



Australian Government

Medical Services Advisory Committee

## Public Summary Document

### ***Application No. 1387.1 – OPTIMIZER™ IVs Implantable Pulse Generator (IPG) – cardiac contractility modulation therapy for patients with heart failure***

**Applicant:** MetaCure Australia Pty Ltd

**Date of MSAC consideration:** MSAC 67<sup>th</sup> Meeting, 28-29 July 2016

Context for decision: MSAC makes its advice in accordance with its Terms of Reference [visit MSAC website](#)

#### **1. Purpose of application and links to other applications**

A resubmission requesting a new Medicare Benefits Schedule (MBS) listing of cardiac contractility modulation (CCM) therapy (OPTIMIZER™ IV system), for patients with chronic heart failure, was received from MetaCure Australia Pty Ltd by the Department of Health.

This public summary document (PSD) should be reviewed in conjunction with the PSD for Application 1387.

#### **2. MSAC's advice to the Minister**

After considering the strength of the available evidence presented in relation to the comparative safety, clinical effectiveness and cost effectiveness of CCM therapy (OPTIMIZER™ IV system) for patients with chronic heart failure, 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.

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

MSAC noted that the proposed population in the resubmission was the same as in the previous submission, with therapy intended for use in patients with symptomatic heart failure due to systolic left ventricular dysfunction despite optimal medical treatment (OMT) who are:  $\geq 18$  years of age, have a New York Heart Association (NYHA) functional class of III, have a QRS duration  $< 120$  ms and have a left ventricular ejection fraction (LVEF)  $\geq 25\%$  and  $\leq 45\%$ .

MSAC reiterated that in contrast to patients with a prolonged QRS duration, there are currently no alternative device treatment options for the patient population with normal QRS duration. MSAC noted that this was the main argument for using OMT as the comparator for this application.

MSAC considered the evidence presented in the resubmission to support the claim that CCM therapy has non-inferior safety compared to OMT. MSAC reiterated that there were no significant differences in the pooled relative risk for all-cause mortality or hospitalisations between patients treated with CCM or OMT (Kwong JSW et al 2012). MSAC also noted that the updated post-market surveillance data provided by the applicant (which related to approximately 2,500 patients) indicated that the rate of device malfunctions and complications remained rare, at approximately 3%.

MSAC noted that the evidence for the clinical efficacy of CCM therapy presented in the previous submission was weak and based on surrogate outcomes. The FIX-HF-5 study was the largest randomised controlled trial (RCT) presented. At the time, MSAC was concerned that although the data indicated that CCM therapy improved patient symptoms, quality of life and exercise parameters, the durability of these effects beyond a 12 month follow-up period was unknown. MSAC recalled that it had recommended that the findings of the subsequent FIX-HF-5C trial be included in any new submission as it foreshadowed it may provide a means of demonstrating the magnitude and durability of the treatment effect.

In its consideration of the current resubmission, MSAC acknowledged the comments made by the applicant regarding the FIX-HF-5C trial. The applicant clarified that the FIX-HF-5C trial is small and confirmatory in nature with a short follow-up duration. The applicant indicated that the study is being carried out only to assess the peak VO<sub>2</sub> surrogate outcome as a primary rather than a secondary endpoint (in contrast to the FIX-HF-5 study). In light of this, MSAC accepted that the findings of this study were unlikely to alleviate the committee's concerns surrounding the clinical efficacy of CCM therapy.

MSAC noted that the FIX-HF-5 study therefore remains the largest RCT provided by the applicant to support the clinical efficacy of CCM therapy. MSAC remained concerned that participants and investigators in this trial were not blinded and that this may have an impact on the subjective endpoints reported. MSAC indicated that in using the last observation carried forward (LOCF) to inform NYHA states for the remaining lifetime, this study also inappropriately assumed that the treatment effect of CCM was maintained over this duration. MSAC was also concerned that the FIX-HF-5 subgroup, which had the closest characteristics to the proposed population, was identified through a post hoc hypothesis-generating analysis rather than being a pre-specified group.

