Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1237 – Cardiac MRI – Coronary Artery Disease

Applicant: **The Cardiac Society of Australia and New Zealand**

Date of MSAC consideration: **MSAC 67th Meeting, 28-29 July 2016**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at MSAC Website

1. Purpose of application and links to other applications

An application requesting two new MBS listings of cardiac magnetic resonance imaging (CMR) for myocardial stress perfusion (Population One) and viability imaging (Population Two) in patients with suspected or known coronary artery disease (CAD) was received by the Department of Health from the Cardiac Society of Australia and New Zealand (CSANZ).

2. MSAC's advice to the Minister

After considering the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of:

- stress perfusion cardiac magnetic resonance imaging (SP-CMR) with late gadolinium enhancement (LGE) for the evaluation of suspected myocardial ischaemia in patients with an intermediate pre-test probability (PTP) of CAD; and

- cardiac magnetic resonance imaging with late gadolinium enhancement (LGE-CMR) for the assessment of myocardial viability in patients with CAD and impaired left ventricular systolic function who are being considered for revascularisation,

MSAC did not support public funding for either indication as the clinical need was not established and the modelled economic evaluation showed that, at the fee proposed, CMR is less cost effective in the management of coronary artery disease than current funded options within the MBS, including CT coronary angiography and stress echocardiography. In view of a higher rate of equivocal or failed examinations, CMR also generates more indeterminate results than

single-photon emission computed tomographic (SPECT) myocardial perfusion imaging, even in high volume centres.

MSAC also noted that due to limited access to rebatable magnetic resonance imaging (MRI) machines, demand for MRI from other specialties, the requirement for specialists specifically trained in CMR, and the time required to conduct the proposed tests, access to CMR is likely to be severely restricted in the foreseeable future.

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

MSAC noted that the proposed imaging would be conducted using a standard MRI machine performed by cardiologists or radiologists with appropriate training. MSAC noted that the applicant was working with The Royal Australian and New Zealand College of Radiologists (RANZCR) to develop a joint training program that would provide accreditation for cardiologists and radiologists to provide this service. However, MSAC noted that in order for cardiologists to be reimbursed for this service through the Medical Benefits Schedule, formal legislative changes to the *Health Insurance (Diagnostic Imaging Services Table) Regulations* will be required. The application proposed the use of this service in two distinct populations. MSAC reviewed the evidence for each population separately.

The first population ("Population One") encompassed patients presenting with symptoms consistent with stable CAD and an intermediate (15-85%) PTP of CAD. For this population, the proposed imaging involves the use of SP-CMR, with adenosine as the pharmacological stress agent, and viability assessment with LGE-CMR. MSAC noted that, combined, these imaging modalities were anticipated to allow diagnosis of CAD.

The applicant claimed that SP-CMR in combination with LGE-CMR (SP-CMR + LGE-CMR) would substitute for existing diagnostic cardiac stress tests. Hence the comparators included: exercise electrocardiography (ex-ECG); exercise or pharmacological stress echocardiography (stress-Echo); exercise or pharmacologic stress SPECT; and computed tomographic coronary angiography (CTCA). However, MSAC considered that, in clinical practice, it is common for patients to undergo one or more prior tests, particularly ex-ECGs and stress-Echos, and that as a consequence the comparator tests may not be entirely replaced by CMR. MSAC noted that invasive coronary angiography (ICA) is currently considered the reference standard for confirming or ruling out CAD.

MSAC considered the estimated risk of serious adverse events (AEs) associated with the proposed imaging and its comparators. MSAC noted that ICA had the highest risk of serious AEs due to the invasive nature of the procedure and that the proposed SP-CMR ± LGE had a similar AE rate to its remaining comparators. With regards to the risk of mortality associated with the imaging procedures, MSAC noted that ex-ECG had the lowest risk, followed by stress-Echo, SP-CMR ± LGE, stress-SPECT, CTCA and ICA. MSAC understood that the risk attributed to the use of the gadolinium contrast agent for SP-CMR + LGE was likely to be overestimated, and likely to be lower than that reported for the iodinated contrast agents used for CTCA and ICA which have a substantially higher risk of nephrotoxicity. MSAC summarised that, using ICA as a reference standard, SP-CMR ± LGE is less safe than ex-ECG and stress-Echo and as safe as or potentially safer than stress-SPECT and CTCA, respectively.

