ST. JUDE MEDICAL

1398

Application to the Medical Services Advisory Committee for listing implantation of a permanent leadless and battery-less haemodynamic sensor and associated remote analysis of pulmonary artery pressure for management of patients with moderate chronic heart failure (New York Heart Association class III)

FINAL PROTOCOL

April 2015

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ABBREVIATIONS AND TERMS

Abbreviation	Term
ACC	American College of Cardiology
ACE-I	Angiotensin-converting enzyme inhibitor
AHA	American Heart Association
ARB	Angiotensin 2 receptor blocker
AR-DRG	Australian Refined Diagnostic Related Group
BMI	Body Mass Index
CC	Complication and/or comorbidity
CCC	Catastrophic complication or comorbidity
CHF	Chronic heart failure OR congestive heart failure
CI	Confidence interval
CRT	Chronic resynchronisation therapy
CSANZ	Cardiac Society of Australia and New Zealand
DPMQ	Dispensed price for Max Quantity
DRG	Diagnostic Related Group
DSRC	Device- or system-related complications
ECG	Electrocardiogram
EF	Ejection fraction
GFR	Glomerular filtration rate
GP	General practitioner
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HR	Hazard ratio
HFrEF	Heart failure with reduced ejection fraction
KOL	Key Opinion Leader
LV	Left ventricle OR left ventricular
LVEF	Left ventricular ejection fraction
MBS	Medicare Benefits Schedule
MLHFQ	Minnesota Living with Heart Failure questionnaire
mm Hg	Millimeters of mercury
MSAC	Medical Services Advisory Committee
NNT	Number needed to treat
NYHA	New York Heart Association
PA	Pulmonary artery
PASC	Protocol Advisory Sub-Committee
PBS	Pharmaceutical Benefits Scheme
PHI	Private health insurer
PICO	Population, Intervention, Comparator and Outcomes
QALY	Quality adjusted life year
QoL	Quality of life

Abbreviation	Term
RHC	Right heart catheterisation
RPBS	Repatriation Pharmaceutical Benefits Scheme
RRA	Rural and Remote Areas
TGA	Therapeutic Goods Administration
TTE	Trans-thoracic echocardiogram
USA	United States of America

1 TITLE OF APPLICATION

Implantation of a permanent leadless and batteryless haemodynamic sensor and associated remote analysis of pulmonary artery pressure for patients with moderate chronic heart failure (New York Heart Association class III).

2 PURPOSE OF APPLICATION

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

Heart failure (HF) (or 'chronic HF' or 'congestive HF) is characterised by insufficient cardiac output to meet the requirements of the body, leading to acute episodes of fluid accumulation often resulting in hospitalisation. Early detection of fluid accumulation via real time access to pulmonary artery (PA) pressure changes permits appropriate corrective management to remove fluid, lower intra-cardiac pressures, and thus minimise decompensation requiring hospitalisation. The addition of haemodynamic monitoring to usual outpatient management leads to improved patient outcomes and allows prevention of unnecessary healthcare resource use. This Protocol relates to Medical Services Advisory Committee (MSAC) approval for subsidisation of implantation of a permanent wireless PA pressure sensor and associated remote analysis of PA pressure, to guide early intervention and proactive management of patients with moderate chronic HF (New York Heart Association (NYHA) class III). The proposed medical service (a permanent leadless and batteryless pulmonary artery pressure sensor; branded 'CardioMEMS™ HF System' or 'CardioMEMS') is associated with improved patient outcomes including quality of life (QoL), hospitalisations and mortality.

Please refer to the abstract in Appendix 1 for further background on CardioMEMS: *Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet 2011; 377:658-66.*

3 PROPOSED MBS LISTING

The proposed MBS item is detailed in Table 1, covering the insertion, removal and replacement of a permanent leadless and batteryless pulmonary artery pressure sensor. It is expected remote monitoring of pulmonary artery pressure data will be incorporated into standard care HF management programs (see 10. Clinical management algorithms) and this assumption has been agreed by PASC. Subsequent sections of the protocol address the population, the intervention and the proposed fee.

Table 1 Proposed MBS item descriptor for the insertion of a permanent leadless and batteryless pulmonary artery pressure sensor

Category 3 – Therapeutic Procedures
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

4 POPULATION AND MEDICAL CONDITION

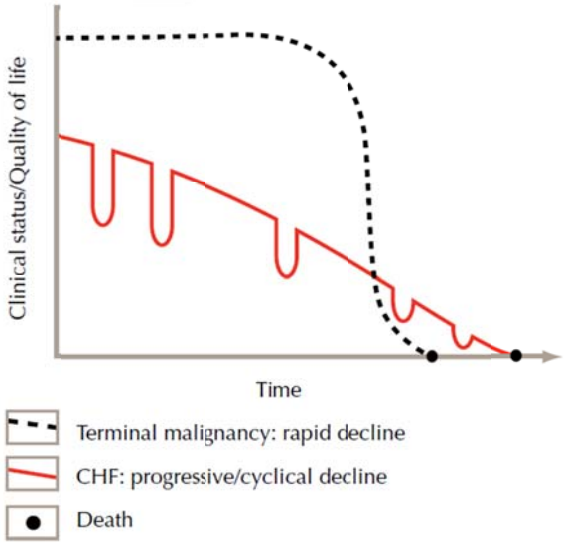
4.1 DESCRIPTION OF MEDICAL CONDITION

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

HF is a progressive and complex clinical syndrome that is characterised by an underlying structural abnormality or cardiac dysfunction that impairs the ability of the heart ventricle to fill and / or eject blood (5). HF is mostly a chronic and long-term condition associated with acute episodes of decompensation, and may also develop suddenly. HF can be caused by a number of clinical conditions including ischaemic heart disease, prior myocardial infarction, hypertension and less commonly, non-ischaemic idiopathic dilated cardiomyopathy.

Figure **1** shows the typical 'trajectory of illness' associated with HF showing the cyclical and progressive clinical instability following each hospitalisation, which is associated with declining QoL (5).

Figure 1. The typical 'trajectory of illness' associated with heart failure



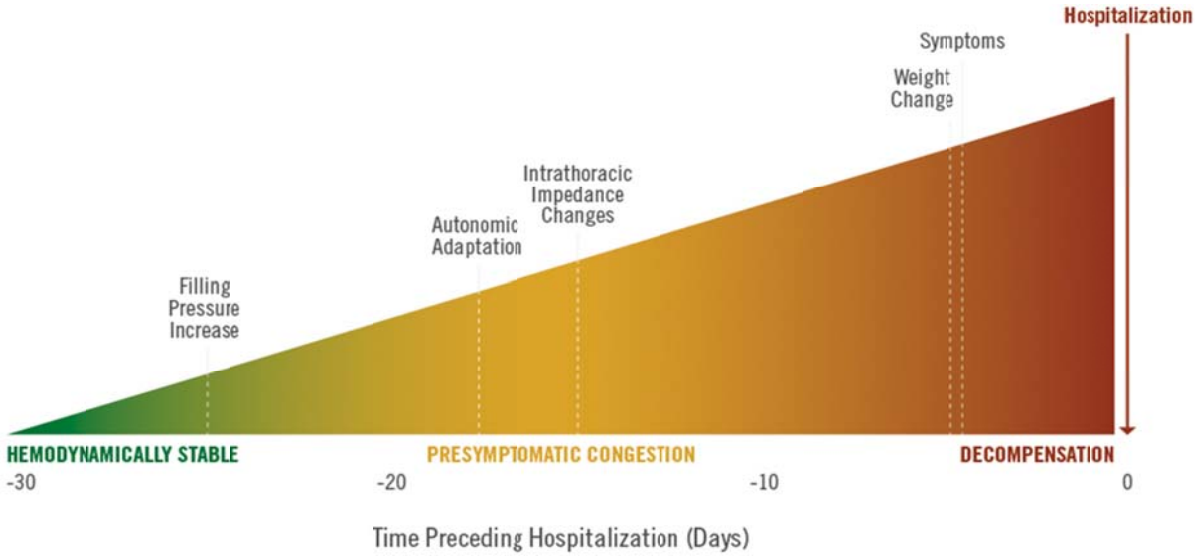
Source: National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Guidelines for the prevention, detection and management of chronic heart failure in Australia (2011).

HF can be further stratified into two distinct disease types based on variations in the underlying pathophysiology, including HF with reduced ejection fraction (or 'HFrEF' or 'systolic HF') and HF with preserved ejection fraction (or 'HrEF' or 'diastolic HF'). HFrEF refers to a weakened ability of the heart to contract in systole, and is typically associated with a left ventricular ejection fraction (LVEF) of < 40%. HFpEF refers to the impaired diastolic filling of the left ventricle because of slow relaxation or increased myocardial stiffness resulting in higher filling pressures. To a large degree the management approach in HF is based on ejection fraction (EF). HFrEF management is relatively well understood with a robust and comprehensive evidence base guiding management. On the other hand, management of HFpEF is poorly understood, and to date, there have been minimal advances in management of this patient subset over the last few decades (5;6).

Clinical symptoms of HF include dyspnoea (shortness of breath), fatigue and ankle swelling, fluid overload or congestion, dizziness and confusion, and additional and eventual organ dysfunction of the heart, kidneys and liver (5;7). Patients with HF often have limited exercise capacity, high mortality rates, and significant impairments in all facets of QoL, including physical, mental and social health (5;8;9). Quality of life is found to be closely correlated with NYHA class, that is, a lower QoL is observed in patients with more severe HF (8-10). Utility values for patients with HF have been reported as 0.67 for patients with NYHA class III which declines to 0.53 for class IV (11). Worsening utility scores are also apparent with increased numbers of hospitalisation (independent of NYHA class), ie 0.79 for one readmission and 0.75 for greater than or equal to three rehospitalisations (11).

Acute decompensated HF, during which patients suffer a sudden worsening or deterioration of signs and symptoms frequently leads to hospitalisation. Hypervolaemia is a common trigger for acute decompensation, with haemodynamic and clinical congestion contributing to fluid accumulation (1). Haemodynamic congestion often precedes clinical congestion, with increases in intra-cardiac pressures shown to manifest days to weeks before the clinical symptoms of congestion (1-4) (see Figure 2). PA pressure is therefore a strong predictor and surrogate of left atrial pressure, the most direct marker of HF progression. Monitoring PA pressure allows clinically important changes to be identified earlier than other common markers such as weight.

Figure 2. Pathophysiology of congestion in heart failure



Source: Adamson P. (2009)

HF is an increasing clinical, social and economic burden in Australia. It is estimated that 300,000 people are living with HF in Australia and a further 30,000 Australians are diagnosed with HF every year (12). Regardless of clinical status about one third of patients with HF are hospitalised each year (5). More than 45,000 Australians were hospitalised due to HF in 2009-2010, equating to greater than 360,000 bed days, with an approximate cost to the national economy of $1 billion a year (12). The largest contributor to this annual cost is hospital care, with an average length of stay of 5 days for the public system and up to 8 days in the private system (5;12). The rehospitalisation rate amongst patients with HF is high, reaching between 29% to 49% within 3 to 6 months, with many of these admissions potentially preventable (7).

4.2 PROPOSED PATIENT POPULATION

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

The proposed patient population that would benefit from use of the proposed medical service includes those with a diagnosis of moderate HF (NYHA class III) for at least 3 months regardless of EF, a stable and optimised medication regimen, and a HF-related hospitalisation[1] within the previous 12 months. Each of these characteristics will be discussed further.

