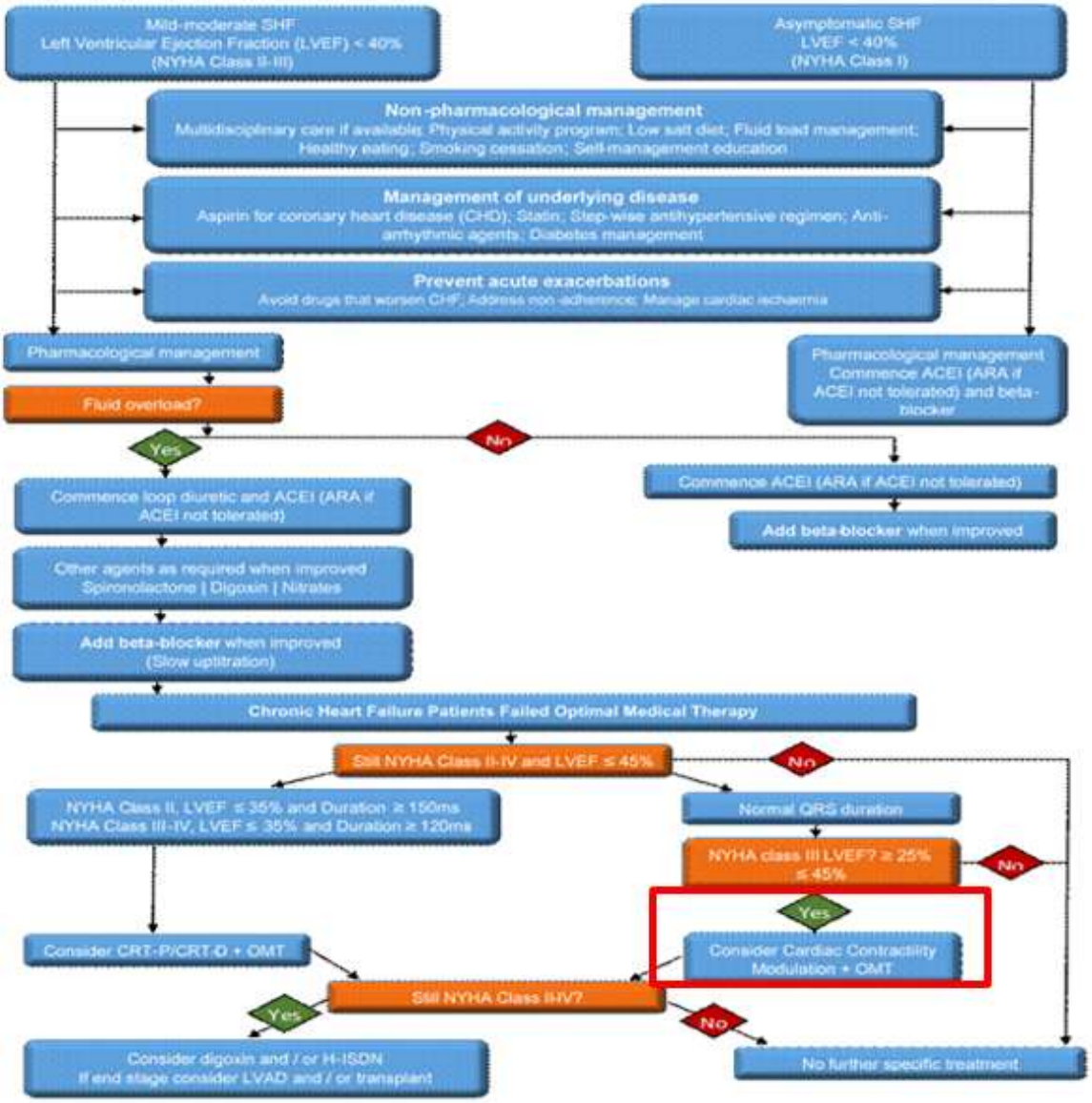


Figure 1 Clinical management algorithm for CCM therapy in patients with Chronic Heart Failure
ACEI = Angiotensin Converting Enzyme Inhibitor; ARA = Aldosterone Receptor Antagonist; CCM = Cardiac Contractility Modulation; CHF = Congestive Heart Failure; CRT-P/CRT-D = Cardiac Resynchronisation Therapy Pacemaker/Cardiac Resynchronisation Therapy Defibrillator; H-ISDN = Hydralazine–Isosorbide Dinitrate; LVAD = NYHA = New York Heart Association; OMT = Optimal Medical Therapy; QRS = SHF = Systolic Heart Failure;