MSAC noted the findings of the Cost-effectiveness of Non-invasive Cardiac Testing (CECaT) trial (Sharples L et al 2007), in their consideration of the effectiveness of the proposed imaging. The trial reported on the diagnostic accuracy of SP-CMR, SPECT and stress-Echo compared with ICA. It was pragmatic in design and, as a consequence, not all

patients received both initial non-invasive imaging test and ICA. MSAC noted that using ICA as the reference standard, SP-CMR was less sensitive but more specific than either stress-Echo or SPECT, although the differences between the modalities were not statistically significant. MSAC acknowledged the limitations of the CECaT trial as highlighted by the applicant, including that the trial included patients with suspected or known CAD, relied on older CMR technology than is currently used and assessed SP-CMR without LGE.

MSAC also considered the findings of a meta-analysis of studies (conducted as part of the contracted assessment) regarding the diagnostic accuracy of SP-CMR + LGE compared to ICA. MSAC noted that the pooled sensitivity and specificity values reported in this meta-analysis were very similar to those reported in the CECaT trial, each at approximately 85%. These values varied slightly depending on the ICA cut-off used in the analysed studies (i.e. whether a 50% or a 70% diameter stenosis was used as the criterion for CAD diagnosis), however the differences were not statistically different. MSAC also considered the post-test probability of CAD after a positive result (positive predictive value) and after a negative result (negative predictive value) for the proposed imaging and its comparators. MSAC noted that ex-ECG had the lowest positive and negative predictive values followed by SPECT. CTCA had the highest positive and negative predictive values, while the values for SP-CMR ± LGE and stress-Echo were very similar. MSAC summarised that, using ICA as a reference standard, SP-CMR ± LGE has lower diagnostic accuracy than CTCA, similar accuracy to stress-Echo, greater accuracy than SPECT and much greater accuracy than ex-ECG.

MSAC reviewed the economic evaluation and was concerned that the higher fee for the procedure suggested by RANZCR in their consultation feedback was not used in the analysis. MSAC noted that the model assumed all patients with a positive result from an initial non-invasive test would undergo an ICA in the base case. In contrast, patients with a negative result would not be referred for an ICA. Where initial test results were equivocal, patients were assumed to receive a CTCA. If CTCA results were negative ICA would not subsequently be undertaken. MSAC highlighted that approximately 11% of SP-CMR test results are indeterminate, compared to approximately 4% and 7% of SPECT and stress-Echo test results, respectively. MSAC noted that this was likely to have an impact on overall costs associated with SP-CMR due to the need for downstream follow-up testing. MSAC noted that, at the lower proposed fee, the modelled economic analysis indicated that SP-CMR + LGE is less cost-effective than CTCA and stress-Echo across the full range of PTPs (15%-85%), and less cost-effective than SPECT for a PTP ≥45%.

MSAC considered the projected net cost to the MBS of listing CMR for the diagnosis of CAD to be highly uncertain. The assumption that uptake of CMR will be equivalent to approximately 10% of the current number of services for all non-invasive tests for CAD was considered to be to be an overestimate due to: limited accessibility to rebatable MRI machines and suitably trained specialists; lengthy imaging and analysis time associated with the procedure; contraindications to CMR including implanted devices, renal impairment and claustrophobia; and the high demand for MRI in other specialties such as orthopaedics and neurology. In consequence, MSAC foreshadowed that access to CMR is likely to be severely restricted in the foreseeable future. The number of non-invasive services offset by the proposed CMR was also considered to be an overestimate given that ex-ECG, stress-Echo and SPECT can currently be requested by general practitioners, in contrast to CMR which is proposed as a specialist-only item.

The second population ("Population Two") encompassed patients with known CAD and left ventricular (LV) systolic dysfunction who are being considered for revascularisation. MSAC

noted that viability assessment with LGE–CMR was the sole test proposed for this group to determine the extent of viable myocardium and consequently patients' suitability for surgery.

MSAC noted that the applicant claimed LGE-CMR would substitute available viability tests including low-dose dobutamine echocardiography (Db-Echo) and resting SPECT (rest-SPECT) which were the nominated comparators for this population.