MSAC considered the new evidence provided in the resubmission in the form of three non-randomised studies which the applicant claimed demonstrated the durability of the benefit of CCM therapy beyond 12 months (Kloppe A et al 2016; Kuschyk JS et al 2015; Liu FF et al 2016). MSAC noted that these studies were observational with a small number of participants (n<100) and a high risk of bias which affected the validity of their results. Consequently, MSAC questioned the applicant's claim that patients who received CCM therapy experienced a long-term survival benefit compared to those who did not receive the intervention. MSAC noted that the only statistically significant difference in observed mortality amongst those receiving CCM therapy in the study by Kuschyk JS et al 2015, and the predicted mortality for those who did not in the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) study, was witnessed at the one-year mark. MSAC noted that all of the differences in mortality between the observed and predicted rates reported by Kloppe A et al 2016 and

using the Seattle Heart Failure Model (SHFM) scores, respectively, were small and non-significant. MSAC concluded that the clinical effectiveness of CCM therapy, particularly its effect on morbidity and mortality, remained uncertain. MSAC noted that the resubmission did not include new data from RCTs to inform the effect of CCM therapy on these outcomes.

MSAC acknowledged the use of a 15-year time horizon in the revised economic model. However, MSAC remained concerned that the revised time horizon remained biologically implausible given the likely poor prognosis of the proposed population and considered that the model was over-extrapolated given the data informing the model was based on only a single year of patient follow up. MSAC noted that in contrast to the previous model, which failed to take into account the progressive nature of heart failure and the inevitable worsening of patient symptoms, the model in the current resubmission allowed for deterioration in NYHA class using an updated assumption that 0.5% of patients would transition to the next worse NYHA class on a monthly basis. However, MSAC noted that this deterioration rate was not justified in the resubmission and could not be verified. MSAC also noted that in contrast to MSAC guideline recommendations, a discount rate of 3.5% was used for both costs and outcomes in the revised model. MSAC remained concerned that the data informing the clinical effectiveness in the model, which were considered uncertain beyond 12 months, remained unchanged from the previous submission.

MSAC noted that the cost-utility analysis generated a discounted ICER of \$33,327 per QALY gained (compared to \$34,539/QALY in previous submission) and \$49,001 per life year gained. MSAC considered NYHA distribution to be one of the key drivers of the revised economic model. MSAC was concerned about the differences in the number of patients allocated to the various NYHA classifications in the intervention and control groups, as revealed by the Markov traces provided in the resubmission. MSAC noted that the data and method used to estimate utility weights remained unchanged from the previous submission and this was another key driver of the model. In turn, MSAC remained concerned about the differences in the utility values used for the same state between the intervention and control groups, with higher values assigned to the NYHA states for the intervention group. MSAC considered the time horizon to be another driver of the economic model, with a five-year time horizon generating an ICER of approximately \$77,000 per QALY compared \$50,000 per QALY for a seven-year time horizon.

MSAC noted that the financial uncertainties raised in regards to the previous submission still remained and was concerned that the resubmission underestimated the projected uptake of the service by underestimating the demographics of the potentially eligible population of heart failure patients.

MSAC noted that the item descriptor proposed in the resubmission was unchanged from the previous submission. MSAC reiterated that there remained a large number of exclusion criteria applied to the clinical trial populations cited by the applicant, which had not been incorporated into the descriptor.

MSAC did not support public funding of CCM therapy for patients with chronic heart failure as the committee was not satisfied with the strength of evidence presented in the resubmission to support its clinical effectiveness, particularly its effect on morbidity and mortality. MSAC considered that the cost effectiveness of CCM therapy was also uncertain and questioned the appropriateness of a 15-year time horizon for extrapolating short-term follow-up data. MSAC emphasised that any future application should present evidence from a RCT demonstrating that CCM therapy leads to significant reductions in morbidity and mortality amongst the proposed population.