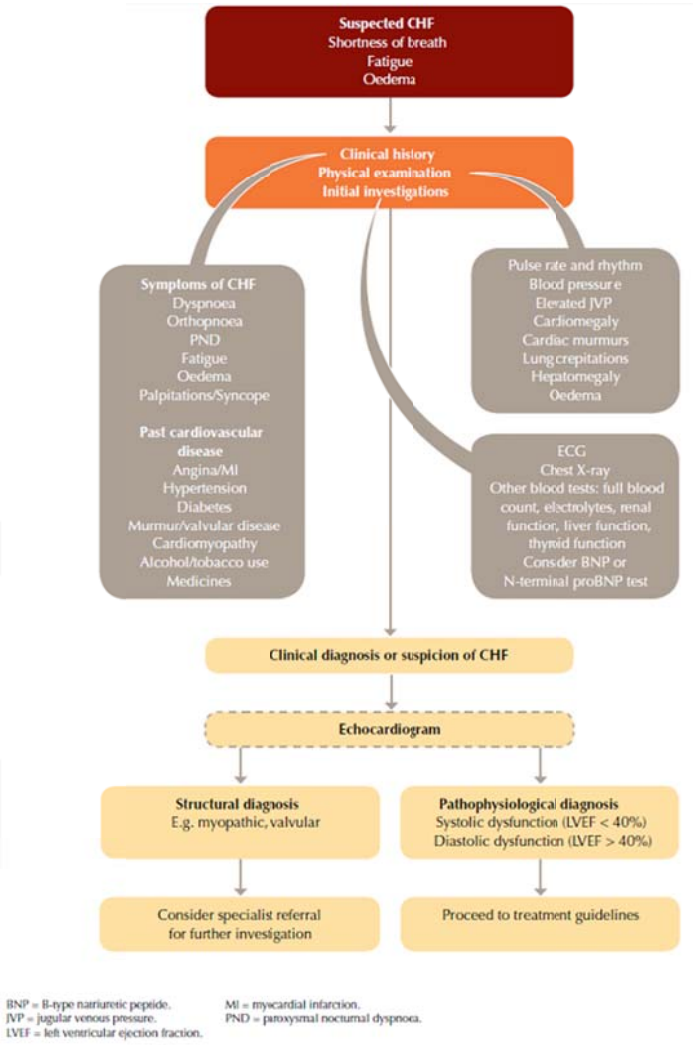
Diagnosis of moderate heart failure for 3 months

Diagnosis of HF can be difficult due to the broad nature of symptoms experienced by patients, the multitude of associated comorbidities, and various HF phenotypes. Particularly in the elderly population, symptoms on exertion or tiring may be mistaken as signs of ageing or as comorbidities such as pulmonary disease, anaemia, or depression. To address the complexity in diagnosing HF, the

[1] A HF-related hospitalisation is defined by meeting the following criteria: (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. (13)

National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (CSANZ)have developed a standardised diagnostic algorithm (see Figure 3), which is widely used in clinical practice. Initial diagnosis of HF encompasses a full medical history and physical examination to determine the severity of the disease and the possible cause of HF (eg signs of underlying cardiac disease, fluid retention, and other abnormal vital signs). Further diagnostic investigations including electrocardiogram (ECG), chest x-ray, and measurement of plasma electrolytes confirm the clinical diagnosis. Finally, echocardiogram is a vital investigation used to determine the mechanism of HF, and to make the distinction between systolic or diastolic dysfunction (5). Additional haemodynamic tests may be carried out when the HF appears refractory to therapy, the diagnosis of HF is in doubt, and diastolic HF is recurrent.

Figure 3. Diagnostic algorithm for heart failure



Source: National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Guidelines for the prevention, detection and management of chronic heart failure in Australia (2011).

Symptom classification using the NYHA grading system organises patients into four groups based on set criteria, including physical capabilities and any associated HF symptoms, with NYHA class III used to describe moderate HF (5) (see Table 2). The grading system is based on clinician assessment of symptoms and functional capacity which may change over time as patients worsen or improve (14). Based on advice from key opinion leaders (KOLs) (N=9), to ensure the most suitable patients receive the proposed medical service, where there is uncertainty around NYHA class at a given point in time,

patients should be considered for the proposed medical service if they have been mostly graded as class III, based on physician discretion, within the previous 3 months.

Table 2. New York Heart Association grading of symptoms in heart failure

NYHA grading		
Class I	No limitations. Ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations	Asymptomatic LV dysfunction
Class II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina pectoris	Mild HF
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms	Moderate HF
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest	Severe HF

Source: National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Guidelines for the prevention, detection and management of chronic heart failure in Australia (2011). *Abbreviations:* CHF, chronic heart failure; HF, heart failure; LV, left ventricular; NYHA, New York Heart Association

Reduced or preserved ejection fraction

In contrast to evidence for many other HF devices, patients with preserved or reduced EF are suitable to receive the proposed medical service. Management of HFpEF over the last few decades has shown minimal advancement. This patient population remain to be sub-optimally managed due to limited treatment options (6).

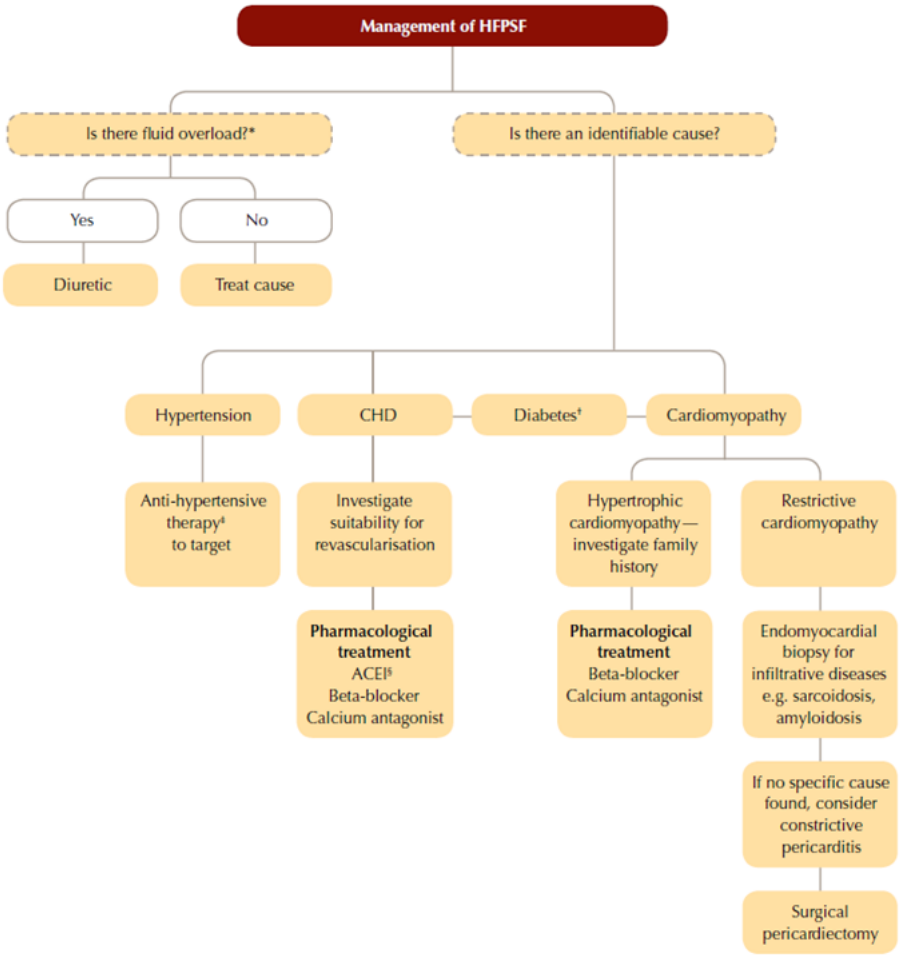
Stable and optimised medication regimen

The treatment goals of HF include reduction in the heart's workload and improvement in heart function. Non-pharmacological management strategies are available to help stabilise patients (eg physical activity programs, salt and fluid management education and programs). Pharmacological management is dependent upon the type of HF, and is deemed to be optimised when doses are titrated to achieve maximum recommended and tolerated doses to balance offering the greatest survival benefit with an enhanced QoL (13). Establishing a stable and optimised medication regimen can be complex and often challenging to clinicians and patients.

PASC accepted that stable and optimised medical management is a term which is clearly defined by the Australian Heart Foundation and widely understood by expected users of the proposed device.

As shown in Figure 4, empirical treatment of HFpEF entails treatment with a diuretic where fluid overload is present, treatment with angiotensin-converting enzyme inhibitors (ACE-Is) or sartans to reduce blood pressure and left ventricular (LV) hypertrophy, and strict glycaemic control (5).

Figure 4. Management of heart failure with preserved ejection fraction (diastolic heart failure)



* With rare exception, patients with HFPSF present with symptoms and signs of fluid overload, either pulmonary or systemic congestion or both.

† Better diabetes control.

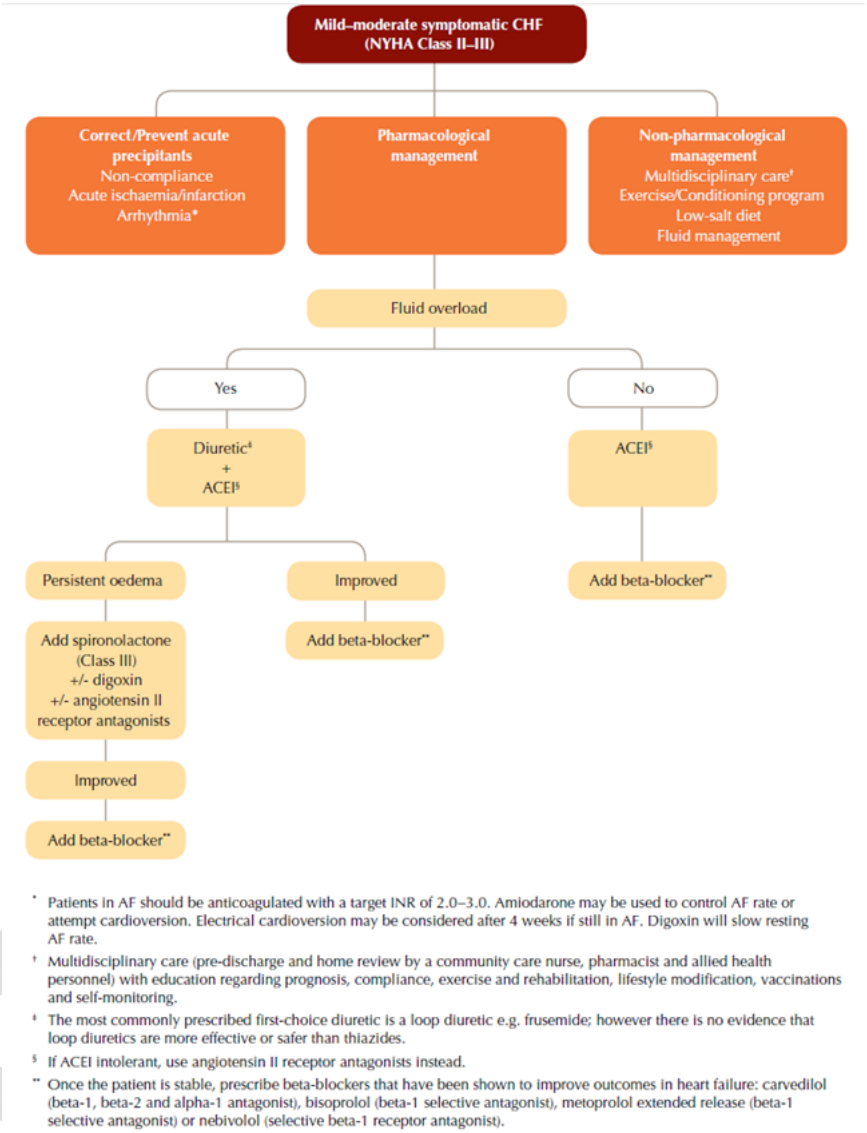
‡ Choice of therapy will vary according to clinical circumstances, e.g. thiazide diuretic — elderly, systolic hypertension; ACEI — LV hypertrophy, diabetes, CHD; beta-blocker — angina.

