



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1398.1 – Implantation of a permanent wireless haemodynamic sensor and associated remote analysis of pulmonary artery pressure

Applicant: Optum on behalf of St Jude Medical

Date of MSAC consideration: MSAC 68th Meeting, 24-25 November 2016

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

1. Purpose of application and links to other applications

A resubmission requesting a new Medicare Benefits Schedule (MBS) listing of a wireless pulmonary artery pressure sensor for patients with moderate chronic heart failure was received from St. Jude Medical Australia Pty Ltd by the Department of Health.

Application 1398 was considered by MSAC at its November 2015 meeting.

2. MSAC's advice to the Minister

After considering the available evidence presented in relation to safety, clinical effectiveness and cost-effectiveness, MSAC did not support public funding for implantation of a permanent leadless and batteryless pulmonary artery sensor and associated remote analysis for patients with moderate chronic heart failure (NYHA class III). MSAC considered there was still substantial uncertainty about the increment in effectiveness of the sensor/analysis system over the comparator. This uncertainty related both to evidence of a reduction in mortality in the longer-term, and to evidence that Australian patients would comply with management changes because of monitoring. MSAC concluded the safety was a reasonable.

MSAC considered it was unlikely to be cost-effective without more clinical data to justify the mortality reduction assumptions in the economic modelling and it would be informative to see the economic modelling results with the mortality reduction removed.

Any resubmission would be considered via ESC. Other issues identified by MSAC for the applicant to address include:

- a trial in a non-United States setting to enhance external validity
- further information from real-world implementation in Australia (although the only institution currently doing this procedure is a transplant centre)
- provision of a 10-year time horizon as the base case for the economic model, with costs of training and monitoring clarified and included, and a sensitivity analysis with a 5-year time horizon
- changes in costs which may drive a more attractive ICER

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

MSAC noted that the service was proposed for the management of patients with: moderate chronic heart failure (HF; NYHA class III) for at least 3 months regardless of ejection fraction; a stable and optimised medication regimen; and a HF-related hospitalisation within the previous 12 months. The proposed medical service involves the use of the CardioMEMS HF system which includes a permanent leadless and batteryless sensor and an external home electronics unit that receives the pulmonary artery pressure transmission from the sensor and sends the data to a centralised data storage facility. The applicant suggested that this data would improve monitoring and management of patients with moderate HF.

The proposed population and comparator remain unchanged from the initial application as previously accepted by MSAC.

No further evidence regarding safety was presented. MSAC noted that although the extension to the CHAMPION trial was presented in the resubmission, MSAC had previously been provided with these results ahead of publication. MSAC agreed that uncertainty remains regarding long term safety, but that overall the safety profile appears to be acceptable.

MSAC recalled that a number of limitations of the CHAMPION trial data (n = 550, Abraham et al 2011 and n = 347 for Abraham et al 2016 CHAMPION extension) relating to clinical effectiveness had been identified at its November 2015 meeting. In reviewing the resubmission MSAC were concerned that the following major areas of clinical uncertainty remain:

- the single-blind assessment of subjectively determined outcomes;
- the long-term effectiveness of the device, given the proportion of patients who dropped out of the CHAMPION extension study (55% in total, of whom 45% were due to reasons other than death);
- the external validity of the trial to the MBS eligible patient population, given that the evidence base consists of a single trial conducted in the United States (US); and
- any effect on mortality was not established.

MSAC noted that in the US, where the trial was conducted there may be different thresholds for admitting patients to hospital and a different model of standard care compared with the Australian system. MSAC questioned whether evidence from the CHAMPION trial is applicable to implementation of a system of care in Australia.

MSAC acknowledged that the extension of CHAMPION shows that the impact of the service on hospitalisation rates appears to translate to the real world setting in the US context. MSAC noted that the European Society of Cardiology 2016 Heart Failure guidelines indicated that the evidence for the service was not sufficient for an outright recommendation, but that use of the device may be considered. MSAC suggested that uncertainty remains around whether adjusting treatment based on haemodynamic results improves patient outcomes (particularly in the longer term).

MSAC agreed that the most significant area of uncertainty with regard to the cost-effectiveness of the device is the use of survival benefit in the economic model. MSAC considered that:

- there is a lack of clinical evidence for survival benefit; and
- the survival benefit has been overstated in the application of survival rates in the model.