#### 4. Background

MSAC considered Application 1387 CCM therapy (OPTIMIZER™ IV system) at its July 2015 meeting. MSAC did not support public funding because of uncertain clinical effectiveness and cost-effectiveness. MSAC considered that the key areas of uncertainty were the magnitude and durability of any effects on symptoms and quality of life, hospitalisation or mortality and whether a treatment-induced improvement in New York Heart Association (NYHA) class would result in a consistent proportional improvement in survival. The PSD for this application can be viewed on the MSAC website.

#### 5. Prerequisites to implementation of any funding advice

The components of the OPTIMIZER™ IV system are registered on the Australian Register of Therapeutic Goods (ARTG).

As per Application 1387, the implantation procedure must be performed by a Fellow of the Royal Australasian College of Physicians with specialty training in cardiology. The application noted that the procedure should only be performed in a hospital equipped for cardiac surgery and it would be assumed that such a hospital would already have the necessary equipment available, so no additional resources would be required.

#### 6. Proposal for public funding

The resubmission proposed MBS listings are:

Category 3 - THERAPEUTIC PROCEDURES
MBS Item number XXXX Permanent Cardiac Contractility Modulation (CCM) Implantable Pulse Generator (IPG) device insertion, removal or replacement of, for a patient with all of the following: (a) Symptomatic heart failure due to systolic left ventricular dysfunction despite failed Optimal Medical Therapy; (b) NYHA Class III; (c) ≥ 18 years; (d) Normal QRS duration (<120ms); (e) LVEF ≥25% and ≤45%. Fee: \$255.45 Benefit: 75% = \$191.60
MBS Item number XXXX Permanent Cardiac Contractility Modulation (CCM) Implantable Pulse Generator (IPG) device insertion, removal or replacement of, for a patient with all of the following: (a) Symptomatic heart failure due to systolic left ventricular dysfunction despite failed Optimal Medical Therapy; (b) NYHA Class III; (c) ≥ 18 years; (d) Normal QRS duration (<120ms); (e) LVEF ≥25% and ≤45%. Fee: \$255.45 Benefit: 75% = \$191.60
MBS Item number XXXXX The permanent insertion, removal or replacement of three bipolar leads, one in the right atrium and two leads in the right

ventricle. All three leads are connected to the Cardiac Contractility Modulation (CCM) Implantable Pulse Generator (IPG).

Fee: \$1,224.60 Benefit: 75% = \$918.45

MBS Item number XXXXX

Interrogation of the Cardiac Contractility Modulation (CCM) Implantable Pulse Generator (IPG) device for the following:

- (f) Interrogate the IPG device parameters as currently programmed;
- (g) Modify the IPG device parameters;
- (h) Read ECG signals from patient and display for analysis;
- (i) Retrieve statistics accumulated by the IPG device as it operates;
- (j) Log the activity of the IPG device;
- (k) Store standard programs for future use;
- (l) Program the IPG device to safe parameter values in emergency situations.

Fee: \$69.75 Benefit: 75% = \$52.35 85% = \$59.30

CCM = cardiac contractility modulation; IPG = implantable pulse generator; NYHA = New York Heart Association classification; LVEF = left ventricular ejection fraction; ECG = electrocardiogram

The resubmission noted that the insertion and removal of both the CCM IPG and bipolar leads will require approximately the same technical complexity and duration. As such, the proposed MBS fees for the process of insertion and removal should be set at the same level.

There are currently no reimbursed CCM therapies on the MBS.

The resubmission proposed that the implantation of the CCM IPG device and bipolar leads are similar to those associated with Implantable Cardiac Devices and cardiac electrodes (leads) (MBS item numbers 38353, 38356, 38365, 38368, 38654 and 11721). These MBS item numbers are appropriate, as they are representative of the technical characteristics of the insertion, removal or replacement of the CCM IPG and bipolar leads and follow-up interrogation.