When considering the safety of LGE-CMR for population two, MSAC highlighted that an unknown proportion of these patients (with LVEF <35%) may have implanted cardiac devices which would serve as a contraindication for the CMR procedure. MSAC noted the estimated risk of serious AEs associated with LGE-CMR was similar to rest-SPECT, with the main risk associated with the use of the gadolinium contrast agent. In comparison, the risk of AEs was estimated to be higher with Db-Echo due to the dobutamine pharmacological stressor; however, MSAC considered this risk was likely to have been overestimated given the low dose of dobutamine used for viability assessment. MSAC noted that the long-term risk of mortality was higher for LGE-CMR than Db-Echo and lower than rest-SPECT. However, MSAC noted that the risk attributed to radiation exposure during rest-SPECT had not been age-adjusted and consequently the mortality rates for the proposed population may have been overestimated. MSAC summarised that, for population two, all three imaging modalities were similar in safety.

MSAC noted that the recovery of regional LV function after revascularisation was the reference standard used to assess the accuracy of LGE-CMR with its comparators. The pooled sensitivity and specificity values for LGE-CMR varied depending on the cut-off used for the extent of myocardium enhanced by the test, known as the hyper-enhancement (HE) value. MSAC noted that when a low cut-off (≤25% HE) was used, the sensitivity of the test was approximately 72% compared to 94% when a high cut-off (≥50% HE) was used. MSAC noted that in comparison, Db-Echo and SPECT had sensitivities of 79% and 83-87% respectively. However, MSAC noted that Db-Echo had the highest specificity (78%) followed by LGE-CMR (≤25% HE) and SPECT, with LGE-CMR (≥50% HE) demonstrating the lowest specificity (46%). MSAC also noted that LGE-CMR (≥50% HE) had the highest negative predictive value of the modalities considered at 83%. MSAC summarised that at a high cut-off (≥50% HE), LGE-CMR was better able to rule out viability than Db-Echo or SPECT.

MSAC also considered the evidence presented on whether the change in patient management expected from viability testing as assessed by LGE-CMR, Db-Echo and SPECT, resulted in reduced mortality. MSAC noted that two poor-quality systematic reviews (Allman KC et al 2002; Schinkel AFL et al 2007) and one cohort study (Gerber BL et al 2012) had indicated that patients who were assessed as having viable myocardium and received revascularisation had a lower mortality compared to those who received medical treatment alone. Therefore, MSAC considered prospective randomised, controlled trial (RCT) evidence from the Surgical Treatment for Ischemic Heart Failure (STICH) study (Bonow RO et al 2011) which found that there was no significant difference in the mortality of patients with or without viable myocardium, assessed by Db-Echo or SPECT, who were revascularised and those who received medical therapy alone. MSAC concluded that there was no interaction between viability and the likelihood of benefit from revascularisation compared with medical therapy alone. MSAC acknowledged the applicant's concern that the STICH trial did not use LGE-CMR as a measure of viability. However, MSAC noted that the trial provided the only RCT evidence available for this population and, in the absence of better evidence, it was not clear that the presence or absence of viability should guide the decision to revascularise. MSAC also highlighted that the 2014 European Society of Cardiology/European Association of

Cardiothoracic Surgery (ESC/EACTS) guidelines on myocardial revascularisation recommendation that, based on the findings of the STICH trial, assessment of myocardial viability should not be the sole factor in guiding decisions about the best therapy for these patients.

MSAC noted that the economic evaluation for population two was very similar in structure to that used for population one, with Db-Echo and SPECT used as the comparators for LGE-CMR. In the base case, it was assumed that those with viable myocardium would receive revascularisation and those with non-viable myocardium would receive optimal medical therapy. MSAC noted that, in terms of the incremental cost per correct diagnosis and per unnecessary revascularisations averted, LGE-CMR was less cost-effective than either Db-Echo or SPECT. MSAC noted that, regarding the cost per revascularisations undertaken with the correct diagnosis, the increments for LGE-CMR compared to Db-Echo ($136,002) and SPECT ($129,301) were high. MSAC was again concerned that the higher fee for the procedure suggested by RANZCR was not used in the analysis. MSAC noted that incorporating this fee would be likely to have a negative influence on the cost-effectiveness of the proposed imaging for both populations.