9. Comparator

The comparator proposed by the current resubmission for CCM therapy is failed OMT, which was previously considered to be an appropriate comparator (for CCM therapy) by MSAC in the first and second submissions (PSD 1387.1 2016, p8). This is because there are currently no alternative treatment options for the patient population with normal QRS duration, and patients would continue to have symptomatic heart failure that may worsen if not managed appropriately. Failed OMT would include the use of diuretics followed by an angiotensin-converting-enzyme inhibitor (ACE) inhibitor and a beta-blocker. For those patients who cannot tolerate an ACE inhibitor, an angiotensin receptor blocker (ARB) would be added. Some patients will also be treated with an add-on aldosterone antagonist.

10. Comparative safety

The current resubmission includes three pivotal trials that were included in Application 1387.1: FIX-HF-5, FIX-HF-5 Pilot, and FIX-CHF-4. An additional (fourth) pivotal trial, FIX-HF-5C (intervention n=74; control, n = 86), is included in the current resubmission.

In addition to the pivotal trials, five supplementary long-term or safety analyses comparing CCM therapy to OMT and the MAGGIC study and Seattle Heart Failure Model were identified and presented in the previous resubmission and have also been included in the current resubmission as supplementary studies – Liu *et al.* (2016), Kuschyk *et al.* (2015), Kloppe *et al.* (2016), Roger *et al.* (2014), and Schau *et al.* (2011). One new safety study (Roger *et al.* (2018)) has also been included. Two new long-term (3 year follow-up), real-world, prospective registry studies (CCM-HF; n=143) and CCM-REG; n=140) were also included. The meta-analyses from the previous resubmission are also included in the current resubmission. The Critique stated the main issues identified with the evidence base are the inherent risk of bias associated with open label trial design (FIX-HF-5C trial) and the limited long-term follow-up (beyond 24 weeks) for RCT data on comparative safety and effectiveness outcomes.

Device-related adverse events were generally rarely reported in the evidence. The most commonly reported serious adverse events were worsening heart failure, arrhythmia, general cardiopulmonary and general medical events. No statistical difference in rates of serious adverse events between CCM and OMT groups were found (see Table 2).

Table 2 Balance of clinical benefits and harms of CCM therapy, relative to OMT (new studies only)

Outcomes (units) Follow-up	Participants (studies)	Quality of evidence (GRADE)	Relative effect (95%CI)	Risk with OMT	Risk with CCM therapy (95% CI)	Comments
Safety						
Proportion of patients without device-related or procedure-related complication	FIX-HF-5C 24 weeks	⊕⊕⊕⊕			89.7% (79.9, 95.8%)	Primary safety endpoint met
Proportion of patients who experienced a serious adverse event	FIX-HF-5C 24 weeks	⊕⊕⊕⊕		22.1%	27.0%	p=0.58

CCM = Cardiac Contractility Modulation; OMT = optimal medical therapy

11. Comparative effectiveness

CCM was associated with statistically significant improvements in six-minute hall-walk test (6MHW), Minnesota living with heart failure questionnaire (MLWHFQ) and NYHA class at 24 weeks follow-up; however wide confidence intervals reflect some uncertainty as to the true magnitude of the effect. No statistical difference in VO_2 was found (results from FIX-HF-5C trial). Results from the FIX-HF-5 subgroup were consistent with those reported in the FIX-HF-5C trial; however, a statistically significant difference in VO_2 was also found.

No statistical difference in mortality was found in the FIX-HF-5C trial (24 weeks follow-up) or the FIX-HF-5 sub group (50 weeks follow-up). No statistical differences were observed between mortality associated with the CCM and mortality predicted by the Seattle Heart Failure Model over three years follow-up (CCM-REG study). The Critique's summary of the effectiveness data is provided in Table 3.