The resubmission stated that the treating cardiologist who manages the patient's chronic heart failure should be eligible to claim interrogation of the device. The results of the test would be communicated to the patient at the time that the interrogation is performed. It is recommended that patients who receive the OPTIMIZER™ IVs have follow-up interrogation twice during the first year, and once yearly thereafter. This will allow the settings to be personalised to achieve the greatest therapeutic benefit. This is based on current clinical experience and after consultations with treating cardiologists.

Currently battery chargers are also equipped with a patient alert system which informs the patient to contact a physician in case of malfunctions of the device or other abnormalities.

## 7. Summary of Public Consultation Feedback/Consumer Issues

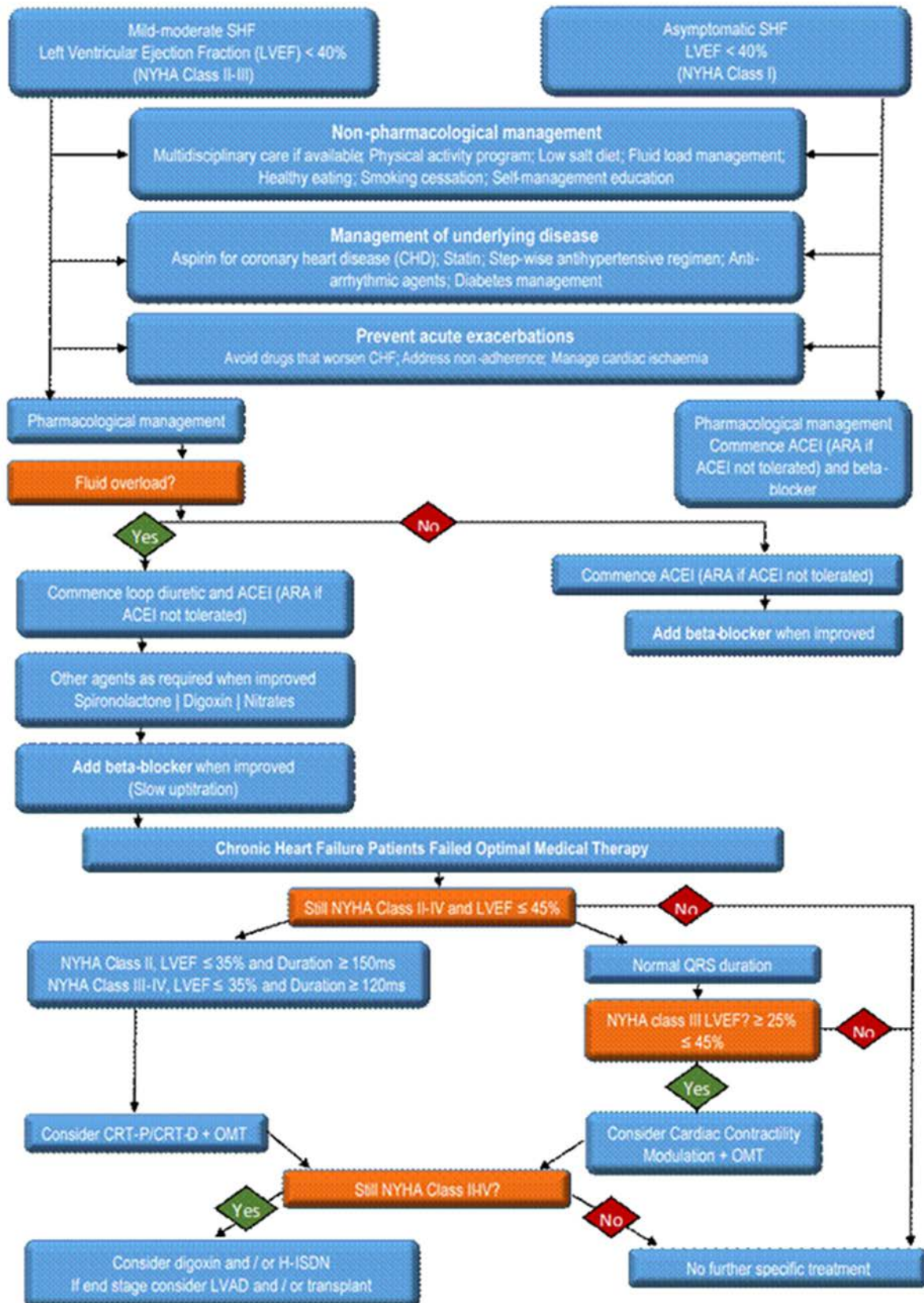
There was no public consultation feedback received.