MSAC considered the projected net cost to the MBS of listing LGE-CMR for the assessment of myocardial viability to be highly uncertain, as: the analysis assumed that 50% of Db-Echo studies (Item 55117) and single SPECT studies (Item 61303) are currently performed for viability assessment – likely to be an overestimate – and that LGE-CMR will replace 10% of these items; and the extent to which LGE-CMR could replace Db-Echo or SPECT is uncertain given the likely limited access to CMR already described. .

MSAC noted that, overall, there was no pressing clinical need for the proposed imaging service in either Population One or Two given that there is a range of alternative imaging tests currently listed on the MBS for both groups. In addition, MSAC noted that, for Population One, all of the comparator modalities are more widely available and accessible than CMR. In particular, CMR was less cost effective than stress-Echo across a broad range of PTPs. For Population Two, MSAC noted that the modelled economic analysis showed LGE-CMR was less cost effective than either Db-Echo or SPECT. MSAC reinforced that current guidelines indicate that assessment of viability should not be the principal factor in selecting the best therapy for this patient population. MSAC also indicated that an MBS review of cardiac imaging services was currently ongoing.

3. Background

There are currently four items related to the use of CMR to diagnose heart conditions listed on the MBS. Two relate to the investigation of vascular abnormalities in patients with a previous anaphylactic reaction to an iodinated contrast medium (MBS item numbers 63401 and 63407). The other two relate to the investigation and diagnosis of congenital heart or great vessel defects (MBS item number 63385), and the investigation of heart or great vessel tumours (MBS item number 63388).

There is currently limited funding provided by the Victorian Government to The Alfred Hospital for CMR investigations of CAD. There may be other state-based public hospital arrangements for CMR, but these arrangements are limited to public hospital inpatients. The applicant indicated that CMR for CAD is not currently covered by private health insurance. Private patients who utilise CMR services are therefore required to pay the full cost of the procedure. This is a major factor in current utilisation of CMR services beyond the current MBS items.

4. Prerequisites to implementation of any funding advice

Therapeutic Goods Administration (TGA) status

There are a large number of MRI devices included on the Australian Register of Therapeutic Goods (ARTG). For the purposes of ARTG classification, MRI machines are considered active medical devices for diagnosis. The device is intended by the manufacturer to be used on a human being, either alone or in combination with another medical device, to supply information for the purpose of detecting, diagnosing, monitoring or treating physiological conditions, states of health, illness or congenital deformities. The classification of devices in this category varies according to the intended purpose of the device. MRI machines are Class IIa (low-medium risk) or Class IIb (medium-high risk) medical devices.

Qualification necessary to perform the proposed medical service

It is the intention of the applicant that both radiologists and cardiologists trained in CMR will be able to perform CMR services. The level of specialist accreditation recommended by the applicant for performing CMR is equivalent to at least the Society for Cardiovascular Magnetic Resonance (SCMR) level 2 training. The requirement for a minimum level of training for specialists eligible to provide CMR services is encouraged by the Department; however, this will have an impact on the initial availability of CMR services as it is presumed that few Australian radiologists or cardiologists have attained these qualifications to date.

The Royal Australian and New Zealand College of Radiologists and the Cardiac Society of Australia and New Zealand are working together to develop the training requirements for specialists supervising and reporting CMR.

5. Proposal for public funding

The proposed MBS item descriptors are shown in

Table 1.

Table 1 Proposed MBS item descriptors

Category 5 – Diagnostic Imaging Services
MBS [item number to be assigned] NOTE: Benefits are payable for each service included by Subgroup 15 on one occasion only in any 12 month period MAGNETIC RESONANCE IMAGING performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician and where the request for the scan specifically identifies the clinical indication for the scan - scan of the heart for: (a) myocardial viability using delayed gadolinium enhancement (Contrast); and (b) stress myocardial perfusion (Contrast); and (c) the request for the scan identifies that the patient presents with: (i) symptoms consistent with stable ischaemic heart disease, with an intermediate pre-test probability of coronary artery disease. Fee: $900 Benefit: 75% = $675; 85% = $765