Table 3 Summary of comparative effectiveness (Critique)

Study ID	Length of follow-up	pVO_2 (mL/kg/min)	MLWHFQ (points)	6MHW (meters)	NYHA improvement (>= 1 class, n/N (%))	VAT(mL/kg/min)	Mortality (all cause) n/N (%)
FIX-HF-5C Source: Submission (Table 36 -40) and Abraham et al. (2018)[1]	24 weeks	0.79 *(-0.09, 1.69)* *p = NR (NS)*	-11.7 *[-5.8, -18.1]* *p* = NR	33.7 *[6, 60]* *p* = 0.0093	I; 57/70 (81%)C: 32/75 (43%)*p* < 0.0001	NR	I: *2/74* (3%)C: *4/86* (5%)*p* = NS
FIX-HF-5 subgroupSource: Submission (Table 36 -40)	24 weeks	1.31 [NR]*p* = 0.001	-10.8 [NR]	21 [NR]*p* = 0.044	Mean change in class: -0.29 [NR] *p* = 0.002	0.64 [NR]*p* = 0.03	NR
FIX-HF-5 subgroupData from Abraham et al. (2018)[1]	*24 weeks*	*1.04 [0.36, 1.72]P = NR*	*-10.7 [-5.8, -15.6]P = NR*	*16.2 [-7.6, 40]P = NR (NS)*	*I: 47/103 (46%)C: 27/94 (29%)P = NR*	*NR*	*NR*
FIX-HF-5 subgroup Source: Submission (Table 36 -40)	50 weeks	1.09 [NR]*P = NR*	NR	NR	Mean change in class -0.34 [NR] *p* = 0.04	NR	4/109 (2%)2/97 (0.9%)*p* = 0.69

Abbreviations: 6MHW = six-minute hall-walk test; MLWHFQ = Minnesota living with heart failure questionnaire; NR = not reported; NS = not significant; NYHA = New York Heart Association; pVO2 =mixed venous oxygen tension; VAT = ventilatory anaerobic threshold.
Note: pVO_2, MWHFQ, 6MHW and VAT outcomes are reported as mean treatment difference between groups [95% CI]. NYHA class and Mortality outcomes are reported as (number affected)/ (total patients).
Source: Data from FIX-HF-5C trial and FIX-HF-5 trials reproduced from Tables 36 to 40 of the Submission. Data taken from the Submission is shown in black font; data which required correction, or which has been added for the Critique is shown in red italicised text. 95% CI data for the FIX-HF-5C trial extrapolated from Figure 2 in Abraham et al. (2018) and are therefore approximate values.

Clinical Claim

On the basis of the benefits and harms reported in the evidence base, the current resubmission proposes that, relative to failed OMT, CCM therapy has non-inferior safety and superior effectiveness.

The Critique stated that comparative effectiveness data available with a follow-up duration greater than 24 weeks is low quality and at high risk of bias; therefore, there is a lack of certainty in the effect of CCM beyond this period. In addition, there was limited evidence (from small subgroup analyses at high risk of bias) that CCM may be more effective in patients with a LVEF of 35-45% (compared to the 25-45% criteria of the proposed population).

12. Economic evaluation

The summary of the current resubmission's economic evaluation is presented in Table 4.

Table 4 Summary of the economic evaluation *(Critique)*

Perspective	Healthcare payer (Government) perspective
Intervention	Cardiac contractility modulation (CCM) therapy (Optimizer® Smart)
Comparator	Optimal Medical Therapy (OMT, or otherwise referred as standard of care or SoC)
Type of economic evaluation	Cost utility analysis
Sources of evidence	Clinical trial and registry data
Time horizon	Life-time (40 years) Shorter cycle lengths were also available
Outcomes	LYGs and QALYs
Methods used to generate results	Trial-based, individual sampling simulation & cohort hybrid model
Health states	NYHA Classes (I/II, III and IV) and death
Cycle length	Monthly
Discount rate	5%
Software packages used	Excel and R

Abbreviations: LYGs = life-years gained; NYHA = New York Heart Association; OMT = optimal medical therapy; QALY = quality-adjusted life years; SoC = standard of care

The Critique stated that the applicant's economic model was complex, with limited information provided to fully appraise the model and noted several significant model defects. As a result, the Critique advised caution when interpreting modelled results.

The current resubmission's base-case incremental cost-effectiveness ratio (ICER) was $35,630 per quality-adjusted life year (QALY) gained over a lifetime time horizon. The result of this base-case was based on a number of unsupported model settings and assumptions. The detailed incremental costs and QALYs are tabulated in Table 5. The Critique identified errors with costing inputs and re-calculated a (partially corrected) base-case ICER of $52,301 per QALY gained.