## **8. Proposed intervention's place in clinical management**

The current treatment algorithm and the proposed place of CCM therapy is shown in Figure 1.

The resubmission stated that CCM therapy is currently the only treatment option for approximately 80% of HF patients with advanced HF symptoms who are inadequately controlled on optimal medical therapy and have normal QRS duration. These patients are not suitable for Cardiac Resynchronisation Therapy (CRT), as CRT is indicated for symptomatic HF patients with QRS duration of  $\geq 120$ ms.

Figure 1 Current Treatment Algorithm including proposed place of CCM



## 9. Comparator

The main comparator, 'failed optimal medical therapy' (OMT) remains unchanged from the previous submission and was considered appropriate by the MSAC in July 2015.

## 10. Comparative safety

The key safety results were from three sources:

- FIX-HF-5 intention-to-treat (ITT group) (n=428):
  - Serious adverse events were common in this population (~50% in FIX-HF-5); however, there were no overall significant differences between patients treated with CCM therapy versus those treated with OMT therapy in the short-term (< 6 months); and
  - Implantation failure of CCM (n=215) occurred in two patients (0.93%).
- Meta-analysis by Kwong et al (2012) (n=629):
  - There were no significant differences in pooled all-cause mortality (Relative risk: 1.19 (95% confidence interval (CI): 0.50 to 2.86)) or pooled all-cause hospitalisations (Relative risk: 0.64 (95% CI: 0.38 to 1.08)) between patients treated with CCM therapy versus those treated with OMT in the short term (< 6 months).
- Post-market surveillance data (n=1,553):
  - Device malfunctions occurred in 44 patients (2.8%) (p6, Public Summary Document), which remained similar for the updated analysis (n > 2,500).

The resubmission maintained the same clinical claim, that when compared with OMT, CCM plus OMT (at both 24 weeks and 50 weeks) were:

- superior in terms of comparative effectiveness; and
- associated with limited and transient adverse events.

## 11. Comparative effectiveness

The resubmission was based on: three direct randomised trials comparing CCM plus OMT with OMT (FIX-CHF-4, FIX-HF-5 Pilot and FIX-HF-5); two meta-analyses of the same three trials (Giallauria *et al* (2014) and Kwong *et al* (2012)); and five supportive studies which assessed the long-term safety of CCM therapy. The three direct randomised trials, two meta-analyses and two of the supportive studies (Schau *et al* (2011) and Roger *et al* (2014)) were included in the previous submission.

The new information in the resubmission were three non-randomised studies (Liu *et al* (2016), Kuschyk *et al* (2015) and Kloppe *et al* (2016)) with up to seven years follow-up (rather than up to one year for the key trials). The resubmission stated that this new long-term data were provided as supportive evidence.

Based on Liu *et al* (2016), the resubmission made an additional claim that the long-term outcomes of CCM plus OMT, including all-cause mortality, cardiovascular deaths and heart failure hospitalisations, were significantly superior when compared with OMT, over a period of up to seven years.



The relevant population for the proposed MBS listing of CCM was adults with New York Heart Association (NYHA) class III heart failure and left ventricular ejection fraction (LVEF)  $\geq 25\%$  and  $\leq 45\%$ . Matching this population, the approach taken in the resubmission was to link the new long-term efficacy results of a subgroup of Liu *et al* (2016) with the previous FIX-HF-5 subgroup analysis. The critique noted that the outcomes were different with Liu *et al* (2016) providing results for mortality and hospitalisations, while the FIX-HF-5 subgroup provided results for peak oxygen consumption, six minute walk test, NYHA class and quality of life using the Minnesota Living with Heart Failure Questionnaire.