§ If ACEI intolerant, use angiotensin II receptor antagonist instead.

Source: National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Guidelines for the prevention, detection and management of chronic heart failure in Australia (2011).

Best practice pharmacotherapy for the treatment of HFrEF with NYHA class II/III is presented in Figure 5 below. Treatment generally includes a combination of a diuretic (commonly a loop diuretic), an ACE-I or sartan, and a beta-blocker when patients are stable. If the patient is unstable with persistent oedema, treatments such as spironolactone, digoxin and sartans can be initiated.

Figure 5. Pharmacological treatment of heart failure with reduced ejection fraction with New York Heart Association class II/III grading



Source: National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Guidelines for the prevention, detection and management of chronic heart failure in Australia (2011).

<u>Heart failure-related hospitalisation within previous 12 months</u>

It is well established and acknowledged that patients with HF may be hospitalised for a number of causes that exacerbate the underlying HF, without HF being the primary cause for hospitalisation. Some of these causes are listed below (15):

- acute coronary syndromes (with large areas of myocardial ischaemic or infarction, acute myocardial infarction mechanical complications);
- acute myocarditis;
- hypertensive crisis (eg hypertension following abrupt discontinuation of antihypertensive treatments);
- valvular regurgitation (eg endocarditis);
- severe aortic valve stenosis;

- high output syndromes (eg septicaemia, thyrotoxicosis, severe anaemia);
- pulmonary embolism;
- aortic dissection;
- Takotsubo cardiomyopathy;
- cardiac tamponade; and
- post-partum cardiomyopathy.

For the purpose of this Protocol and in accordance with the criteria used in the pivotal trial, the following criteria should be followed when defining a HF-related hospitalisation (13):

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.

Key opinion leader insights

KOLs (N=9) have advised that the proposed patient population as described above is applicable in the clinical setting. Feedback has indicated that patients with NYHA class IV HF are considered too sick to benefit from the proposed medical service, whilst there is no current evidence to show that patients with NYHA class II HF would be yet to reach a disease severity from which the proposed medical service could adequately demonstrate a clinically meaningful benefit.

KOLs have also suggested that the patient cohort they see the most value in receiving the proposed medical service are those that are casually labelled as 'frequent flyers'. 'Frequent flyers', per the HF management community, is a term used to describe patients with chronic HF who have frequent hospital admissions (16). This does not deviate from the proposed patient population described in Section 4.2, nor does it deviate from the patient population used to generate the evidence base in the pivotal trial (Section 4.3), but rather provides some reassurance that in clinical practice the proposed medical service will likely target at a subset of patients that fulfil the broader criteria described above.

Finally, KOLs have advised that this technology will of significant benefit in patients with HFpEF, for whom current management options are limited.

4.3 EVIDENCE FOR PROPOSED PATIENT POPULATION

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

The CHAMPION trial was a prospective, multi-centre, single-blinded randomised clinical trial that demonstrated evidence for implantation of a permanent PA sensor and associated remote analysis of PA pressure in the patient population described in Section 4.2 (2).

A total of 550 patients from 64 sites in the United States of America (USA) were enrolled, all of whom had underwent implantation of the PA sensor. Prior to hospital discharge, all subjects were trained on how to operate the home electronic monitoring unit and instructed to take his/her pulmonary artery pressure measurements daily. All patients took daily pressure readings regardless of randomisation assignment. These measurements were transmitted via modem to a secure patient database (2).

In the treatment group, investigators provided standard of care HF management plus HF management based on hemodynamic information obtained from the PA sensor readings via the secure patient database. In the control group, investigators provided standard of care HF management but did not have access to patient hemodynamic data.

The eligibility criteria used in the trial, as presented in **As requested** by PASC, issues of applicability between the CHAMPION trial population and the real world population will be addressed in the assessment report. This includes potential discrepancies in age and clinical characteristics (eg history of pulmonary embolism or DVT, stage IV or V chronic kidney disease, BMI requirements). The Sponsor notes that feedback from Prof. Henry Krum provided at PASC meeting suggests a younger trial population is common in heart failure research.

PASC also provided comment on patient compliance. In the CHAMPION trial, the overall daily patient adherence/compliance to home monitoring (a minimum of 1 pressure waveform transmitted per day) was 90% in the 60 days after sensor implantation, with patients taking an average of 8.6 readings per week. There is no real-world data on compliance rates, however experienced clinicians currently using the CardioMEMS system in clinical practice have advised that since patients are very keen to avoid decompensation and a hospitalisation, compliance is generally high. As noted in the PASC meeting, compliance monitoring is not anticipated to be any different to those patients with medication or other intervention related issues.

Table 3, forms the basis of the proposed patient population described in Section 4.2. As requested by PASC, issues of applicability between the CHAMPION trial population and the real world population will be addressed in the assessment report. This includes potential discrepancies in age and clinical characteristics (eg history of pulmonary embolism or DVT, stage IV or V chronic kidney disease, BMI requirements). The Sponsor notes that feedback from Prof. Henry Krum provided at PASC meeting suggests a younger trial population is common in heart failure research.

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Table 3. Eligibility criteria for selection of the study population in the CHAMPION trial

Inclusion criteria	Exclusion criteria
18 years of age or older; Diagnosis of HF for ≥ 3 months, with preserved or reduced LVEF; Diagnosis of NYHA functional class III HF at screening visit; If subject has a reduced LVEF, they must be receiving a beta-	Active infection; History of recurrent (> 1) pulmonary embolism or deep vein thrombosis; Unable to tolerate an RHC, in the investigator's opinion;

Inclusion criteria	Exclusion criteria
blocker for 3 months and an ACE-I or ARB for 1 month unless, in the investigator's opinion, the subject is intolerant of beta-blockers, ACE-I or ARB. Beta-blocker and ACE-I (or ARB) doses should be stable for 1 month before study entry; At least 1 HF-related hospitalisation[a] within 12 months of screening visit; BMI ≤ 35kg/m2. Subjects with BMI > 35kg/m2 require additional screening. If the BMI is > 35kg/m2 and the chest circumference is > 52 in and < 65 in, the distance from the skin on the subject's back to the pulmonary artery must be < 10cm and confirmed by angiogram of the lateral view during the catheterisation before the placement of the pressure sensor. If the distance is > 10cm, the subject will not receive a sensor and will not be eligible for the study; Pulmonary artery branch diameter between 7 and 15mm; Female subjects of childbearing age with a negative urine or serum pregnancy test at the screening visit and agreeing to use a reliable mechanical or hormonal form of contraception during the study.	Implantation of CRT < 3 months before enrolment; Experienced a major cardiac event (eg. myocardial infarction, stroke) within 2 months of screening visit; GFR < 25mL/min or chronic renal dialysis; Likely to undergo heart transplantation within 6 months of screening visit; Congenital heart disease or mechanical right heart valve(s); Diagnosed coagulation disorders; Hypersensitivity or allergy to aspirin and/or clopidogrel; Enrolled in concurrent studies that may confound the results of the study; Clinical condition that would not allow them to complete the study, in the investigator's opinion.

Source: Abraham et al (2011). *Abbreviations:* ACE-I, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin 2 Receptor Blocker (or sartans); BMI, body mass index; CRT, cardiac resynchronisation therapy; GFR, glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RHC, right heart catheterisation;. *Table notes:* [a]A HF-related hospitalisation is defined by meeting the following criteria: (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 (13).

Patients were kept blinded to treatment assignment until the last patient in the trial completed their 6 month follow-up visit. The single-blind was maintained until analysis of the 6 month data was complete for the entire patient population, at which point, the investigators had access to all subjects' data at their site.

Follow-up study visits for both the treatment and control groups were scheduled at Month 1, Month 3, Month 6, and every 6 months thereafter. Follow-up visits included a physical exam, evaluation of NYHA class, adverse event assessment and medication review.

The two primary safety endpoints of device- or system-related complications (DSRC) were met. In total, 98.6% of patients in whom implantation of the sensor was attempted were free from DSRC at 6 months, meeting the pre-specified objective performance criteria of 80% ($p < 0.0001$). Of the total of 550 patients with sensors implanted, all (100%) were operational at 6 months and there were no sensor explants or repeat implants ($p < 0.0001$ compared to the pre-specified objective performance criteria of 90%) (2). No events required the sensor to be removed. Further evidence for the safety profile is discussed in Section 8.2.

The primary efficacy endpoint of HF-related hospitalisation at 6 months was also met, with the treatment group exhibiting a 28% relative risk reduction in the rate of HF-related hospitalisations at 6 months (0.32 vs. 0.44, $p = 0.0002$) (2). The treatment group also demonstrated a statistically significant improvement versus the comparator group in the following secondary endpoints:

- change from baseline PA pressure at 6 months;
- proportion of patients admitted for HF at 6 months;
- days alive and out of hospital at 6 months;

- QoL as measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) at 6 months; and
- a pre-specified supplementary efficacy endpoint (HF-related hospitalisations during the entire randomised follow-up).

In a post-hoc analysis the treatment group had a lower risk of death or first HF-related hospitalisation versus the comparator group over the entire randomised follow-up period (2). Furthermore, during an open access period, physicians in the former control group were given full access to PA pressure readings from the CardioMEMS HF website to guide patient management. This resulted in a 48% reduction in HF-related hospitalisations ($p < 0.0001$) (17).

Further evidence from the trial is described in Section 8.

4.4 EXPECTED UTILISATION

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

As suggested by PASC, the assessment report will provide more evidence to justify the size of the population likely to receive the medical service. The Sponsor acknowledges that uptake rates were conservative in the originally submitted protocol. Revised figures are presented in Table 4, which shows the expected utilisation over 5 years covering 2015 to 2019. The original estimates were based on uptake in established HF centres in urban locations, expanding to other urban and regional centres over time. It is acknowledged that centres not identified by the Sponsor may choose to use the medical service, including rural and remote centres. Therefore, uptake rates have been adjusted to reflect unrecognised centres using the medical service.

A publication by Clark et al (2009) reported that there were approximately 62 HF management programs of varying sizes across Australia in 2009 (18). This figure was doubled from 2003, and therefore it can conservatively be assumed that there are approximately 100 HF management programs in Australia today.

Initial uptake for the proposed medical service is expected to be limited to specialised centres in the first year, with two sites initiated in 2015 prior to MBS listing. Following MBS listing in 2016, it is assumed that at least one centre in each state with a HF management program (QLD, NSW, SA, WA) will adopt the medical service (N=5, year 2). Following this, additional sites will be added in NSW and Victoria at three sites per year respectively.

It is assumed that all sites will utilise two services per month in year 1 and four services per month in subsequent years. These assumptions result in the following figures presented in Table 4, with approximately one quarter of the total estimated HF management programs adopting the service by year 5.

Table 4. Expected 5-year utilisation

Year	**2015**	**2016**	**2017**	**2018**	**2019**
Services performed	48	168	384	672	960
Sites	2	5	11	17	23

To further validate these figures, a top down review of the eligible population was conducted (Table **5**).

Table 5. Estimated patient prevalent pool in Australia

Total number of NYHA class III HF patients in Australia (personal communication with Baker IDI)	136,000
Number of HF patients hospitalised each year (30%) (5)	40,800
Percentage of population with a BMI < 35% (80%) (19)	32,640
Percentage of patients classified as unstable, ie having a repeat hospitalisation within a month (20%) (20)	6,528

Source: Total number of NYHA class III HF patients in Australia was sourced via personal communication with the Baker IDI. *Abbreviations*: BMI, Body Mass Index; HF, heart failure; NYHA, New York Heart Association

Based on a total prevalent patient pool of 136,000, and excluding patients who are not hospitalised (5), have a high BMI (≥35) (19) or who are clinically stable (20), the estimated total prevalent pool of eligible patients in Australia is 6528. This does not factor in other ineligibilities or contraindications such as renal failure or intolerance to anticoagulant therapy. The expected utilisation rate of 960 per annum in year 5 (Table 4) would therefore represent a 15% uptake of the eligible patient population in 5 years. This uptake rate is not dissimilar to uptake for other similar technologies such as cardiac resynchronisation therapy.