Table 5 Base-case results for CCM (40 year time horizon)

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Applicant's modelled results					
CCM therapy	$128,255	$36,744	5.790	1.03	$35,630
OMT	$91,511		4.759		
Critique re-calculated modelled results					
CCM therapy	*$162,296*	*$53,937*	5.790	1.03	*$52,301*
OMT	*$108,359*		4.759		

CCM = cardiac contractility modulation; ICER = Incremental Cost Effectiveness Ratio; OMT = optimal medical therapy; QALY =quality-adjusted life year
Italics represents Critique's updated base-case economic evaluation

The MSAC previously considered the key drivers of the revised economic model to be NYHA distribution, the method used to estimate utility weights and the time horizon (PSD 1387.1 2016, p3). The resubmission presented results from probabilistic sensitivity analyses and deterministic sensitivity analyses, including assessments of previously identified model drivers (Table 6).

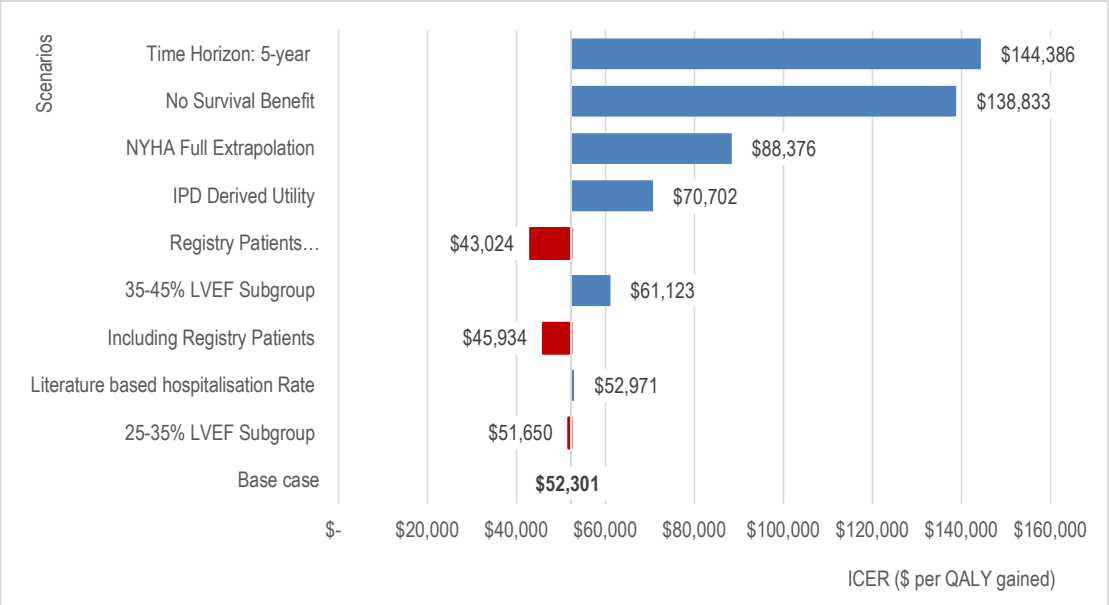
Table 6 Deterministic sensitivity analysis results

	Incremental cost	Incremental effectiveness	ICER
Time horizon 10 years (base case = 40 years) *Critique re-calculated modelled results (updated base case)*	$32,299	0.61	$52,753 *$69,758*
Utility values (base case = literature values from NICE CG108) +0.1 utility NYHA class -0.1 utility NYHA class	 $36,744 $36,744	 1.13 0.93	 $32,485 $39,450
Hospitalisation cost (base case = weighted avg. of AR-DRGs)[a] Higher estimate Lower estimate	 $36,267 $37,101	 1.03 1.03	 $35,167 $35,976

CCM = cardiac contractility modulation; DRG = Diagnosis related group; ICER = Incremental Cost Effectiveness Ratio; NYHA = New York Heart Association; OMT = optimal medical therapy; QALY =quality-adjusted life year
[a] F62A and F62B, based on number of separations
Italics represents Critique's updated base-case economic evaluation

Using the recalculated base-case model, the Critique presented additional deterministic sensitivity analyses (Figure 2).

Figure 2 Deterministic sensitivity analyses performed for the Critique, Tornado Diagram.



Source: Compiled for the Critique.
NYHA = New York heart association; IPD = individual patient data; LVEF = left ventricular ejection fraction; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life years
Note, results ranked based on the magnitude of impact to the base case

13. Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications of introducing CCM (i.e. Optimizer® Smart device) to the MBS. The MBS costs were estimated assuming a 75% MBS rebate (i.e. in-hospital service). The expected financial implications over the first 5 years following listing of CCM therapy on the MBS are summarised in Table 7.