These subgroups were relevant to the population of the proposed MBS listing of CCM. The new long-term evidence is divided into:

- i. CCM plus OMT versus OMT (subgroup analysis); and
- ii. CCM plus OMT.

#### CCM plus OMT versus OMT (subgroup analysis)

The resubmission concluded that CCM plus OMT was associated with improved survival and fewer hospitalisations than OMT alone, as shown with rates of:

- all-cause mortality: Patients treated with CCM therapy had a statistically significant survival benefit compared with patients treated with OMT (36% vs. 80%, respectively,  $p < 0.001$ );
- cardiovascular mortality: Patients treated with CCM therapy had a statistically significant survival benefit compared with patients treated with OMT (40% vs. 76%, respectively,  $p = 0.001$ ); and
- heart failure hospitalisation: Patients treated with CCM had significantly fewer heart failure hospitalisations compared with patients treated with OMT (36% vs. 64%, respectively,  $p = 0.005$ ).

#### CCM plus OMT

The resubmission concluded that patients who received CCM therapy experienced a long-term survival benefit. The only statistically significant results were the observed 1-year mortality rate (Table 1), and a separate log rank analysis from Kuschyk *et al* (2015), which included all events up to three years ( $p = 0.022$ ).

**Table 1: Observed mortality with CCM therapy versus predicted mortality without CCM (MAGGIC and SHFM)**

—	Kuschyk <i>et al</i> (2015) (n=81)		Kloppe <i>et al</i> (2016) (n=68)	
	Observed (CCM)	Predicted (MAGGIC)	Observed (CCM)	Predicted (SHFM)
1-year mortality rate	5.2%	18.4%	0.0%	6.1%
2-year mortality rate	~15%	~30%	3.5%	11.8%
3-year mortality rate <sup>a</sup>	29.5%	40%	—	—
5-year mortality rate	—	—	14.2%	27.7%

Source: *Figure from the resubmission; Table 4, p79 of Kuschyk et al (2015); and compiled during evaluation*

CCM = cardiac contractility modulation; MAGGIC = Meta-Analysis Global Group in Chronic Heart Failure; SHFM = Seattle Heart Failure Model; **bold** = statistically significant

<sup>a</sup> Log rank analysis for all events up to 3 years showed that patients treated with CCM therapy had statistically significant ( $p=0.022$ ) lower mortality rates as compared with the respective predicted mortality without CCM (MAGGIC)

*Italics represent values estimated from the resubmission*

The re-submission concluded that CCM therapy was associated with a long-term survival benefit. The critique stated that this might not be reasonable; because:

- beyond one year, the observed versus predicted mortality rates were not statistically significant; and
- the patient populations were substantially heterogeneous (i.e. NYHA class, QRS duration, ICD use, and types of CCM devices used) and not relevant to the proposed MBS restriction for CCM therapy.

## 12. Economic evaluation

The resubmission presented an updated stepped economic evaluation comparing CCM plus OMT therapy with OMT alone. The results of the updated cost-utility analysis are presented in Table 2.

**Table 2: Results of the modelled economic evaluation**

—	CCM + OMT	OMT	Increment
Costs	\$63,166	\$29,268	\$33,538
Quality-Adjusted Life Years	4.96	3.95	1.01
Life Years	1.84	1.29	0.55
<b>ICER (per Quality-Adjusted Life Year gained)</b>	—	—	<b>\$33,327</b>
ICER (per Life Year gained)	—	—	\$49,001

Source: Table D-19 to D-22 pp131-133 of the re-submission

CCM = cardiac contractility modulation; ICER = incremental cost-effectiveness ratio; OMT = optimal medical therapy

The resubmission estimated a discounted incremental cost-effectiveness ratio (ICER) of \$33,327 per quality-adjusted life year (QALY) gained, and \$49,001 per life year gained. The ICER was \$34,539 per QALY in the previous submission.