5 INTERVENTION

5.1 DESCRIPTION OF PROPOSED MEDICAL SERVICE

Provide a description of the proposed medical service.

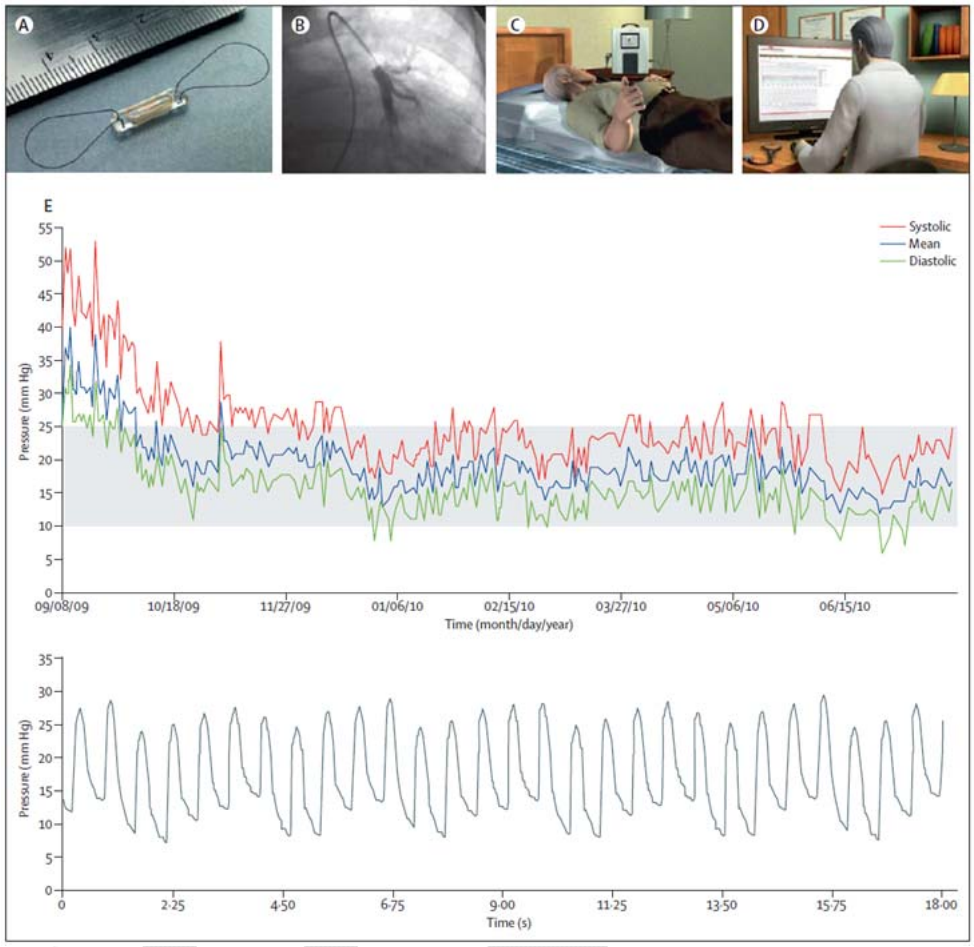
Recent meta-analyses, reviews, and literature reports provide strong evidence for the value of telemonitoring of HF patient ambulatory status in improving patient QoL and outcomes (21-24). There is also increasing evidence demonstrating the value of real time access to data from haemodynamic devices (25-29) to predict decompensation events and hence prevent hospitalisations. Based on this capability, CardioMEMS has been described as 'a pioneering contribution' towards a new paradigm that allows physicians to evolve from reactive management to proactive management (30).

The Sponsor will review the outcomes of Application 1197.1 (which is also for remote cardiac monitoring) when available and intends to discuss the implications with the Secretariat.

PASC agreed that there were two components to the overall service relating to the device, one for its insertion and another for the monitoring of the data from the device. PASC also noted that the clinical effectiveness of the insertion of the device would be based on consequences for subsequent clinical management based on data derived from monitoring data generated by the device.

<u>Components of CardioMEMS and how it works</u>
CardioMEMS provides a method for measuring PA pressure using a wireless pressure sensor that is implanted into the distal PA (Figure 6, (A) and (B)), with transmission of pressure measurements to an external electronics unit (Figure 6, (C)) (2). Pressure measurements are converted into pressure waveforms, PA pressure values, and heart rate measurements, which can be compared with a normal range (Figure 6, (E)). Data is stored in a secure website for review by clinicians or specially trained nurses, allowing real time, continuous and non-invasive access to haemodynamic data to be viewed in the clinician office, clinic, hospital, or the patient's home (Figure 6, (D)) (31).

Figure 6. Implantable haemodynamic monitoring system



Source: Abraham et al (2011)

(A) CardioMEMS sensor or transmitter. (B) Transcatheter is implanted into a distal branch of the descending pulmonary artery. (C) Patient is instructed to take daily pressure readings from home using the home electronics unit. (D) Information transmitted from the monitoring system to the database is immediately available to the investigators for review. (E) Transmitted information consists of pressure trend information and individual pulmonary artery pressure waveforms.

Implantation of the pulmonary artery sensor

The PA sensor is supplied pre-loaded and attached to a tether wire within a delivery catheter. Implantation is performed via Swan-Ganz right heart catheterisation (RHC) using fluoroscopic guidance. The target artery is identified via pulmonary angiography to ensure the catheter is in the correct position and that the branch size of the PA is appropriate (13). The delivery catheter with PA sensor attached is advanced over a guide wire and released, and the delivery catheter is removed (32). For calibration the Swan-Ganz catheter is placed proximal to the PA sensor, and an antenna is held to the patient's back to take PA pressure readings from the PA sensor. Readings are obtained from both the PA sensor and Swan-Ganz catheter, and the Swan-Ganz catheter is then removed (32). Advice from KOLs has indicated that implantation of the PA sensor is a simple process based on RHC procedure, and adds minimal complexity or risk to patients compared to RHC (30).

Following implantation of the PA sensor, patients are required to lay flat on their back for a few hours to monitor for any bleeding from the catheter insertion site, followed by an overnight hospital stay during which patients are trained on how to take pressure measurements at home.

Recording of daily pressure readings at home

Patients are provided with a patient electronic system which comprises of a pillow and electronics unit (Figure 6, (C)). Patients are advised to take daily readings each morning by lying down on the pillow for only a few minutes and pressing a button on the electronics unit.

PASC noted that the data transmitted by each patient's device would go through an off shore server for access via password by the managing clinician, and as such patient data would be subject to all the normal requirements of data security.

Data analysis and management

The purpose of having real time access to haemodynamic data is to guide early intervention and proactive management of HF before decompensation and subsequent hospitalisation occurs. Table 6 presents the PA pressure goals utilised in the CHAMPION trial (13) and recommended by the CardioMEMS Treatment Guidelines (33).

Table 6. Pulmonary artery pressure goals

PA Measure	Pressure Range
PA Systolic	15 – 35 mm Hg
PA Diastolic	8 – 20 mm Hg
Mean PA pressure	10 – 25 mm Hg

Source: Abraham et al (2011). *Abbreviations:* mm Hg, millimeters of mercury; PA, pulmonary artery

To clinically manage a patients PA pressures the clinician (eg treating physician or nurse) must review the measurements on a frequent basis, or set up customised automatic alert functionalities if PA pressures fall out of the pressure ranges. A protocol for management of PA pressures based on the ACC/AHA Guidelines is available; these are not dissimilar to the Australian treatment guidelines presented in Figure 4 and Figure 5, and are currently used effectively in clinical practice in the USA. Table 7 presents the guidelines for managing trends of ambulatory PA pressures.

Table 7. Guidelines for managing trends of ambulatory pulmonary artery pressures

Low PA pressures (hypovolaemia) **PA pressure trending below the haemodynamic range** **Patient has poor perfusion in the absence of signs and symptoms of congestion**	**Normal PA pressures (optivolaemia)** **PA pressure trending within the haemodynamic range** **Patient has minimal symptoms or minimal evidence of poor perfusion**	**Elevated PA pressures (hypervolaemia)** **PA pressure trending above the haemodynamic range**
If on a thiazide and loop diuretic, lower or decrease the thiazide dose (If only on a loop diuretic, lower the dose or discontinue; Consider liberalisation of oral fluid or salt restriction)	No medication changes based on haemodynamic information	Add or increase diuretic (add, increase or change loop diuretic; add thiazide diuretic; add IV loop diuretic)
Lower or hold vasodilators (if postural hypotension is present)	Continue ACC/AHA Guideline recommended therapies	Add or increase vasodilator (add/increase nitrate)
Re-evaluate PA pressures (2-3 days per week until PA pressures stabilise)	Evaluate PA pressures weekly	Re-evaluate PA pressures (2-3 days per week until PA pressures stabilise)
Lower or hold ACE-I (or ARB) dose (if worsening renal function is present with hypotension)	-	Evaluate other aetiologies (if PA pressures remain elevated consider dietary indiscretion, sleep apnoea, etc)

Source: CardioMEMS Treatment Guidelines (2014). *Abbreviations:* ACE-I, Angiotensin-Converting Enzyme Inhibitor; ACC, American College of Cardiology; AHA, American Heart Association; ARB, Angiotensin 2 Receptor Blocker (or sartans);PA, pulmonary artery

5.2 TECHNICAL SPECIFICATION

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

The CardioMEMS delivery system is a transvenous catheter with 120cm of usable length, which is designed to deploy the PA sensor into the PA (34;35). The PA sensor is a battery-free capacitive pressure sensor, which is externally powered by radiofrequency energy and functions as a permanent implant (34;35). The Hospital and Patient Electronics Systems are similar, consisting of two components, an antenna, which receives the data from the PA sensor and main unit, which creates bursts of radiofrequency energy to power the PA sensor and processes the information it receives from the antenna (31;36). The Hospital Electronics System has additional capacity to display and print data (35). The final element of the Electronics Systems is a secure CardioMEMS HF website, which enables clinicians to view and utilise the data obtained (35).

5.3 REGISTERED TRADEMARK WITH DISTINGUISHING CHARACTERISTICS

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

Current methods available to measure PA pressure include cardiac catheterisation (37) and echocardiogram (Doppler or trans-thoracic echocardiogram (TTE) (38-40). These methods can only be used in the non-ambulatory setting, provide measurements for a single point in time, and amongst other measurements are used for diagnostic purposes. CardioMEMS can be distinguished from these methods as it allows real time data analysis to occur in the ambulatory setting, enables regular and frequent PA pressure measurements to be obtained, and can be used as an adjunct to usual practice to guide management in patients already diagnosed with HF.

CardioMEMS is further distinguished from other implantable haemodynamic monitoring systems such as the Chronicle® models 9520 and 9520B (not available in Australia). There are no battery or other components associated with CardioMEMS that would limit the usable life; in comparison Chronicle is battery operated with an average projected service life of 3.7 years (41).

5.4 PROPOSED SETTING FOR DELIVERY

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

Implantation of the pulmonary artery sensor

It is proposed that patients may be identified and referred for implantation of the permanent wireless haemodynamic PA sensor as an inpatient (ie during a HF-related hospitalisation) or as an outpatient following specialist consultation (ie HF clinic, HF management program, clinician consultation in private rooms). As such, implantation of the sensor may be performed during the same HF-related hospital stay in either a public or private hospital with access to a catheterisation laboratory (cathlab). In this case, patients are likely to be situated within the Coronary Care or Cardiac Ward and subsequently implanted with the sensor in a cathlab. Patients may also be referred for implantation of the device if they are being managed within a General Medical Ward with cardiologist consultation; the implantation procedure would be performed in the cathlab with the patient returning to the medical ward for overnight stay.