Table 7 Total number of services and financial burden to the MBS over 5 years

	Year 1	Year 2	Year 3	Year 4	Year 5	Reference
CCM Therapy						
Insertion/removal of IPG A *(no. of services)*	123	500	764	1,039	1,325	A1
Subtotal cost	$23,474	$95,749	$146,460	$199,137	$253,837	(A1*$192) = P1
Insertion/removal of leads B, C* *(no. of services)*	123	500	764	1,039	1,325	A1
Subtotal cost	$86,072	$351,088	$537,033	$730,185	$930,758	(A1*$703) = P2
Interrogation of IPG D *(no. of services)*	245	1,122	2,151	3,465	5,067	A2
Subtotal cost	$14,530	$66,533	$127,558	$205,494	$300,986	(A2 × $59) = P3
Sub-total number of services	490	2,121	3,680	5,544	7,725	((A1 × 2) + A2) = B1
Sub-total cost	$124,076	$513,370	$811,050	$1,134,816	$1,485,581	(P1 + P2 + P3) = S1
Co-administered services currently MBS listed						
No. of services per year for each co-administered MBS service	123	500	764	1,039	1,325	A1
Consultant Surgeon *(subtotal cost)*	$14,077	$57,419	$87,830	$119,420	$152,223	(A1 × $115) = P4
Anaesthetist *(subtotal cost)*	$4,012	$16,366	$25,034	$34,038	$43,388	(A1 × $33) = P5
Anaesthesia initiation *(subtotal cost)*	$12,735	$51,947	$79,460	$108,039	$137,716	(A1 × $104) = P6
Anaesthesia (1 hour) *(subtotal cost)*	$7,277	$29,684	$45,406	$61,737	$78,695	(A1 × $59) = P7
X-ray *(subtotal cost)*	$3,253	$13,268	$20,295	$27,594	$35,174	(A1 × $27) = P8
Sub-total number of services	613	2,499	3,822	5,197	6,624	(A1 × 5) = B2
Sub-total cost	$41,355	$168,685	$258,025	$350,828	$447,196	(P4 + P5 + P6 + P7 + P8) = S2
Total services	1,103	4,620	7,502	10,741	14,349	B1 + B2
Total cost (Intervention)	*$165,430*	*$682,055*	*$1,069,075*	*$1,485,644*	*$1,932,777*	S1 + S2

Source: Compiled from the Critique using information presented in tables 65, 67 and 68, p.154-56, Section E of the Submission.
Abbreviations: MBS = Medicare Benefits Schedule, IPG = Implantable Pulse Generator.
*The leads price is based on average price of the insertion/removal of 2 or 3 leads (of $628.05 and $777.05 at 75% benefit respectively)

The financial implications of introducing CCM therapy to the government health budget is summarised in Table 8.

Table 8 Total costs to the MBS and other government budgets associated with introduction of CCM therapy

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients treated with CCM therapy[a]	123	500	764	1,039	1,325
Cost to government from PBS/RPBS	$0	$0	$0	$0	$0
Cost to government from MBS[b]	$165,430	$682,055	$1,069,075	$1,485,644	$1,932,777
Cost of hospitalisation	$1,040,784	$4,245,360	$6,493,808	$8,829,415	$11,254,744
Cost offset of CCM hospitalisation	-$133,772	-$411,885	-$288,994	-$300,196	-$311,728
Cost of CCM device (Optimizer®)	$3,995,786	$16,298,810	$24,931,067	$33,897,941	$43,209,282
Total net cost of CCM	**$5,068,228**	**$20,814,340**	**$32,204,957**	**$43,912,803**	**$56,085,075**

CCM = Cardiac contractility modulation; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme
[a] Resubmission estimated a 2% uptake rate for CCM, rising to 20% over 5 years
[b] Resubmission calculated using the 75% rebate level (in-hospital service)