MSAC noted that the CHAMPION trial showed a favourable trend toward reduction in mortality but the difference was not significant, nor was the trial sufficiently powered to detect differences in mortality. In its previous consideration of this device, MSAC had identified that assumptions of survival benefit were an area of uncertainty in the model, however at that time there was insufficient information regarding the model provided in the application to identify that survival benefit is the key driver of the model. MSAC noted that, as identified by ESC, in the model 96% of the QALY gains from the intervention are due to mortality gains and MSAC was concerned there were no sensitivity analyses presented that tested the full confidence intervals for the mortality relative risk reduction observed in the CHAMPION trial or assuming no mortality risk reduction. Given the lack of clinical evidence for mortality benefit, MSAC considered that an analysis using the cost per hospitalisation avoided or a cost-effectiveness model without any inclusion of survival benefit would be more appropriate.

MSAC noted that at the **redacted** for patients in the CHAMPION trial, however at this time point the model used a 6.1% survival benefit. As such, MSAC considered that the trial-based survival benefit has been overstated in its application in the model. MSAC noted that the use of mortality rates in the model is unchanged from the previous submission and remains a key source of uncertainty.

MSAC agreed that a 10-year time horizon would be more appropriate than the lifetime horizon presented in the model. MSAC recommended that any resubmission should be based on a 10-year time horizon with a sensitivity analysis using a 5-year time horizon. MSAC noted that compliance rates in the model are assumed to be 100% and questioned whether this was appropriate given the high rates of discontinuation in the extension study.

The model provided in the resubmission includes utilities linked to health states as requested by MSAC following the initial application. MSAC acknowledged that the changes made were appropriate and that although utility values are higher than some in the literature they appear to be reasonable.

MSAC noted that costs for training, monitoring and follow-up testing have not been incorporated in the resubmission model and was concerned that these costs may be substantial. MSAC acknowledged that HF patients are reviewed frequently, but concluded it is likely that there would still be an increase in consultation rates associated with the proposed monitoring system and that these costs should be included in the economic model.

The method of estimating the potential patient population was unchanged from the previous submission. MSAC has previously identified uncertainties regarding these estimates.

MSAC recalled that it had expressed concerns regarding the ongoing management of patients after implantation when reviewing the initial application. The resubmission provides an implementation framework to address these concerns. MSAC noted that the real world experience in Australia was limited to seven Australian patients in a single specialist transplant centre. MSAC noted that the use of the pulmonary artery pressure sensor is likely to change the model of care for patients with the device. MSAC suggested that it would be informative to extend the pilot study to less specialised (non-transplant) centres and community centres where the model of care is likely to be different and changes to the model of care are likely to have different repercussions. MSAC stated that it would also like to see clearer engagement with relevant HF care societies. MSAC agreed that additional studies outside the US could help to address the limited external validity of the CHAMPION trial. MSAC agreed that the data from the International registry is likely to provide useful real world information regarding compliance, failure rates and hospitalisation rates, however MSAC reaffirmed that it is unlikely to address MSACs major concerns regarding cost-effectiveness.

MSAC acknowledged that monitoring devices such as CardioMEMS are likely to become more common in the future and that the Department may need to consider a new policy framework and ways of evaluating these kinds of monitoring devices. MSAC agreed that, if used appropriately, there may be targeted populations who would benefit from including this new way of monitoring in the standard of care. In the pre-MSAC response the applicant noted the lack of established funding pathways for implanted diagnostic devices and the limitations this places on uptake and equitable access. MSAC was concerned that any recommendation to support the public funding of implantation of the pulmonary artery sensor, without listing of the device on the Prostheses List, would result in equity issues.

4. Background

Application 1398 was considered at the November 2015 MSAC meeting. MSAC deferred its advice for public funding and recommended reconsideration of the application via the Evaluation Sub-Committee (ESC):

- After the Prostheses List Advisory Committee (PLAC) has reviewed the recommendation of the Cardiac Prostheses Clinical Advisory Group (CPCAG) to not support inclusion of the device in the Prostheses List
- when economic analyses have been re-evaluated
- when patient selection has been clearly delineated.

The PSD for this previous application can be viewed on the MSAC website.

5. Prerequisites to implementation of any funding advice

The various components of the Cardio MEMSTM HF system are registered by the Therapeutic Goods Administration (TGA) on the Australian Register of Therapeutic Goods (ARTG).

6. Proposal for public funding

The MBS item descriptor proposed in the submission based assessment (SBA) is shown in Table 1.