The subsequent monitoring service can be performed anywhere there is access to the associated website, and as such, a patient can undergo continued management through a centre that provides a HF service without the implantation of the sensor occurring within that centre. This will most likely be applicable to remote and rural settings, where access to a cathlab and HF service within the same centre may be limited.

Pulmonary artery measurements

Patients are required to take daily measurements of their PA. This can be performed in the patient's home or other residence (eg residential aged care facilities) using the patient electronics unit. PA measurements can also be undertaken during patient follow-up during a HF clinic consultation, during a consultation in the clinician's public or private consulting rooms, or during a subsequent hospital stay using the hospital electronics unit.

Data analysis and management

Data analysis, including interpretation and modification to patient management, can occur anywhere there is access to the CardioMEMS website. It is proposed that data analysis will predominantly occur by the treating physician or specially trained nurses, and hence data can be viewed in the hospital, consulting rooms, or during clinics. Protocol driven changes to patient management may also occur in outpatient clinics, during delivery of other HF management services (eg HF clinics, home visits, telemonitoring), or during a consultation in consulting rooms.

5.5 SERVICE DELIVERY IN CLINICAL SETTING

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

As described in Section 5.4, patients may be identified and referred for implantation of the permanent wireless haemodynamic PA sensor as an inpatient (ie during a HF-related hospitalisation) or as an outpatient following specialist consultation (ie HF clinic, home visits, clinician consultation in private rooms). Following identification and referral, implantation of the permanent wireless haemodynamic sensor will occur at a single point in time, ie once only per patient. Measurement of PA pressures by the patient is recommended to occur daily for optimal output. Data analysis by the treating physician or nurse is recommended to occur at least weekly and on an ongoing basis however this may vary depending on patient severity and other clinical indicators. The system has automatic alert capabilities, whereby the PA pressure goal range can be customised per patient and an automated notification informs the clinician if pressure readings fall out of range.

It is anticipated that initial uptake of the system once available will be led by cardiologists that are also HF specialists. This is because HF specialists can best judge the risk:benefit profile of the service for their patient population, have well established HF management infrastructure (eg HF clinics, home visits, telemonitoring), and are leaders in best practice HF management. In addition to HF specialists, general cardiologists, cardiac surgeons, and electro-physiologists can manage aspects of the system, whilst the monitoring service component can be led by specially trained nurses. These physicians are deemed adequately qualified for initiation and implantation of the PA sensor, and no additional qualifications or accreditation prerequisites are necessary.

HF nurse practitioners or specially trained registered nurses can monitor the PA pressure data via the online portal and forward results the treating physician for further interpretation and modification to patient management as required. In line with current HF management services where a HF nurse practitioner or HF nurse consultant is present, a protocol will be adapted from existing guidelines to guide nurse-led management parameters where appropriate (eg up-titration of diuretics to a certain point). The Sponsor anticipates this will occur as part of advisory board activities in 2015.

Incremental training on sensor implantation, data analysis and the management protocol are expected. Overall it is expected that data analysis and ongoing patient management will be integrate into existing HF management services as a part of usual practice.

For PA sensor implantation, access to a cathlab is required along with access to an overnight hospital bed. Initially the overnight stay is likely to be within the cardiac ward, however with increased familiarisation, patients may be transferred to a general medical bed as there is no specific cardiac monitoring that is required following implantation.

Based on geography and general health care system barriers in rural and remote areas (RRA) of Australia, patients residing in these areas may have limited access to the proposed medical service. In RRAs, patients with HF are managed by general practitioners (GPs) in the community or general physicians within hospitals, and may have some access to a cardiologist but are unlikely to have direct access to HF specialists. Per normal care for this patient population, referral to institutions where experience and facilities are available for implantation is likely to occur. Patients are likely to be transported to a metropolitan hospital for management within the HF team, and are likely to be listed for elective surgery (as opposed to implantation during a HF-related hospitalisation). Once implanted, ongoing data analysis can occur remotely and integrate into the HF management program

available for that area (eg nurse follow-up via telemonitoring). Ongoing data analysis and management of these patients is likely to be led by the treating GP or general physician, with opportunity to liaise with the metropolitan based HF team if needed. Overall, the proposed medical service is likely to significantly improve patient management in RRAs relative to usual care following successful integration into existing HF management services.

As described by KOLs locally as well as KOLs currently using the proposed medical service in the clinical setting, the workload associated with the proposed medical service is described as being 'front-loaded', with significant efficiency gains over time.

6 CO-DEPENDENT INFORMATION

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

The permanent leadless and batteryless pulmonary artery pressure sensoris not associated with any co-dependent technologies. Listing of the permanent leadless and batteryless pulmonary artery pressure sensor on the Prostheses List is being considered.

7 COMPARATOR AND CLINICAL CLAIM

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

The comparator for the proposed medical service refers to the standard care strategy adopted in the pivotal trial (2), which reflects current usual practice in the clinical setting(or 'standard care' or 'usual care' involving (42):

- non-pharmacological strategies (eg physical activity programs and dietary / fluid management protocols);
- best practice pharmacotherapy (eg ACE-Is and beta-blockers);
- supportive devices; and
- post-discharge HF management programs (eg home-based interventions).

Structured multidisciplinary HF management programs are recommended for all patients hospitalised for HF with NYHA class II-III at the time of discharge. It is recommended that these programs are commenced within one week of hospital discharge with follow-up care continuing for at least 12 weeks (42). A core element that is common to most programs includes establishing effective protocols for symptom management and monitoring of signs and symptoms to enable early identification of decompensation and / or deterioration with the aim of preventing hospitalisation. Patients are educated in self-monitoring of their daily weight and are provided with a personalised HF action plan. Multidisciplinary HF care is implemented in a range of clinical settings via a range of delivery models including home-based, clinic-based, telephone-based, or a hybrid of these (42).

Based on the evidence available for the proposed medical service (refer to Section 8), HF management guided by remote analysis of PA pressure is considered to be non-inferior in terms of safety, noting an elevated risk of implantation related transient events, and superior in terms of patient outcomes compared to usual practice.

PASC agreed that pulmonary artery catheterisation (PAC) is not a comparator because it is not currently used for assessing the intended population, and is invasive and non-continuous. PASC agreed the comparator is usual monitoring of HF as currently provided without the device. PASC noted that the device should be used for monitoring purposes only, not initial diagnosis or determining etiology.

PASC noted that the intensity of follow-up in Australian practice may not match the intensity of follow-up in the CHAMPION trial. The CHAMPION study design required that in the treatment arm, review of pressure data was done at least once a week and more frequently if changes occurred in medications. All patients were scheduled to be seen by their clinician at 1 month, 3 months, and 6 months, and every 6 months thereafter. The treatment group had a significantly greater number of changes to HF medications (2468, mean 9.1 per patient) than did the control group (1061, 3.8 per patient; p<0.0001).

This intensity of follow-up and applicability to the Australian context will be comprehensively addressed in the assessment report.

8 EXPECTED HEALTH OUTCOMES

8.1 EXPECTED PATIENT RELEVANT HEALTH OUTCOMES

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

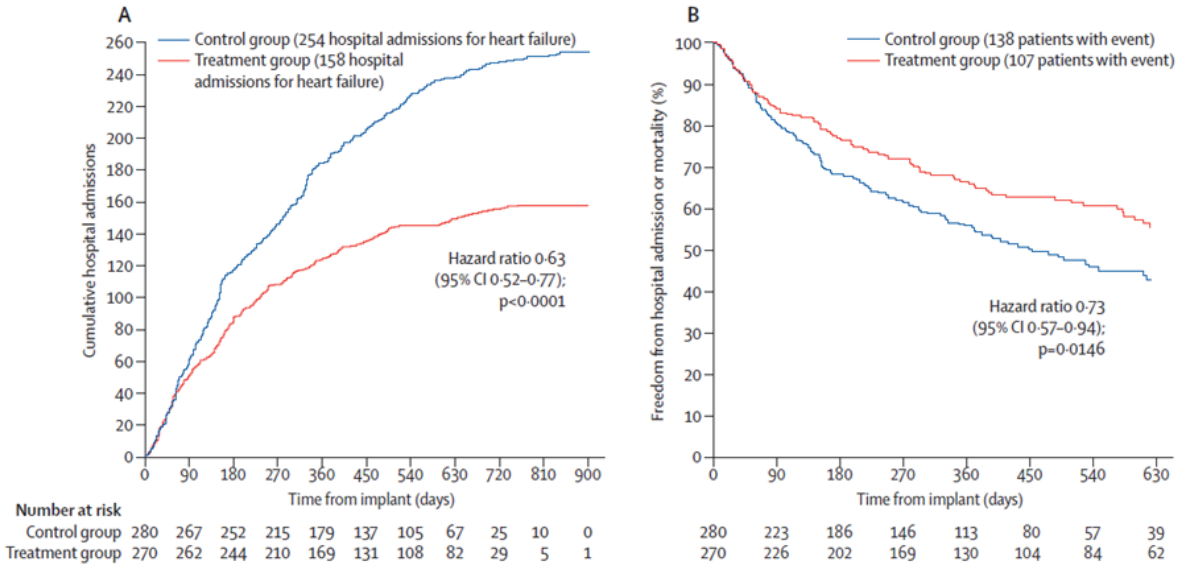
As discussed in Section 4.3, the CHAMPION trial was a prospective, single-blind, multi-centre, randomised controlled trial in which CardioMEMS, represented by the treatment group (ie physician access to patient PA pressure measurements to guide HF management in addition to usual care), demonstrated a statistically significant improvement in the primary efficacy endpoint of HF-related hospitalisations up to 6 months versus the comparator group (ie HF management guided by usual care alone). The number needed to treat (NNT) to prevent one HF-related hospitalisation was eight patients. The significant reduction in HF-related hospitalisation was maintained during an open access period with mean follow-up of 13 months (17) with the NNT reducing to only four patients over the entire study duration. The treatment group also demonstrated a statistically significant improvement versus the comparator group in the following secondary endpoints:

- change from baseline PA pressure at 6 months;
- proportion of patients admitted for HF at 6 months;
- days alive and out of hospital at 6 months;
- QoL as measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) at 6 months; and
- a pre-specified supplementary efficacy endpoint (HF-related hospitalisations during the entire randomised follow-up).

In a post-hoc analysis the treatment group had a lower risk of death or first HF-related hospitalisation versus the comparator group over the entire randomised follow-up period (2). Furthermore, during an open access period, physicians in the former control group were given full access to PA pressure readings from the CardioMEMS HF website to guide patient management. This resulted in a 48% reduction in HF-related hospitalisations ($p < 0.0001$) (17).

Based on these results, a reduction in hospitalisations is expected if the proposed medical service is recommended for public funding. Specifically, a 28% reduction in HF-related hospitalisations at 6 months was demonstrated in the treatment group (N=270) compared to the control group (N=280) (84 vs 120, hazard ratio (HR) 0.72, 95% confidence interval (CI) 0.60-0.85, p = 0.002). Compellingly, a 37% reduction over the entire randomised follow-up period was demonstrated (158 vs 254, HR 0.63, 95% CI 0.52-0.77, p < 0.0001) (2). Figure 7 presents the results of the cumulative HF-related hospitalisation rates and a composite of first HF-related hospitalisation and mortality.