The Critique stated the net cost to the MBS is predicted to be greater than the current resubmission's estimates due to uncertainty in defining the eligible population, potentially underestimated uptake, and the additional service costs which may be associated with the use of CCM devices.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Comparative safety	Device-related adverse effects appear to be rare. Intervention appears to be safe.
Comparative effectiveness	There is insufficient evidence to be certain of clinical effectiveness.
Proposed patient population	The inclusion of patients with atrial fibrillation will require further evidence.
Implementation issues if approved	Accreditation of specialists as required by current Cardiac Implantable Electronic Devices guidelines of the Cardiac Society of Australia and New Zealand (CSANZ). Decisions will need to be made about who is able to implant the device, their competence and how often they should be monitored. It would be useful to seek advice from CSANZ on this issue.
Over-extrapolation remains a key issue	The effectiveness data and extrapolation methods do not address the concerns previously identified by MSAC: the economic model relies on a consistent proportional reduction in survival for up to 40 years post treatment, based on RCT evidence of a treatment-induced improvement in NYHA class 12 months after treatment. The assumptions in the model, that a) NYHA class will not decline over time due to disease progression, and b) that all heart failure patients have the same probability of death regardless of NYHA class, are clinically implausible.
Errors and misleading descriptions of the model, and use of unsubstantiated methods and assumptions	The ICERs reported in the SBA are incorrect and MSAC should rely on the corrected ICERs presented in the Critique. MSAC should also note the many remaining issues with the model that were not sufficiently described or justified by the applicant and could not be verified and/or corrected by the Assessment Group.

ESC key issue	ESC advice to MSAC
Uncertainty in financial estimates	Although the projected impact to the MBS budget appears modest, there is significant uncertainty regarding the size of the total likely eligible patient population and the rate of uptake of the IPG devices, and hence uncertainty regarding the total cost to the health system.

ESC Discussion

Application 1387.2 is a resubmission requesting Medicare Benefits Schedule (MBS) listing of cardiac contractility modulation (CCM) therapy (Optimizer™ SMART system) for patients with chronic heart failure (HF) who have failed to respond to optimal medical therapy (OMT). ESC recalled that CCM therapy has been previously considered twice by MSAC and rejected on the basis of uncertain clinical and cost-effectiveness, particularly related to lack of evidence on long-term morbidity and mortality.

ESC noted that the resubmission includes results of the FIX-HF-5C confirmatory trial, which was published in 2018. New data also includes a subgroup analysis of the original FIX-HF-5 trial. The resubmission also included data from an ongoing registry study (CCM-REG), with data provided for 140 patients.

ESC noted that the CCM device considered in the previous submissions was the Optimizer IV System (which requires three leads: two ventricular and one atrial). The current resubmission relates to the latest Optimizer SMART System (which only requires two ventricular leads, with an optional atrial lead). Most patients will have three leads implanted; patients with atrial fibrillation (AF) only require the two ventricular leads. ESC noted the implicit assumption in the resubmission that the clinical evidence presented, which largely relates to the Optimizer IV device, can be directly applied to the SMART device. However, ESC noted that AF was among the exclusion criteria for the FIX-HF-5(C) trials.

ESC noted that an application has been made for the device to be listed on the Prostheses List (13 February 2019). The application has been referred to the Cardiac Prostheses Clinical Advisory Group for advice on whether the device satisfies the criteria for listing on the Prostheses List. If the device is not listed on the Prostheses List, there is the potential for significant out-of-pocket costs for patients.

ESC considered that the proposed item descriptors adequately cover the proposed population, although there is no evidence to support use in AF patients. ESC also queried how frequently (and why) interrogation of the device would be required.

ESC noted that the low rate of adverse events in the Critique's updated analysis using the new trial data (from more than 2500 patients) was consistent with data in previous submissions. The FIX-HF-5C trial showed no statistical differences in serious adverse events between the CCM and OMT groups. ESC therefore considered CCM has non-inferior safety as previously accepted by MSAC.

ESC noted outcome data from the FIX-HF-5C trial. For pVO_2, results were mixed and there was no significant difference between CCM and OMT arms. CCM was associated with statistically significant improvements in the 6MWT, the Minnesota Living With Heart Failure Questionnaire (MLWHFQ) and New York Heart Association (NYHA) class at 24 weeks follow-up. However, ESC considered the wide confidence intervals reflect uncertainty about the true magnitude of the effect. ESC also noted that the 6MWT is a subjective test and

depends on factors other than HF, and that although there appears to be improvement in NYHA class, it too is an essentially subjective measure and hence the reliability of this result is uncertain because the trials were not blinded. The more objective outcome of ventilatory anaerobic threshold showed no improvement with CCM.

ESC noted that the FIX-HF-5C trial (24 weeks follow-up) and the FIX-HF-5 subgroup (50 weeks follow-up) showed no statistical difference in mortality after CCM. There was also no statistical difference between mortality associated with CCM and mortality predicted by the Seattle Heart Failure Model over three years follow-up (CCM-REG study). ESC noted that comparative effectiveness data with a follow-up duration longer than 24 weeks is of low quality and at high risk of bias.