Category 5 – Diagnostic Imaging Services
MBS [item number to be assigned] NOTE: Benefits are payable for each service included by Subgroup 15 on one occasion only in any 12 month period MAGNETIC RESONANCE IMAGING performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician and where the request for the scan specifically identifies the clinical indication for the scan - scan of the heart for: (a) myocardial viability using delayed gadolinium enhancement (Contrast); and (b) the request for the scan identifies that an adult patient being considered for revascularisation presents with: (i) an existing diagnosis of significant CAD, a history of ischaemic heart disease and impaired left ventricular function. Fee: $700 Benefit: 75% = $525; 85% = $595

The application indicated that pharmacologic SP-CMR with LGE is a more complicated technique than rest myocardial viability imaging with LGE, and therefore should attract a higher fee to cover the additional time and resources required to perform the scans. Feedback from Health Expert Standing Panel (HESP) indicated that SP-CMR requires the use of a greater amount of the contrast agent compared with myocardial viability imaging, as well as an infusion of the pharmacological stress agent. These factors are reflected in the proposed fee for each item.

The total dose of contrast agent required is dependent on the gadolinium chelate used and the weight of the patient. The applicant suggested that the volume of contrast agent required for myocardial stress perfusion and/or viability testing is greater than for non-CMR and magnetic resonance angiography applications, which is covered under MBS item number 63491. Therefore, the current MBS item is unlikely to offset the additional cost of the proposed

service. In gadolinium-contraindicated patients, the ability to detect diseases through tissue characterisation would be compromised.

The application requested that new MBS items be made available via specialist referral only. Guidance from the PICO Advisory Subcommittee (PASC) indicated that, as evidence emerges, the first proposed MBS item may need to be revised to allow for GP referral, as CMR may act as a replacement for current GP-ordered tests for CAD.

The applicant recommended that the condition of 'exercise and/or electrocardiogram (ECG) stress testing unfeasible' not be used to limit this population for two reasons. First, there are patients in whom ECG will report a high proportion of false positive results, and in whom CMR is superior regardless of the feasibility of exercise or ECG stress testing, and second, the MBS items for the comparator tests are not limited in this way.

6. Summary of Public Consultation Feedback/Consumer Issues

The PASC received one response from a peak body and three responses from organisations and specialists.

Consultation feedback for the protocol was positive. Issues raised in the responses were:

- The proposed population should be expanded to include low to intermediate risk patient groups to remove the need for multiple tests.
- The Protocol states that specialist referral is required for the procedure due to its complexity, specialist understanding of its uses and limitations, and the interpretation of image scans. The inclusion of General Practitioner referral for the procedure would assist patients to receive the appropriate imaging study in the first instance.
- The proposed MBS item fees are below the current cost of the procedure and should be increased to $1,100-$1,200.
- Patient access to the procedure may be limited due to difficulty in accessing MRI that has Medicare eligibility.

Consumer impact summary

The main issues arising from the public consultation period in November 2014 were:

- Patient access:
    - There are currently long waiting times for CMR within public hospitals due to the high demand for MRI from other specialties, such as orthopaedics and neurology;
    - In the private diagnostic imaging environment, access for CMR is extremely limited due to high demand in other areas and the time required to undertake each CMR (45–60 minutes per scan).
- Performing CMR and interpreting CMR scans:
    - Due to the complexity and experience necessary, there is a wide gap in experience/knowledge in performing and reporting CMR to a high level.
- The proposed MBS fee:

- $900 for MBS item 1 and $700 for MBS item 2 are less than the costs of performing the CMR investigation and will require the patient to pay a significant gap. A fee of $1,100–1,200 would be more appropriate.

7. Proposed intervention's place in clinical management

CMR images the heart and vascular structures, ventricular function and myocardial perfusion (blood flow). It is applied in the diagnosis of cardiac disease including ischaemic heart disease, valvular heart disease, cardiomyopathy, heart failure, congenital heart disease, and other vascular diseases.

The use of CMR is proposed in two distinct populations:

Population One

SP-CMR and LGE would be used to diagnose CAD in patients presenting with symptoms consistent with stable CAD and with an intermediate (15-85%) PTP) of CAD. The PTP would be determined using a clinical decision matrix, which would take into account risk factors such as age, gender, family history, hypertension, hypercholesterolaemia, diabetes and smoking, as well as the presence of symptoms such as dyspnoea and chest pain.