The resubmission provided a sensitivity analysis of ICERs at different time horizons. From this, the resubmission concluded that CCM therapy was cost-effective at a time horizon of seven years or longer (ICER < \$50,000 per QALY gained).

The critique considered that the key issues with the economic model were that:

- the resubmission's model calculations of the extrapolation of NYHA class did not show that NYHA class would deteriorate by 0.5% per month, beyond 12 months. However, it should be noted that this applies to both CCM plus OMT and OMT; and
- the data that informed the clinical effectiveness of the model, which was considered uncertain beyond 12 months, remained unchanged from the previous submission.

### 13. Financial/budgetary impacts

Compared with the previous submission, which assumed that the prevalent population was subject to a population growth rate (1.58%) per year, the resubmission assumed heart failure would grow 25% higher than population growth (1.98%) per year. Table 3 presents the estimated number of patients treated with CCM therapy and the number of services provided on the MBS.

**Table 3: Total net cost to the MBS of CCM plus OMT**

—	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Treated with CCM + OMT</b>	<b>72</b>	<b>295</b>	<b>451</b>	<b>613</b>	<b>781</b>
Insertion/removal of implantable pulse generator	72	295	451	613	781
Insertion/removal of leads	72	295	451	613	781
Interrogation of implantable pulse generator	145	662	1,269	2,044	2,993
Net cost of CCM + OMT	\$87,763	\$361,765	\$566,781	\$787,312	\$1,023,890
Net cost of additional MBS items <sup>a</sup>	\$24,230	\$98,834	\$151,180	\$205,554	\$262,017
<b>Total net cost to MBS</b>	<b>\$111,993</b>	<b>\$460,600</b>	<b>\$717,961</b>	<b>\$992,866</b>	<b>\$1,285,907</b>

CCM = cardiac contractility modulation; MBS = Medicare Benefits Schedule; OMT = optimal medical therapy  
<sup>a</sup> Including MBS cost of consultant surgeon, anaesthetist and radiology (assuming 1 service each per patient)

The resubmission estimated that the total cost of MBS items required for the listing of CCM therapy would be \$111,993 in Year 1 and \$1.3 million in Year 5, totalling \$3.6 million over the first five years of listing.

Table 4 presents the overall impact of listing CCM therapy on the MBS to the Government health budgets.

**Table 4: Financial implications to the Government health budget**

—	Year 1	Year 2	Year 3	Year 4	Year 5
Cost to government from PBS	\$0	\$0	\$0	\$0	\$0
Cost to government from MBS	\$111,993	\$460,600	\$717,961	\$992,866	\$1,285,907
Overall net cost to government	\$111,993	\$460,600	\$717,961	\$992,866	\$1,285,907
Cost of hospitalisation	\$27,167	\$110,815	\$169,505	\$230,470	\$293,778
Cost of CCM device	\$2,356,534	\$9,612,301	\$14,703,216	\$19,991,473	\$25,482,881
<b>Total cost of CCM + OMT</b>	<b>\$2,495,694</b>	<b>\$10,183,716</b>	<b>\$15,590,682</b>	<b>\$21,214,809</b>	<b>\$27,062,566</b>

CCM = cardiac contractility modulation; MBS = Medicare Benefits Schedule; OMT = optimal medical therapy; PBS = Pharmaceutical Benefits Scheme

The resubmission stated that when the costs of hospitalisations and the CCM device were included, the total cost of CCM therapy was estimated at \$2.5 million in Year 1, increasing to \$27.1 million in Year 5. The resubmission stated that there are no anticipated changes to other Government health budgets aside from the MBS.