Figure 7. (A) Cumulative heart failure-related hospitalisations during the entire period of randomised single-blind follow-up, and (B) freedom from first heart failure-related hospitalisation or mortality during the entire period of randomised follow-up



Source: Abraham et al (2011). *Abbreviations:* CI, confidence interval

The CHAMPION trial also demonstrated a significantly shorter length of stay for HF-related hospitalisations among patients in the treatment group compared to the control group (2.2 days vs 3.8 days, p = 0.02) (2), demonstrating a clinically relevant reduction of 1.6 days. Patients in the treatment group also had a significantly greater number of changes to HF medication regimen relative to the control group, providing supporting evidence for the proactive nature of clinical management enabled by CardioMEMS (2).

Based on PASC meeting outcomes, changes in the number of consultation services and treatments, and their consequences on health outcomes will also be discussed in the assessment report.

PASC agreed that outcomes relating to PAC could be excluded, based on it not being a comparator.

8.2 POTENTIAL RISKS TO PATIENTS

Describe any potential risks to the patient.

The two primary safety endpoints assessed in the CHAMPION trial were met (2). In total, 98.6% of patients in whom implantation of the sensor was attempted were free from DSRC at 6 months, meeting the pre-specified objective performance criteria of 80% (p < 0.0001). Of the total of 550 patients with sensors implanted, all (100%) were operational at 6 months and there were no sensor explants or repeat implants (p < 0.0001 compared to the pre-specified objective performance criteria of 90%). No events required the sensor to be removed.

There were 15 deaths in the treatment group and 20 deaths in the control group at 6 months (p = 0.4484) indicating no difference in overall survival (2). The treatment group had significantly better survival without HF-related hospitalisations compared to the control group (HR 0.69, 95% CI 0.50-0.95, p = 0.0239).

The trial reported 15 serious adverse events, which occurred during 575 implant attempts (< 3%) (2). Of these, four were bleeding events, three were hospitalisations due to anticoagulation treatment, two were exacerbations of pre-existing atrial dysrhythmias during RHC, one pulmonary *in situ* thrombus during RHC, two febrile illnesses, one cardiogenic shock, one atypical chest pain and one delivery system failure.

The overall safety profile demonstrated that the CardioMEMS is well tolerated during the prolonged single-blind follow-up. Further follow-up beyond the primary safety endpoint assessments at 6 months remained positive and demonstrated a sustained patient benefit (2;17).

Feedback sought from KOLs has also indicated that there are minimal safety concerns associated with the proposed medical service that may impact uptake in practice, as the safety profile is deemed to be similar to that of an RHC procedure.

Based on PASC meeting outcomes, further safety details, including an updated long term safety data, will be provided in the assessment report.

8.3 TYPE OF ECONOMIC EVALUATION

Specify the type of economic evaluation.

A cost-utility analysis will be conducted comparing patients receiving HF management guided by a permanent leadless and batteryless pulmonary artery pressure sensor in addition to standard care, compared to standard care alone. Outcomes will include incremental cost per HF-related hospitalisation avoided, cost per life year gained and cost per QALY gained.

9 FEE

9.1 PROPOSED FUNDING TYPE

Explain the type of funding proposed for this service.

The type of funding proposed for the medical service is via listing on the Medical Benefits Schedule (MBS).

9.2 DIRECT COSTS

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

The direct cost of equipment and resources that are may be associated with the proposed medical service are listed below. Hospital and post-procedure costs have been adapted from published costs for AR-DRGs F09C (Other cardiothoracic procedures without cardiopulmonary bypass pump without complication and/or comorbidity (CC) (Surgical)) and F16B (Interventional coronary procedures without acute myocardial infarction without stent implantation without CC (Surgical)) (43).

Procedure

- Hospital costs (including operating rooms, special procedure suites, supplies): approximately $2168-$2859 (based on costs for AR-DRGs F09C and F16B in the public setting) (43).
- Device consumables (delivery catheter and sensor): to be determined.
- Anaesthesia (MBS Item 21941: Initiation of management of anaesthesia for cardiac catheterisation including coronary arteriography, ventriculography, cardiac mapping, insertion of automatic defibrillator or transvenous pacemaker - Fee: $138.60, Benefit: 75% = $103.95, 85% = $117.85).
- Indicative costs related to sensor implantation: based on MBS item 38200 Right heart catheterisation any one or more of the following: fluoroscopy, oximetry, dye dilution curves, cardiac output measurement by any method, shunt detection or exercise stress test (Fee: $445.40, Benefit: 75% = $334.05, 85% = $378.60).

Overnight hospital stay

- Post-procedure hospital stay (including critical care, ward medical, non-clinical salary, pathology allied, pharmacy, hotel, on-costs): approximately $1802-$4232 (based on costs for AR-DRGs F09C and F16B in the public setting) (43).

Pharmaceuticals

- Aspirin: PBS General Schedule codes 1010E and 8202Q (DPMQ $102.12 and maximum price to consumer $166.20 for 12 months) and Repatriation Pharmaceutical Benefits codes 4076M, 4077N and 4078P (DPMQ $192.12 and maximum price to consumers $72.00 for 12 months).
- Clopidogrel or warfarin: required for 1 month only and supplied via hospital pharmacy.

Data analysis and patient monitoring:

The routine analysis of information from a permanent leadless and batteryless pulmonary artery pressure sensor is a negligible addition to usual practice, and therefore, future costs related to the data analysis are expected to be absorbed as part of usual practice. The improvements associated with implantation of the PA sensor and access to patient haemodynamic data will ultimately improve practice efficiency and prevent unnecessary hospitalisations. Based on version 6.0x of the Public National Cost Weights (Round 14), the average cost of a patient admitted for AR-DRG F62B (HF and shock without catastrophic complication or comorbidity (CCC)) is $5241, and $11,196 for AR-DRG F62A (HF and shock with CCC) (44).

9.3 DETAILS OF PROPOSED FEE

Provide details of the proposed fee.

Based on the implantation being performed as part of a standard RHC and existing similar MBS items, it is proposed that the fee structure for implantation of the permanent wireless haemodynamic sensor is likely to reflect the current remuneration for MBS item 38200 (Fee: $445.40, Benefit: 75% = $334.05, 85% = $378.60). Incremental costs are expected with the additional time and steps that are associated with sensor implantation, beyond a standard cardiac catheterisation. These include insertion of a delivery catheter, positioning of the sensor into the PA lumen, and calibration of the sensor (45). For guiding purposes, MBS item 49360 (Hip, diagnostic arthroscopy of, not being a service associated with any other arthroscopic procedure of the hip) and 49363 (Hip, diagnostic arthroscopy of, with synovial biopsy, not being a service associated with any other arthroscopic procedure of the hip) differ in fee as follows: $343.95 (49360) versus $414.20 (49363). The fee for

MBS item 49363 has an incremental cost associated with the additional service of performing a synovial biopsy.

The total procedure time for both groups in the CHAMPION trial averaged 54.3 ± 31.6 minutes skin to skin (13). Initial experience reported a total procedure time of as short as 19 minutes, to 110 minutes in some situations (32). Cardiac catheterisation can take approximately 30 minutes, however depending on individual cases this may take more or less time (46). Therefore, the incremental time for insertion of the PA sensor (relative to a RHC) is likely to be approximately 25 minutes (increase of 83%). Adjusting the fee for item 38200 accordingly, the revised fee is proposed to be $816.57 ($445.4 x 1.83 = $816.57). The Sponsor remains open to further discussions with PASC and MSAC regarding this amount. Further to the PASC meeting outcomes, the Sponsor will include further evidence to justify the fee on complexity and qualifications of provider in the assessment report.

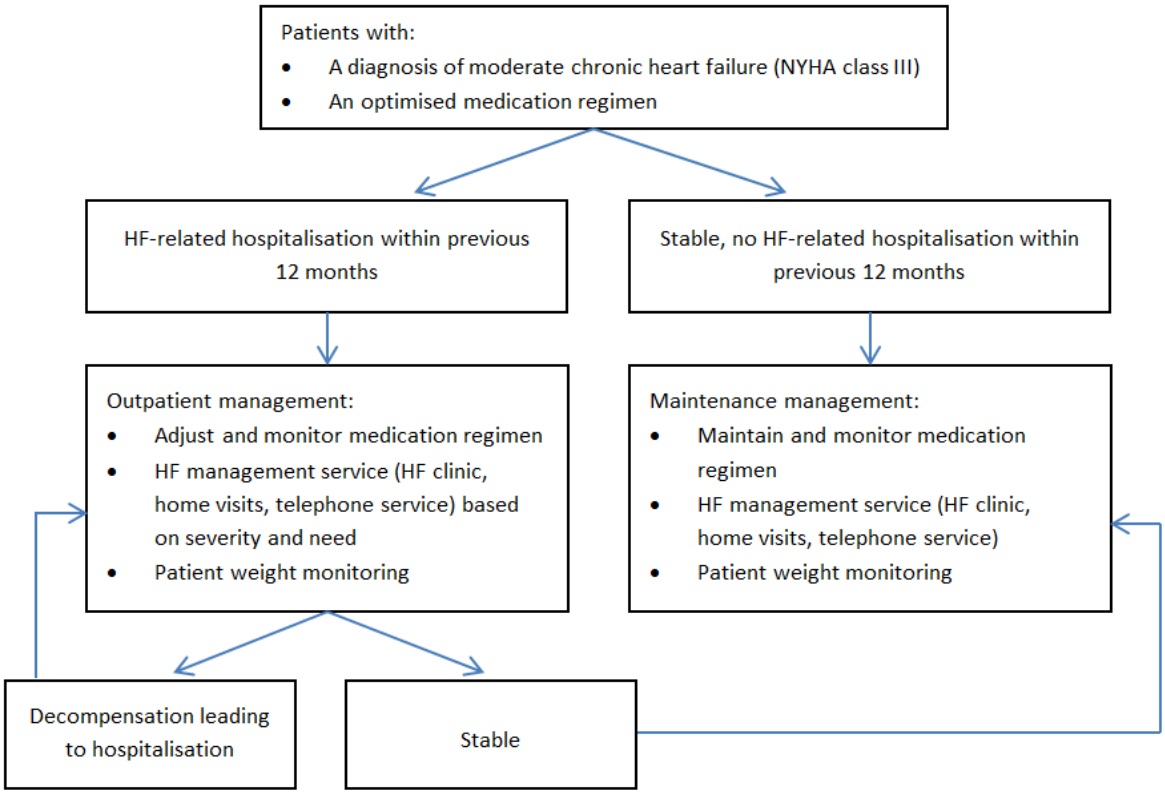
10 CLINICAL MANAGEMENT ALGORITHM

10.1 CURRENT CLINICAL MANAGEMENT ALGORITHM

Provide a clinical management algorithm (e.g.: flowchart) explaining the current approach (see (7) Comparator section) to management and any downstream services (aftercare) of the eligible population/s in the absence of public funding for the service proposed preferably with reference to existing clinical practice guidelines.

Figure 8 shows the current clinical management algorithm for the proposed patient population. It encompasses outpatient and maintenance management based on hospitalisation status, including modifications to medication regimen, HF management programs, and patient self-care. Specifically, patients with a diagnosis of moderate chronic HF (NYHA class III) and a HF-related hospitalisation in the previous 12 months are assumed to be managed via a HF management service (eg HF clinics, home visits, telemonitoring), with recommended daily weight monitoring. Although it is acknowledged that care will vary based on patient severity and clinical need, KOL advice (N=9) suggests that this algorithm is reflective of the best practice standards accepted across Australia.