In Population One, the two tests would be performed consecutively during the same MRI procedure. The rest and stress perfusion (SP) images would be taken first, the order depending on the protocol, followed by LGE imaging.

In Population One, CMR is proposed as an alternative investigative test to existing stress testing modalities and CTCA. Patients using CMR instead of SPECT or CTCA also avoid exposure to ionising radiation. The advantages and disadvantages are summarised in the 2013 ESC guidelines on the management of stable coronary artery disease (Montalescot et al. 2013).

Population Two

LGE would be used to assess myocardial viability in patients with an existing diagnosis of significant CAD who have LV systolic dysfunction (LVD), and are being considered for revascularisation.

In Population Two, the use of CMR for myocardial viability evaluation is intended to replace existing methods of viability evaluation due to: (a) improved safety compared with nuclear imaging technologies so that patients will not be exposed to ionising radiation; and (b) superior diagnostic accuracy compared with existing imaging modalities on the basis that it provides more detailed and reliable data with reduced inter- and intra-observer variability. Thus, the use of CMR should:

i. reduce the test failure rate, leading to earlier diagnosis myocardial viability, or earlier exclusion of viability;

ii. allow additional/earlier case detection and management, with fewer false negatives; and

iii. produce fewer false positives, reducing the likelihood of inappropriate revascularisation.

The two included studies that informed the impact of LGE-CMR on clinical management were non-comparative and were individually assessed for risk of bias using the IHE checklist (Moga et al. 2012).

In patients with known CAD and LV dysfunction who are being considered for revascularisation, LGE-CMR is proposed to be non-inferior to existing modalities with improved safety. The application also claimed that CMR has a significant impact on therapy planning and patients' preferred choice of therapy (Taylor et al. 2013).

8. Comparator

Population One

SP-CMR and LGE is proposed as a diagnostic test in patients with an intermediate pre-test probability of having CAD. Four comparators were recognised: ex-ECG, stress-Echo, exercise or pharmacological SPECT, and CTCA. In this population ICA is considered to be the reference standard.

CMR is posed as an alternative investigative test to existing ischaemia stress testing modalities and CTCA. Patients using CMR instead of SPECT or CTCA also avoid exposure to ionising radiation.

Population 2

LGE-CMR is used in patients with CAD and LVD to determine their eligibility for revascularisation. Three comparators were identified: low-dose dobutamine stress echo (Db-Echo), rest SPECT and computed tomography with delayed contrast enhancement (CT-DCE).

The applicant's preESC and preMSAC response stated that CT-DCE is not in current clinical use to assess myocardial viability and should therefore not be considered as a comparator in Population Two.

CMR for myocardial viability imaging is intended to replace existing methods of viability imaging due to improved safety and improved diagnostic performance compared to Db-Echo and SPECT; patients will not be exposed to a stressor (as in Db-Echo) or to ionising radiation (as in SPECT).

9. Comparative safety

Population One

Most acute adverse events (AEs) associated with non-invasive imaging modalities are attributable to the use of a stressor. The number of serious AEs experienced by patients during ICA far outnumbers those resulting from any non-invasive imaging modality.

The ICA procedure was associated with the highest risk of acute AEs, and the use of a stressor was the most common cause of acute AEs with non-invasive imaging. Long-term mortality, mostly from radiation-induced cancer or renal failure, is due to the use of X-rays (CTCA, ICA), radiopharmaceuticals (SPECT) and contrast agents (CTCA, ICA and CMR). Conversely, the long-term mortality rate associated with exercise ECG and stress Echo are lowest because ionising radiation is not used with these tests, and contrast agents are only rarely used with echo.

The applicant's preESC and preMSAC response stated that the acute risk of these tests includes death (albeit small) which would affect long-term mortality rates. Stress echo, particularly with a pharmacological agent, may cause adverse effects including cardiac arrhythmia (such as non-sustained ventricular tachycardia) and myocardial infarction, which may be life threatening. A major stress echo registry of 85,997 patient examinations indicated major complications occurred in 86 cases and 6 died as a direct result of the stress echo *(Varga A et al. Am J Cardiol. 2006 Aug 15;98(4):541-3)*.