ESC noted limited evidence from the FIX-HF-5 subgroup analysis that CCM may be more effective in patients with an LVEF of 35–45% (compared with 25–45% specified for the proposed population). However, ESC agreed with the Critique that this analysis is at high risk of bias and this result should be interpreted with caution.

ESC noted that the Critique identified and corrected a number of calculation errors in the economic model presented in the resubmission. The errors significantly favoured CCM. The Critique's corrections increased the reported base case ICER from $36,000 per QALY to $52,000 per QALY. ESC noted that the applicant did not specifically dispute any of the claimed corrections in their pre-ESC response. ESC therefore advised MSAC to use ICERs calculated by the Critique when assessing this application, noting the sources of uncertainty that still remain with the modelling (see below).

ESC agreed with the Critique that there was little information in the resubmission about how the model was developed and implemented, which made assessment and verification of the model difficult. ESC considered that the model was effectively a trial-based individual sampling simulation and cohort hybrid model. The health states included in the model were NYHA Classes (I/II, III and IV) and death, but ESC noted that mathematically the model behaved with only two states – alive and dead.

ESC noted the following issues with the revised economic model:

- the model appeared to be based on a previously published model for ivabradine but many aspects of the model seem to have been adopted without any apparent scrutiny or justification; ESC considered that the applicant's pre-ESC response did not adequately address these concerns; and
- the time horizon was extended to 40 years (lifetime), despite MSAC's advice that time horizons of 30 years and 15 years in the two previous submissions (respectively) were over-extrapolations from the available 12 month data and not consistent with the 50% 5-year mortality rates associated with heart failure with reduced ejection fraction.

ESC noted that although the resubmission includes data from the FIX-HF-5C trial, the model still relies on 12-month effectiveness data. Although the model includes the option to run the extrapolation using single-arm registry data, this only extends the basis of the extrapolation from one year data to three year data. ESC agreed with the Critique that the use of the 40-year model introduces additional issues and higher levels of uncertainty than the models previously considered by MSAC. ESC considered that the applicant's pre-ESC response did not adequately address the issue of over-extrapolation from 1 year of data. ESC considered a more appropriate time horizon to be 5–10 years.

ESC noted that patients enter both arms of the model (CCM and OMT) in NYHA class III, which aligns with the proposed MBS population. ESC queried whether the rapidity of patient movement from NYHA III to NYHA I/II in the CCM arm is appropriate given the subjectivity of assessment and outcome measures. ESC also noted that, not only is the model overly reliant on 12-month data, maintaining patient distributions at 12 months for the following 39 years of the time horizon, the premise of the model is not clinically plausible.

ESC noted that the distributions across NYHA classes at 12 months drives the between-arm differences in costs and outcomes for the remainder of the model. ESC queried why modelling of survival benefit did not include the accepted relationship between NYHA class and mortality. Instead, survival curves were fitted to individual patient data (IPD) from trials (noting that no description was provided by the applicant as to exactly which trial data were used for this). Given the very low frequency of death in the FIX-HF-5 trial (which was not statistically significant), ESC queried whether this was a valid approach.

ESC noted that the resubmission claimed to incorporate mortality data from general HF populations to prevent the survival of the CCM cohort from exceeding general population mortality. However, as noted in the Critique, the extrapolated survival data (based on either the trial data or the registry data) yielded higher survival for CCM recipients than for the general population. This undermines the results generated by the model. The Critique identified the issues associated with the method for extrapolating survival as one of the most significant defects of the model.

ESC noted that the description provided in the resubmission for how patients move between NYHA classes was inadequate. The applicant's pre-ESC response explained that the statistical model describing the distribution of patients across NYHA classes in the first 12 months was prepared by York Health Economics Consortium (YHEC), but provided no further detail. ESC noted that although the applicant claimed that fixing NYHA classes after 12 months (last observation carried forward, LOCF) is a conservative approach, this is clinically implausible and indicates erroneous assumptions within the model. ESC agreed with the Critique that LOCF is not an appropriate way to correct the model.

ESC noted that, despite the claim in the submission that MLWHFQ scores from IPD in the FIX-HF-5(C) trial were mapped to EQ-5D utility weights (using two published algorithms) and applied in the model, the base case used utility weights sourced from the literature. The Critique concluded that the literature-based weights and the way they were applied in the model appeared to be more reliable, but using these weights in the model slightly favoured CCM. ESC noted that an option to use IPD values was available in the model.