Figure 8. Current clinical management algorithm in heart failure



Abbreviations: HF, heart failure; NYHA, New York Heart Association

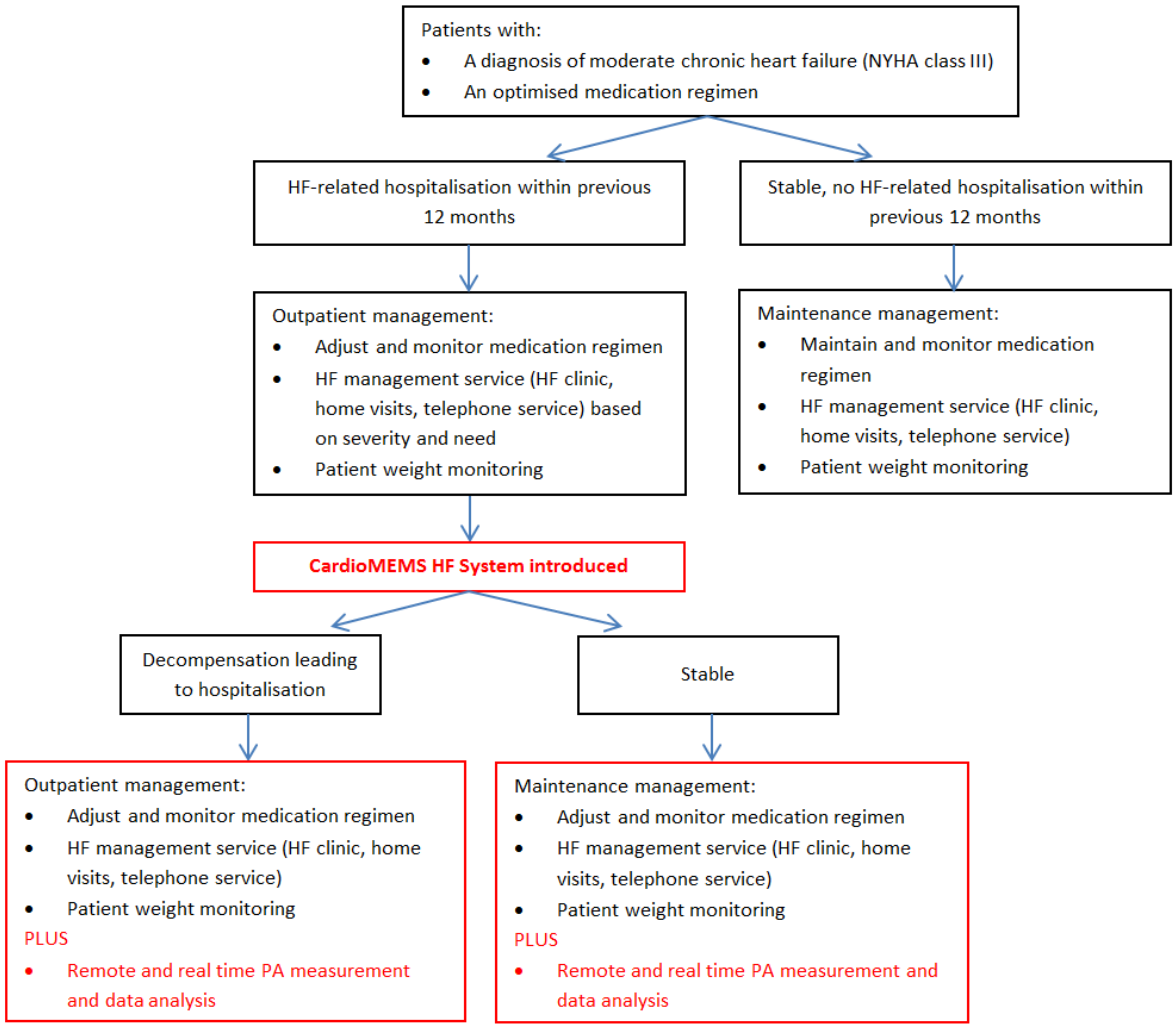
10.2 PROPOSED CLINICAL MANAGEMENT ALGORITHM

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

Figure 9 shows the proposed clinical management algorithm with a permanent leadless and batteryless pulmonary artery sensor. Similar to Figure 8, it encompasses aspects of standard care including outpatient and maintenance management based on hospitalisation status, including modifications to medication regimen, HF management programs, and patient self-care. The only difference is introduction of the permanent leadless and batteryless pulmonary artery sensor and associated real time PA pressure monitoring and analysis, which would be incorporated into the standard care HF management programs.

KOL advice (N=9) has been sought to validate the alterations to the management algorithm below. It is agreed that this algorithm is reflective of the changes that will integrate into the current best practice standards accepted across Australia. It is also agreed that implementation in practice will be dependent upon the HF management services available and structure within individual hospitals and health care systems.

Figure 9. Proposed clinical management algorithm with a permanent leadless and batteryless pulmonary artery sensor



Abbreviations: HF, heart failure; NYHA, New York Heart Association; PA, pulmonary artery

11 REGULATORY INFORMATION

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

An application to the Therapeutic Goods Administration (TGA) is estimated to be submitted for consideration in December 2014. The proposed wording for the TGA indication is:

> 'The CardioMEMS HF System is indicated for measuring pulmonary artery pressure in patients with heart failure. The data provided by the system can be used by the physician to initiate or modify heart failure treatment and manage heart failure disease. The CardioMEMS HF System provides a method for measuring pulmonary artery (PA) pressure using a wireless pressure sensor that is implanted into the distal PA and an external electronics device to interrogate the sensor and view the pressure measurements. Once implanted, the HF System can provide non-invasive hemodynamic information in the physician's office, clinic, hospital, or patient's home.

The CardioMEMS HF System is also intended to measure pulmonary artery pressure in heart failure patients who are likely to receive an implantable ventricular assist device or undergo heart transplant as part of their heart failure treatment.'

12 DECISION ANALYTIC

Provide a summary of the PICO as well as the health care resource of the comparison/s that will be assessed, define the research questions and inform the analysis of evidence for consideration by MSAC (as outlined in Table 1) (Table 8).

Table 8 describes the PICO criteria for the proposed medical service. Patients are reflective of the proposed patient population for the service described in Section 4.2. Treatment options include usual practice or a permanent leadless and batteryless pulmonary artery sensor in addition to usual practice, which allows physicians real time access to haemodynamic information. Patient outcomes are reflective of the pivotal trial evidence from CHAMPION described in Section 8, including HF-related hospitalisations, quality of life and mortality.

Table 8. Summary of PICO to define research question

PICO	Comments
Patients	Diagnosis of moderate HF (NYHA class III) for 3 months, on a stable and optimised medication regimen, and have had a HF-related hospitalisation within the previous 12 months
Intervention	Permanent leadless and batteryless pulmonary artery sensor, in addition to usual practice
Comparator	Usual practice
Outcomes	HF-related hospitalisations, QALYs, mortality, safety (device-related and procedure-related)

Abbreviations: HF, heart failure; NYHA, New York Heart Association; PICO, Patients/Population, Intervention, Comparator, Outcomes; QALYs, quality adjusted life years.

Three indicative decision analytic protocols are presented in Figure 10, 11 and 12 below. Per the PICO criteria described in Table 8, both protocols compare usual practice to the addition of the permanent leadless and batteryless pulmonary artery sensor to usual practice.

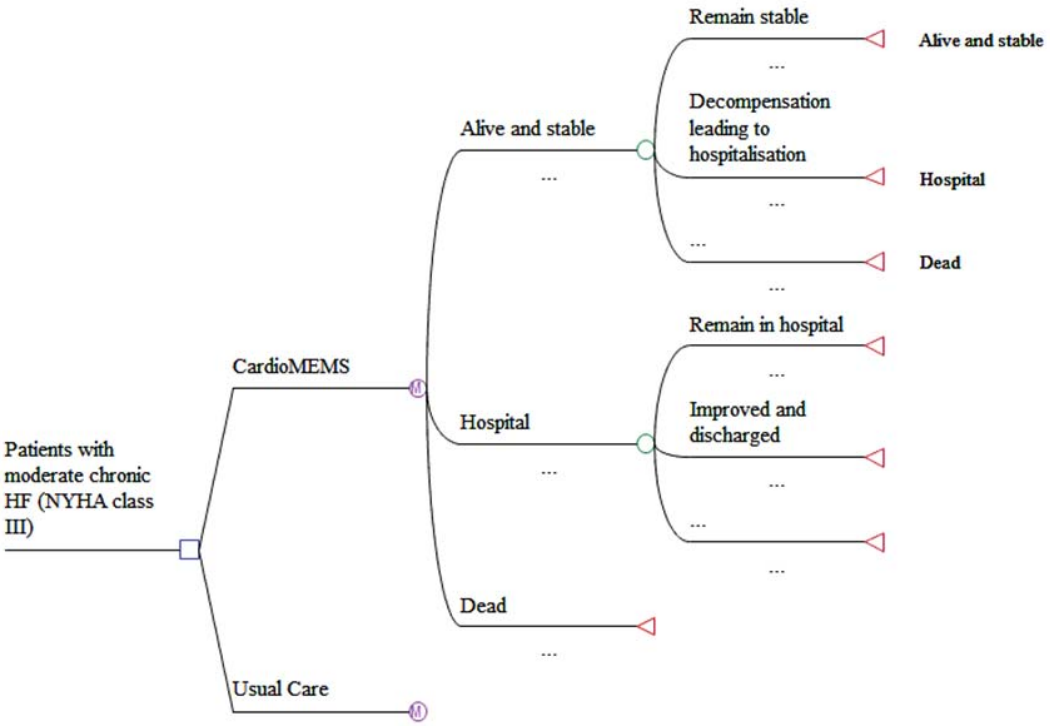
Option 1a (Figure 10) provides a simplistic structure which compares treatments based on differences in hospitalisation rates and mortality. As part of Option 1a, Figure 10 shows a separate hospitalisation health state for illustrative purposes, however this is likely to be a transitional health state within the 'Alive and stable' health state in the final model. This structure is further developed in Option 1b (**Error! Reference source not found.**) which includes a post-rehospitalisation health state to capture ongoing quality of life and resource use for patients discharged from hospital. The structure of Option 1b aligns with a global model currently under development and is therefore presented as a another option.

In contrast, Option 2 (Figure 12) compares treatments based on NYHA class health states. In doing so, this option compares the relative time spent in NYHA class health states between treatments, with increasing NYHA class associated with increasing cost, reduced QoL and increased risk of hospitalisation (5;8-11). To develop this option, individual patient data is required from the CHAMPION trial to inform transition probabilities.

At the time of writing it is not known if the CHAMPION trial individual patient data will be accessible for the purpose of developing a cost-utility model. The Sponsor believes that Option 2 will more accurately reflect disease progression for patients with chronic HF, and therefore, Option 2 is proposed as the preferable option. However, Option 1a and 1b are considered a viable alternative for the situation where the CHAMPION trial individual patient data is unavailable. In both options, safety

outcomes will be incorporated by including a transient health state in the CardioMEMS arm to capture the small risk of insertion related events such as hospitalisations due to anticoagulation treatment.