Population Two

The number of serious AEs experienced by patients during Db-Echo outnumbers those resulting from the other two non-invasive imaging modalities in current clinical use (rest SPECT and LGE-CMR) due to the use of a stressor. LGE-CMR has similar safety with respect to serious AEs to SPECT; for LGE-CMR, the majority of the serious AEs are caused by the contrast agent.

Whilst patients undergoing Db-Echo are more likely to suffer an acute event resulting in death than those having LGE-CMR or SPECT due to the use of a stressor, patients undergoing Db-Echo are unlikely to die from the long-term effects potentially caused by SPECT radiopharmaceuticals or the contrast agents used in LGE-CMR. LGE-CMR is therefore likely to have similar long-term safety to SPECT.

On the basis of the benefits and harms reported in the evidence-base, it is suggested that LGE-CMR has non-inferior safety relative to Db-Echo and SPECT.

10. Comparative effectiveness

Population One

A pragmatic trial of non-invasive cardiac testing (CECaT) compared the effect of initial diagnosis of CAD using SP-CMR, SPECT, stress Echo or ICA on patient management and outcomes. The trial reported that having an initial non-invasive imaging test reduced the number of patients having ICA by 25%, consisting mostly of patients with negative non-invasive test results. There were no significant differences between imaging modality groups. However, SP-CMR had a successful completion rate of only 78%, compared with 98%, 94% and 90% for the ICA, SPECT and stress echo groups, respectively. Thus, SP-CMR may not be suitable for use in approximately 20% of the eligible testing population.

There were no clinically or statistically significant differences in morbidity, mortality or quality of life (QoL) between the three non-invasive imaging groups when compared with the ICA group.

Non-invasive imaging may allow 20%–25% of patients suspected of having CAD to avoid having an ICA by ruling out those who are at low risk of cardiac events.

For Population One, on the basis of the benefits and harms reported in the evidence base, it is suggested that SP-CMR with/without LGE has:

- non-inferior safety and inferior effectiveness relative to CTCA
- inferior safety and non-inferior effectiveness relative to stress echo
- non-inferior safety and non-inferior effectiveness relative to SPECT

- inferior safety and superior effectiveness relative to exercise ECG.

Population Two

There was no direct evidence for Population Two.

One good-quality RCT was identified, the Surgical Treatment for Ischemic Heart Failure (STICH) trial, which showed that when patients with and without evidence of myocardial viability on SPECT or Db-Echo were randomised to medical therapy or revascularisation, there was no significant difference in mortality between treatments in either the viability or non-viability arms. Therefore, regardless of the accuracy of LGE-CMR for ruling out viability, using viability information to guide whether or not patients should be revascularised does not appear to improve mortality. Assessment of viability cannot therefore be considered to be effective.

On the basis of the benefits and harms reported in the evidence-base, it is suggested that LGE-CMR has:

- non-inferior safety and superior ability to rule out significant myocardial viability relative to Db-Echo and SPECT, with recovery of regional LV function as the reference standard;

- superior safety and unknown effectiveness relative to CT-DCE.

However, strong evidence suggests that testing for viability does not improve mortality over 5 years.

11. Economic evaluation

Population One

The economic model for Population One compared SP-CMR with CTCA, ECG, Echo and SPECT in the population with an intermediate PTP of CAD. There are inadequate data to reliably construct an economic model to generate a full cost-utility analysis. However, a comparative cost analysis of SP-CMR with LGE and its comparators, incorporating downstream diagnostic costs and utilising data from the clinical evaluation regarding the accuracy, re-testing and AE rates has been undertaken and the consequences of the different testing strategies is discussed. Additionally, cost-effectiveness analyses with outcomes of interest being (i) incremental cost per correct initial test result (ii) cost per unnecessary ICA avoided and (iii) cost per useful ICA referred are provided.

The absolute costs and outcomes for each of the non-invasive testing strategies are presented in Table 2.