ESC noted results of the Critique's sensitivity analyses (using the Critique's corrected base-case ICER of $52,000):

- time horizon of 5 years – ICER $144,000/QALY
- using the same probability of survival for both arms (i.e. removing survival benefit and assuming survival of CCM recipients is the same as for the general population) – ICER $138,000/QALY
- using full extrapolation for NYHA class (i.e. removing the LOCF assumption and allowing the NYHA state to be fully extrapolated using the model supplied in the submission) – ICER $88,000;
- using the utility weights derived from trial IPD – ICER $70,000.

ESC noted that financial and budgetary impacts were determined using a combined market share and epidemiological approach. ESC noted that the Critique incorporated 2018

Australian HF guidelines (published after the application was submitted), and considered this to be a more appropriate approach.

ESC noted uncertainty in the population estimate provided in the submission, arising from:

- potential underestimation of the number of patients with HF (1.75%) – according to 2018 national guidelines, 2.1% of Australian adults have HF;
- potential overestimation of the number of HF patients who have systolic left ventricular dysfunction (SLVD) (78%) – the Critique noted that larger studies have estimated that about 50% of HF patients exhibit SLVD;
- lack of a clear definition of 'failed OMT' (26.5%) – this makes it difficult to judge the applicability of the estimate used (failed OMT was inferred from the percentage of patients in an RCT, with different population demographics, who died or were hospitalised for HF after use of ACE inhibitors);
- potential overestimation of the number of patients with QRS <120ms (69%) based on analysis of Swedish Heart Failure Registry data (2000–2011) - whereas the estimate from an analysis of Registry data for 2000–2013 was 56%;
- the estimate for the proportion of patients in NYHA class III (31%) – uncertain given misalignments between the data source and the proposed populations;
- estimates of the percentage of patients with reduced ejection fraction were applied twice, once as the proportion with SLVD and once as the proportion with LVEF of 25–45%; this was considered to be inappropriate.

ESC noted that after the Critique applied corrections to compensate for these issues, the estimated eligible patient pool nearly doubled to more than 11,200 compared with the resubmission estimate of about 6,100.

ESC noted that the resubmission did not appropriately account for incident versus prevalent cases of HF. ESC also noted that the uptake rates applied over years 1 to 5 (2%, 8%, 12%, 16% and 20%, respectively) were not adequately justified and appear unreasonable. ESC noted advice received by the Assessment Group that uptake may be closer to 25–50%.

ESC noted that cost estimates in the resubmission were similar to previous estimates but that some costs were underestimated. After including adverse event costs, the Critique estimated an updated base case for financial burden to the health system slightly higher than that in the resubmission ($56.6 million after 5 years vs $56.1 million).

ESC noted results of the Critique's sensitivity analyses which used the updated base case and applied +/–25% eligible patient numbers, +/–25% uptake rate each year, updated initial eligible population pool, and uptake of 25% in Year 1 and 50% each year thereafter. ESC noted that these were all one-way analyses, with estimated total costs to the health system of potentially up to $140 million in Year 5.

ESC noted that potential MBS service utilisation is uncertain. Current use of CCM devices in Australia is low (to date the device has been used in only 18 patients). Consumer groups were unaware of the devices and were therefore unable to advise as to their likely value to consumers.

ESC also noted a potential implementation issue because the Cardiac Implantable Electronic Devices guidelines of the Cardiac Society of Australia and New Zealand (CSANZ) require specialists to be accredited. Decisions will need to be made about who is able to implant the device, their competence and how often they should be monitored. ESC suggested it would be useful to seek advice from CSANZ on this issue.

15. Other significant factors

Nil

16. Applicant's comments on MSAC's Public Summary Document

Impulse Dynamics is disappointed with MSAC's decision not to support public funding of cardiac contractility modulation (CCM) therapy. Improvement in NYHA class is a well-established, independent predictor of mortality benefit and CCM therapy significantly improves this outcome. Therefore, it is highly likely that patients will benefit from a mortality reduction should CCM be funded. Pooled data from the FIX-HF-5C and FIX-HF trials also demonstrated a significant difference in the composite endpoint of cardiovascular mortality and heart failure hospitalisation. Impulse Dynamics strongly disagrees with the analysis provided in the Critique in which a number of changes were made to the model and alternate ICERs and sensitivity analyses were generated. Due to the lack of transparency regarding these changes, Impulse Dynamics was unable to verify whether they had validity and in fact it is likely they underestimate the cost-effectiveness of CCM therapy. It is unfortunate that patients with very few viable treatment options will be denied access to this potentially useful therapy.

17. Other significant factorsFurther information on MSAC

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