Table 1: Proposed MBS item descriptor

Category 3 – Therapeutic Procedures	
MBS Item number XXXX	PERMANENT LEADLESS AND BATTERYLESS PULMONARY ARTERY PRESSURE SENSOR, insertion, removal and replacement of, for patients with a diagnosis of moderate HF (NYHA class III) for at least 3 months regardless of ejection fraction, a stable and optimised medication regimen, and a HF-related hospitalisation within the previous 12 months.
	Criteria for a HF-related hospitalisation includes: (a) a hospitalisation during which a patient is admitted for HF or HF is the primary reason for admission; and (b) the patient displays signs and symptoms of HF on admission; and (c) the use of intravenous diuretic, vasodilator, inotropic, or ultrafiltration therapy is required for the purposes of treating HF. The augmentation of oral therapy may be allowable for defining the admission as HF, if no other reasonable diagnosis can be attributed to the admission.
	Fee: \$816.60 Benefit: 75% = \$612.45 Benefit: \$85% = \$694.10

HF = heart failure; NYHA = New York Heart Association

7. Summary of Public Consultation Feedback/Consumer Issues

No consumer feedback was received.

8. Proposed intervention's place in clinical management

The clinical management algorithm remained unchanged from the previous application.

9. Comparator

As in the previous application, ‘standard care’ was nominated as the main comparator, which includes best practice pharmacotherapy, non-pharmacological strategies, other implantable cardiac devices and heart failure management programs.

10. Comparative safety

No further information or evidence regarding safety was presented in the re-submission.

The evidence presented was from the CHAMPION trial (Abraham et al, 2011). The key safety findings at 6-month follow up are presented in Table 2.

Table 2: Overall summary of adverse events up to six month follow-up visit

	Intervention (N=270)		Control (N=280)	
	Participants (%)	Events (n)	Participants (%)	Events (n)
-				
Unanticipated SAEs	0 (0.0%)	0	1 (0.4%)	1
SAEs	2 (0.7%)	2	0 (0.0%)	0
Non-Serious ADEs	5 (1.9%)	6	7 (2.5%)	11
Anticipated AEs (up to 30 days)	38 (14.1%)	47	31 (11.1%)	34
Anticipated SAEs	0 (0.0%)	0	0 (0.0%)	0
SAEs	121 (44.8%)	339	155 (55.4%)	385
Non-Serious AEs	175 (64.8%)	603	174 (62.1%)	505

ADEs = adverse device events; AEs = adverse events; SAEs = serious adverse device events; SAEs = serious adverse events

On the basis of the harms reported in the evidence base, the SBA proposed that, relative to standard care, permanent leadless and batteryless haemodynamic monitoring has non-inferior safety. The critique considered that this may not be reasonable because the control arm in the CHAMPION trial was not strictly ‘standard care’, given that patients in the control arm were implanted with the device before randomisation, and there were device-related and system-related complications in both arms.

11. Comparative effectiveness

Additional evidence from the CHAMPION extension study was presented in the resubmission.

The CHAMPION trial reported significant improvements in clinical outcomes for the intervention group compared to control including a reduction in HF-related hospitalisation (84% control compared to 46% intervention) and a reduction in all-cause hospitalisations (1.65 per patient control compared to 1.38 per patient intervention). Mortality was not significantly different (23% control compared to 19% intervention), however the trial was not powered to assess mortality.

The CHAMPION extension study now reports that for patients previously in the control group, new access to their PA pressure readings during the open access study period also resulted in significantly improved outcomes including a 48% reduction in HF-related hospitalisations, and a 21% reduction in all-cause hospitalisations.

The CHAMPION extension study reports that patients previously in the intervention group with continued access to their PA pressure readings during the open access study period (but not under trial conditions) appear to retain the outcomes achieved during the randomised period of the trial. HF-related hospitalisations were 45% in the follow up period compared to 48% in randomised period. All-cause hospitalisations were an average of 1.32 per person in

the follow up period compared to 1.51 per person in the randomised period. 18% of patients died in the follow up period compared to 19% in the randomised period. Key results across study time periods are presented in Table 3.

Table 3: Long term clinical outcomes from randomised access and open access periods