Figure 10. Decision analytic protocol - Option 1a



Abbreviations: HF, heart failure; NYHA, New York Heart Association

Figure 11. Decision analytic protocol - Option 1b

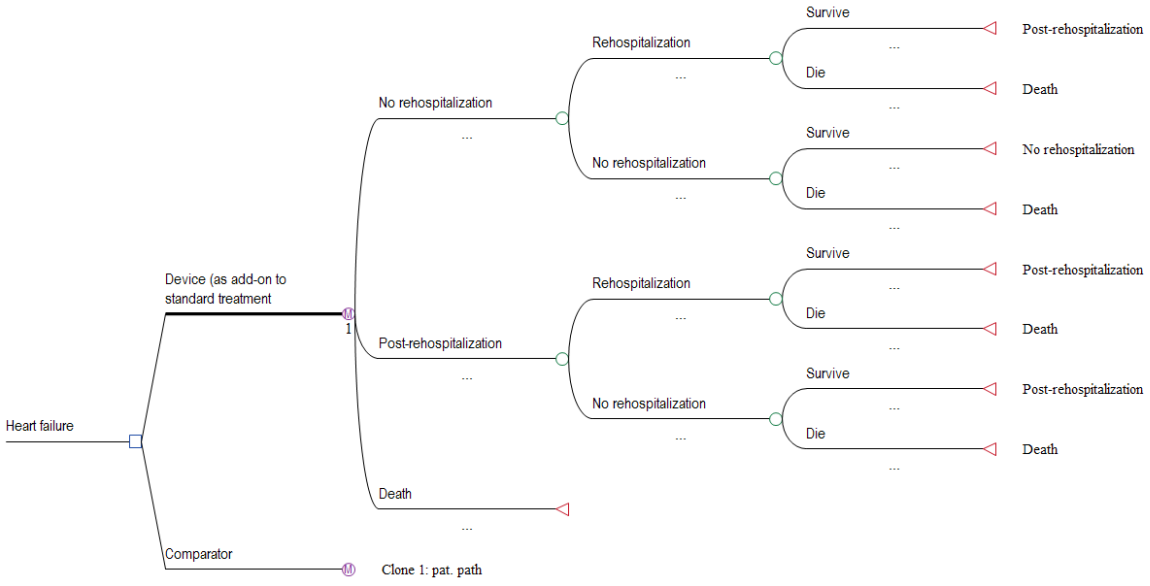
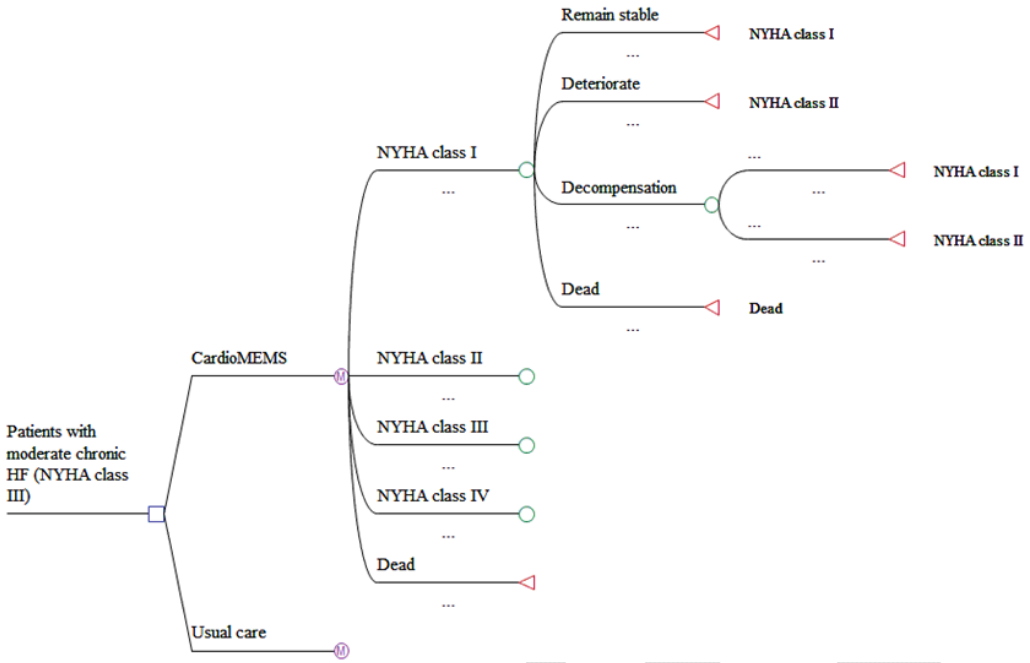


Figure 12. Decision analytic protocol - Option 2



Abbreviations: HF, heart failure; NYHA, New York Heart Association

13 HEALTHCARE RESOURCES

Using tables 2 and 3 (Table 9)*, provide a list of the health care resources whose utilisation is likely to be impacted should the proposed intervention be made available as requested whether the utilisation of the resource will be impacted due to differences in outcomes or due to availability of the proposed intervention itself.*

The Sponsor will consider and discuss the downstream resource implications in the assessment report, per PASC meeting outcomes.

Table 9. List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets (Include costs relating to both the standard and extended safety net)	Other government budget	Private health insurer	Patient	Total cost
Resources provided to identify eligible population (for both proposed medical service and standard care)										
No additional resources required	-	-	-	-	-	-	-	-	-	-
Chest X-ray	-	-	-	-	-	-	-	-	-	-
Blood tests	-	-	-	-	-	-	-	-	-	-
Echocardiogram	-	-	-	-	-	-	-	-	-	-
Clinical assessment	-	-	-	-	-	-	-	-	-	-
Optimised medical therapy	-	-	-	-	-	-	-	-	-	-
Resources provided to deliver proposed medical service										
CardioMEMS™ HF System	St. Jude Medical / PHI / Hospital	Public or Private Hospital	-	1 unit	-	-	-	-	-	Approx. $17,000[a]
Public hospital costs (including operating rooms, special procedure suites, supplies)[b]	Other government	Surgical	-	1 inpatient episode	-	-	-	-	-	Approx. $2168-$2859

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets (Include costs relating to both the standard and extended safety net)	Other government budget	Private health insurer	Patient	Total cost
Anaesthesia[c]	MBS	Surgical	-	1 service	75% = $103.95 85% = $117.85 (MBS item 21941)	-	-	(Increment of patient costs – may vary)	25% = $34.65 15% = $20.75	$138.60
Indicative costs related to sensor implantation[d]	MBS	Surgical	-	1 service	75% = $334.05 85% = $378.60 (MBS Item 38200) plus incremental fee[d]	-	-	(Increment of patient costs – may vary)	25% = $111.35 15% = $66.80	$445.40 plus incremental fee[e]
Clopidogrel or warfarin	Hospital / other government	Hospital / Pharmacy	-	1 month worth	-	-	-	-	-	-
Post-procedure hospital stay (including critical care, ward medical, non-clinical salary, pathology allied, pharmacy, hotel, on-costs)[b]	Other government	Public or private hospital	-	1 inpatient episode	-	-	-	-	-	Approx. $1802-$4232
Physician consultation[f]	MBS / Patient / PHI	Hospital / clinician consulting rooms	-	-	75% = $64.20 85% = $72.75 (MBS Item 104)	-	-	(Increment of patient costs – may vary)	75% = $21.35 85% = $12.80	$85.55 (specialist added cost may vary)
Resources provided in association with proposed intervention										
Aspirin	Other government	Hospital / Pharmacy	-	12	-	-	$8.51 (PBS 1010E and 8202Q) $16.01 (RPBS 4076M, 4077N and 4078P)	-	$13.85 (PBS) $6 (RPBS)	$268.32 (PBS) $264.12 (RPBS)
Resources provided to deliver standard care										

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets (Include costs relating to both the standard and extended safety net)	Other government budget	Private health insurer	Patient	Total cost
Physician consultation[f] (Patient monitoring / HF management service)	MBS / Patient / PHI	Hospital / clinician consulting rooms	-	-	75% = $64.20 85% = $72.75 (MBS Item 104)	-	-	(Increment of patient costs – may vary)	75% = $21.35 85% = $12.80	$85.55 (specialist added cost may vary)
Nurse practitioner led patient monitoring / HF management service	MBS / Patient	Hospital outpatient clinic / patients home	-	-	-	-	-	-	-	-
Resources used to manage patients successfully treated with the proposed medical service or standard care										
Physician consultation[f] (Data analysis and patient monitoring / HF management service)	MBS / Patient / PHI	Hospital / clinician consulting rooms	-	-	75% = $64.20 85% = $72.75 (MBS Item 104)	-	-	(Increment of patient costs – may vary)	75% = $21.35 85% = $12.80	$85.55 (specialist added cost may vary)
Nurse practitioner led patient monitoring / HF management service	MBS / Patient	Hospital outpatient clinic / patients home	-	-	-	-	-	-	-	-
Resources used to manage patients who are unsuccessfully treated with the proposed medical service or standard care										
Data analysis and patient monitoring	Specialist / Nurse	Home / Clinic / Hospital	-	-	-	-	-	-	-	-
HF hospitalisation without complications	MBS / other government	Public or private hospital	-	1 inpatient episode	-	-	AR-DRG F62B	-	-	$5241[g]
HF hospitalisation with complications	MBS / other government	Public or private hospital	-	1 inpatient episode	-	-	AR-DRG F62A	-	-	$11,196[g]

Abbreviations: AR-DRG, Australian Refined Diagnostic Related Group; HF, heart failure; MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme; PHI, private health insurer; RPBS, Repatriation Pharmaceutical Benefits Scheme. *Table notes:* [a]The final cost is still to be determined by the sponsor; [b]Based on AR-DRGs F09C and F16B (also covers cost of insertion related safety events); [c]MBS Item 21941 Initiation of management of anaesthesia for cardiac catheterisation including coronary arteriography, ventriculography, cardiac mapping, insertion of automatic defibrillator or transvenous pacemaker; [d]MBS Item 38200 Right heart catheterisation any one or more of the following: fluoroscopy, oximetry, dye dilution curves, cardiac output measurement by any method, shunt detection or exercise stress test; [e]Refer to Section 9.3; [f]MBS Item

104 Specialist, referred consultation – surgery or hospital (Professional attendance at consulting rooms or hospital by a specialist in the practice of his or her specialty where the patient is referred to him or her) – Initial attendance in a single course of treatment, not being a service to which ophthalmology items 106, 109 or obstetric item 16401 apply. [8]Based on version 6.0x of the Public National Cost Weights (Round 14).

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APPENDICES

Appendix 1

Abstract provided for further background on CardioMEMS: *Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet 2011; 377:658-66.ppendi*

Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial

*William T Abraham, Philip B Adamson, Robert C Bourge, Mark F Aaron, Maria Rosa Costanzo, Lynne W Stevenson, Warren Strickland, Suresh Neelagaru, Nirav Raval, Steven Krueger, Stanislav Weiner, David Shavelle, Bradley Jeffries, Jay S Yadav, for the CHAMPION Trial Study Group**

Summary

Background Results of previous studies support the hypothesis that implantable haemodynamic monitoring systems might reduce rates of hospitalisation in patients with heart failure. We undertook a single-blind trial to assess this approach.

Methods Patients with New York Heart Association (NYHA) class III heart failure, irrespective of the left ventricular ejection fraction, and a previous hospital admission for heart failure were enrolled in 64 centres in the USA. They were randomly assigned by use of a centralised electronic system to management with a wireless implantable haemodynamic monitoring (W-IHM) system (treatment group) or to a control group for at least 6 months. Only patients were masked to their assignment group. In the treatment group, clinicians used daily measurement of pulmonary artery pressures in addition to standard of care versus standard of care alone in the control group. The primary efficacy endpoint was the rate of heart-failure-related hospitalisations at 6 months. The safety endpoints assessed at 6 months were freedom from device-related or system-related complications (DSRC) and freedom from pressure-sensor failures. All analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00531661.

Findings In 6 months, 83 heart-failure-related hospitalisations were reported in the treatment group (n=270) compared with 120 in the control group (n=280; rate 0·31 *vs* 0·44, hazard ratio [HR] 0·70, 95% CI 0·60–0·84, p<0·0001). During the entire follow-up (mean 15 months [SD 7]), the treatment group had a 39% reduction in heart-failure-related hospitalisation compared with the control group (153 *vs* 253, HR 0·64, 95% CI 0·55–0·75; p<0·0001). Eight patients had DSRC and overall freedom from DSRC was 98·6% (97·3–99·4) compared with a prespecified performance criterion of 80% (p<0·0001); and overall freedom from pressure-sensor failures was 100% (99·3–100·0).

Interpretation Our results are consistent with, and extend, previous findings by definitively showing a significant and large reduction in hospitalisation for patients with NYHA class III heart failure who were managed with a wireless implantable haemodynamic monitoring system. The addition of information about pulmonary artery pressure to clinical signs and symptoms allows for improved heart failure management.