#### 14. Key issues from ESC for MSAC

The resubmission provided no change to the following compared to the previous submission:

- Proposed MBS listing
- Comparator
- Clinical management algorithm
- Clinical and safety claim

##### *Issues: Clinical evidence*

ESC noted that the new clinical evidence provided in the resubmission to support evidence of long-term effectiveness is primarily based on three non-randomised studies, while the 3 randomised control trials (RCTs) + 2 meta analyses (of the same RCTs) contained in the original submission were also resubmitted to support the clinical claim.

ESC advised that the new clinical evidence provided in the resubmission is uncertain, and it should be interpreted with a high degree of caution (e.g. small number of patients + likely impact of imbalance in baseline characteristics on health outcomes).

ESC noted that there is an ongoing clinical trial (the FIX-HF-5C study) which is a prospective open label RCT based on the specific subgroup of patients relevant to MSAC consideration. The results of this trial were not yet published at the time of ESC consideration. However, ESC noted that MSAC in their previous consideration had advised the applicant that any resubmission should present results from a larger study in order to adequately evaluate the magnitude and durability of treatment effect.

### *Issues: Economic Evaluation*

The following items remained unchanged:

- Main type of EE: Cost-utility analysis Base case: Model-based evaluation
- Perspective: Health care system
- Modelling technique: Markov model with 6 health states and monthly cycles

ESC previously noted that the 30 year time horizon was excessive for extrapolating one year trial data. The applicant amended the time horizon from 30 years to 15 years. ESC also noted that the applicant had updated the Markov model by including the probability of moving from NYHA II to NYHA III, and from NYHA I to NYHA II (same probability for both arms).

ESC noted that the key drivers of economic model in the resubmission were as follows:

- NYHA distribution: The data obtained from subgroup of FIX HF5 that informed the probabilities of transition (within and beyond 12 months) among the NYHA states remained unchanged from the original submission. Analysis of Markov traces shows a progressive increase in the proportion of patients in class I and II in the intervention group compared with the control group (and a decrease in Class IV in the intervention group).
- Utility weights assigned to NYHA states: The data and method used to estimate utility weights remained unchanged from the previous submission, and are uncertain (e.g. using different utility values for the same state with higher values assigned to the NYHA states in the intervention group). Combined with the NYHA distribution, Markov traces show that this was one of the key drivers of the QALY results.
- Time horizon: The resubmission provided a figure representing the ICER at different time horizons (years), e.g. ICER = \$77,000/QALY at a time horizon of 5 years;

ICER = \$50,000/QALY at a time horizon of seven years).ESC still questioned the plausibility of the amended time horizon.

### *Issues: Financial*

ESC noted that the resubmission assumes growth rate of 1.98% (25% higher than the population growth rate), (781 patients in year 5). The total cost to the MBS will initially be 111K in year 1 growing to \$1.2 million in year 5 if adopted.

## **15. Other significant factors**

Nil.

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

It is unfortunate that MSAC has decided not to accept that CCM therapy is likely to offer a long term morbidity and mortality improvement for CHF patients, due to the absence of a powered, long term randomised controlled clinical trial designed for that purpose. It is unrealistic to expect relatively small devices companies to run such a large long-term clinical trial early on in the life cycle of the technology. As noted in the submission, the RCTs which have been completed so far did demonstrate statistically and clinically significant benefits. Specifically, CCM therapy leads to improved NYHA functional class (p=0.0023), VAT (p=0.026); Peak VO<sub>2</sub> (p=0.002); and Quality of life as assessed by the

MLWHFQ (p=0.0119). Each of these outcomes have been independently linked in numerous studies with long term morbidity and mortality benefits. This is confirmed by investigator initiated observational studies, all of which consistently point in the same direction. CCM therapy has just recently been referenced in the European Heart Failure Guidelines as an appropriate treatment option for heart failure. Unfortunately, Australian patients with CHF will not now have access to MBS subsidised treatment, which appears to be effective, cost effective and likely to have only a modest budget impact, whilst it is acknowledged that there is no alternative treatment option for them.

## **17. Further information on MSAC**

MSAC Terms of Reference and other information are available on the MSAC Website [visit MSAC website](#).