Outcome	Randomised access treatment group (n=270)	Randomised access control group (n=280)	Risk (95% CI)	p-value	Randomised access control group (n=280)	Open access former control group (n=170)	Risk (95% CI)	p-value	Randomised access treatment group (n=270)	Open access former treatment group (n=177)	Risk (95% CI)	p-value
HF-related hospitalisations	182 (0.46)	279 (0.84)	0.67 (0.55, 0.80)	<0.0001 ^a	279 (0.68)	64 (0.36)	0.52 (0.4, 0.69)	<0.0001 ^a	182 (0.48)	78 (0.45)	0.93 (0.7, 1.22)	0.58 ^a
Death and HF-related hospitalisations	232 (0.58)	343 (0.84)	0.69 (0.59, 0.82)	<0.0001 ^a	343 (0.84)	85 (0.51)	0.61 (0.48, 0.78)	<0.0001 ^a	232 (0.61)	109 (0.67)	1.09 (0.86, 1.39)	0.46 ^a
Death	50 (19%)	64 (23%)	0.80 (0.55, 1.15)	0.23 ^b	64 (23%)	21 (12%)	0.71 (0.43, 1.17)	0.17 ^b	50 (19%)	31 (18%)	1.40 (0.89, 2.23)	0.15 ^b
Death or first HF-related hospitalisation	121 (45%)	145 (52%)	0.77 (0.60, 0.98)	0.033 ^b	145 (52%)	49 (29%)	0.53 (0.38, 0.73)	0.0034 ^b	121 (45%)	55 (31%)	0.85 (0.61, 1.17)	0.32 ^b
All-cause hospitalisations	554 (1.38)	672(1.65)	0.84 (0.75, 0.95)	0.0032 ^a	672 (1.65)	230 (1.30)	0.79 (0.67, 0.92)	0.0034 ^a	554 (1.51)	218 (1.32)	0.87 (0.74, 1.03)	0.10 ^a
Deaths and all-cause hospitalisations	604 (1.51)	736 (1.80)	0.84 (0.76, 0.94)	0.0017 ^a	736 (1.80)	251 (1.52)	0.85 (0.72, 0.99)	0.0351 ^a	604 (1.65)	249 (1.61)	0.97 (0.83, 1.14)	0.75 ^a

The critique stated that the following issues, raised previously, remain:

- The evidence base is restricted to one study only.
- Overall survival is a relevant outcome and there was no difference in survival between the intervention and control arms at study end.
- The new CHAMPION extension study provides additional information on the long term outcomes up to 31 months, however there are serious concerns with patients dropping out from both study arms. At 31 months only 45% of those randomised remained in the study. Notably the majority of these (56% control and 54% intervention) are due to death but there are significant numbers of patients who remain alive and have dropped out of the study. This will impact on the interpretation and applicability of the long term results.
- In conclusion there is reasonable evidence that the intervention positively impacts hospitalisations. The concerns regarding impact on mortality remain. The longer term outcomes to 31 months appear to support shorter term findings but with serious concerns due to loss to follow up.

On the basis of the benefits reported in the evidence base, the SBA proposed that, relative to standard care, permanent leadless and batteryless haemodynamic monitoring systems has superior effectiveness. The critique considered that this may be reasonable but is more uncertain longer term.

12. Economic evaluation

The economic evaluation is summarised in Table 4.

Table 4: Summary of the economic evaluation

Perspective	Health care system
Comparator	Standard care for HF patients
Type of economic evaluation	Cost-utility
Sources of evidence	RCT
Time horizon	Lifetime (up to 38 years)

Outcomes	QALYs
Methods used to generate results	Markov model
Health states	4
Cycle length	1 Month
Discount rate	5% for both costs and outcomes
Software packages used	TreeAge Pro 2015

In response to previously raised concerns the resubmission changed how utilities were applied (they were assigned to health states rather than cycles), which the critique noted appears appropriate. A 10-year time horizon was also presented as an alternative analysis but the lifetime time horizon remains the base case. The critique considered, as previously, that 10 years is likely to be a more appropriate time horizon. The critique also noted that the mortality rates used across the model were not changed in the resubmission and remain a key limitation and source of uncertainty.

The overall costs and outcomes, and incremental costs and outcomes as calculated for the intervention and comparator in the model, and using the base case assumptions, are shown in Table 5 below.

Table 5: Incremental cost effectiveness results Cost

	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
10-YEAR				
LABS-IHMS	\$50,839	\$24,396	3.01	0.43
SOC		\$26,443		2.58
LIFETIME				
LABS-IHMS	\$55,096	\$25,097	3.61	0.69
SOC		\$29,999		2.92

An additional sensitivity analysis was conducted using the 10-year horizon as the base case (Table 6) and varying the relative risk of mortality.

Table 6: Results of additional sensitivity analysis

Sensitivity analysis	Rationale	ICER	% change relative to base case
Base case (10 year time horizon)		\$56,495	
Univariate sensitivity analysis			
(A) Revised relative risk of mortality: 0.91 vs. 0.79	Better align mortality improvement with CHAMPION trial	\$99,791	76%
(B) Revised utility values: 0.65 vs. 0.69-0.74	Utility values for older Australian cohort as sourced from literature	\$59,504	5%
(C) Revised compliance rate: 0.9 vs 1.0	Incorporate some amount of non-compliance	\$64,063	13%
(D) Revised relative risk of mortality: 0.55 vs. 0.79	Best case scenario from CHAMPION trial confidence intervals	\$30,559	-46%
(E) Revised relative risk of mortality: 1.15 vs. 0.79	Worst case scenario from CHAMPION trial confidence intervals	Dominated	NA
Multivariate sensitivity analysis			
(A)+(B)		\$104,327	84%
(A)+(B)+(C)		\$114,248	101%

13. Financial/budgetary impacts

The financial implications to the MBS resulting from the proposed listing of the device from the resubmission are summarised in Table 7.

Table 7: Total costs to the MBS associated with the intervention

	Year 1 2017	Year 2 2018	Year 3 2019	Year 4 2020	Year 5 2021
Number of implantation (total number of patients) per year	48	168	384	672	960
Total MBS cost (full benefit)	\$45,850	\$160,474	\$366,797	\$641,894	\$916,992
Total MBS cost (at 75% benefit)	\$34,387	\$120,355	\$275,098	\$481,421	\$687,744

14. Key issues from ESC for MSAC

ESC advised that there was limited new data from the CHAMPION trial extension study along with the CHAMPION randomised trial evidence presented in the original submission. An updated Economic Model has been provided and that the comparator (standard care) is reasonable and consistent with current practise.

The CHAMPION trial extension study provided additional information on long term outcomes, up to 31 months however, there are serious concerns with patients dropping out from both studies (18% exited in extension phase C, 50% died, and there were uncertain reasons for others). At 31 months only 45% remain in the study. There are significant numbers who remain alive and have dropped out of the study which impacts the interpretation and applicability of the long term results.

Safety

ESC advised MSAC that clinical uncertainties remain regarding surgical adverse events and/or complications related to both the insertion of the device and the long term placement of the device. In regards to the safety data available, ESC noted that there had been no reported sensor failures in patients implanted with the device and no further device related events were observed during extended follow up period.

Effectiveness

ESC noted that the results of the extension study supported the clinical claim with outcomes consistently favouring the intervention over the control group in regards to heart failure related hospitalisations. Further the control group who had their device activated in the extension period also made similar gains in terms of effectiveness and the intervention group maintained gains observed in the randomised period.

ESC advised that despite the additional analysis suggesting blinding was maintained and the outcomes not being influenced by physicians being unblinded to treatment allocation, clinical uncertainty remains in regards to the impact of the device on overall mortality. However ESC noted that reducing HF-related hospitalisations is a widely accepted surrogate endpoint in heart failure trials.

ESC advised that there are issues with the proposed item descriptor. The proposed descriptor includes the combination of insertion, removal and replacement of the device into a single descriptor, exclusion criteria discrepancy between the trial population and target population for MBS listing and a lack of information on who performs the procedure including required qualifications and competencies.

Cost-Effectiveness

ESC advised that Economic uncertainties still exist. The utility scores from Champion are relatively high and the population considerably younger than expected in Australia (at 62 years in the base model). ESC advised that a 10-year model would be more appropriate than

the life time (up to 38 years) time-horizon as base model for NYHA Class III patients as the biggest driver of this model is mortality.

ESC noted the residual uncertainty in relation to the mortality rate applied in the model given the difference in mortality rates reported between Abrahams (2016) and the Clinical Investigation Report (2011).

There were still financial uncertainties; the financial impact only covers between 0.6 and 11.1% of estimated eligible patients using the epidemiological approach. Further uncertainty relates to inclusion of a right heart catheterisation (RHC) fee or co-claiming. There is a potential for bundling payment options. The proposed expansion of the service does not appear to be equally distributed nationally with significant costs appearing to be patient out of pocket or hospital system costs.

15. Other significant factors

Nil.

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

The Sponsor is disappointed with MSACs decision and notes many issues raised in the previous submission (application 1398) were addressed in this resubmission (application 1398.1). MSAC has now raised new issues in application 1398.1 which are a major barrier to achieving access to this innovative technology. In particular, the new requirement to present non-US based trial data is not aligned with MSAC Technical Guidelines for Therapeutic Services (v2.0) and sets an unacceptable precedence. The identified issues could instead be addressed more efficiently through translational evidence. The Sponsor agrees that ongoing evaluation of the service is important and local data may be informative. During the recruitment phase of the ex-US post approval study, any Australian site using CardioMEMS at their hospital will be invited to join the study. The Sponsor will continue to cover all costs related to training for CardioMEMS – and therefore this should not influence MSAC decision making.

17. Further information on MSAC

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