Table 2 Absolute results—test results and costs across all comparators

	CMR	CTCA	Stress Echo	SPECT	Exercise ECG
Costs	-	-	-	-	
Test costs (including treatment of AEs)	$1,005	$747	$459	$880	$196
Modelled cost of re-testing	$83	$0	$50	$30	$49
Modelled cost of ICA	$2,165	$2,319	$2,172	$2,308	$2,017
Total	**$3,252**	**$3,065**	**$2,681**	**$3,217**	**$2,262**
Testing outcomes	-	-	-	-	-
Total correct diagnoses	75.6%	92.1%	80.7%	76.5%	68.2%
Total incorrect diagnoses	13.3%	8.0%	12.7%	19.5%	25.3%
No result (initial equivocal or failed test)	11.1%	0.0%	6.6%	4.0%	6.6%
Total ICA	*46.9%*	*50.3%*	*47.1%*	*50.0%*	*43.7%*
ICA in CAD+	38.8%	43.7%	39.4%	37.6%	31.5%
ICA in CAD-	8.1%	6.6%	7.6%	12.4%	12.3%

AE = adverse event; CAD = coronary artery disease; CMR = stress perfusion cardiac magnetic resonance imaging with late gadolinium enhancement; CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; ICA = invasive coronary angiography; SPECT = single-photon emission computed tomography

The incremental costs, outcomes and cost-effectiveness ratios comparing CMR with the comparators are presented in Table 3.

Table 3 Incremental results and results of the cost-effectiveness analyses, all comparisons

	Increment vs. CTCA	Increment vs. Stress Echo	Increment vs. SPECT	Increment vs. Exercise ECG
Costs				
Test costs (including treatment of AEs)	$258	$546	$125	$808
Modelled cost of re-testing	$83	$33	$53	$34
Modelled cost of ICA	–$154	–$7	–$143	$148
Total	**$187**	**$571**	**$35**	**$990**
Testing outcomes				
Total correct diagnoses	–16.5%	–5.1%	–0.9%	7.4%
Total incorrect diagnoses	5.4%	0.7%	–6.1%	–11.9%
No result (initial equivocal or failed test)	11.1%	4.4%	7.0%	4.5%
Total ICA	*–3.3%*	*–0.2%*	*–3.1%*	*3.2%*
ICA in CAD+	–4.8%	–0.6%	1.2%	7.4%
ICA in CAD–	1.5%	0.4%	–4.3%	–4.2%
Incremental cost per correct initial test result	**Dominated**	**Dominated**	**Dominated**	**$13,304**
Incremental cost per unnecessary ICA avoided	**Dominated**	**Dominated**	**$802**	**$23,651**
Incremental cost per indicated ICA missed	**Dominated**	**Dominated**	**$2,798**	**$13,394**

AE = adverse event; CAD = coronary artery disease; CMR = stress perfusion cardiac magnetic resonance imaging with late gadolinium enhancement; CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; ICA = invasive coronary angiography; SPECT = single-photon emission computed tomography

The modelled results were most sensitive to changes in the accuracy inputs, the proportion of patients requiring re-testing and the cost of CMR.

Population Two

Due to the lack of consistent evidence informing health outcomes following revascularisation versus medical management in the population tested (i.e. patients with CAD and LVD), neither a cost-utility, nor any long-term model could be reliably constructed. Therefore modelled cost-effectiveness analyses examining cost per additional correct diagnosis, cost per additional low benefit (non-viable) revascularisations avoided, and cost per additional appropriate revascularisation performed were undertaken.

The costs and outcomes for each of the non-invasive testing strategies are presented in Table 4.

Table 4 Test results and costs across all comparators

	LGE-CMR	DbE	SPECT
Costs			
Test (including treatment of AEs and specialist referral)	$788	$480	$608
Cost of revascularisation + OMT+ complications	$35,438	$25,138	$29,929
Total	**$36,226**	**$25,618**	**$30,537**
Testing outcomes			
Total correct diagnoses	71.8%	78.5%	74.9%
Unnecessary revascularisations averted	19.8%	34.3%	27.3%
Revascularisations undertaken with correct diagnosis	52.0%	44.2%	47.6%

AE=adverse event; DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; OMT = optimal medical therapy SPECT=single-photon emission computed tomography

The incremental costs, outcomes and cost-effectiveness ratios comparing LGE-CMR to the comparators are presented in Table 5.

Table 5 Incremental results and results of the cost-effectiveness analyses, all comparisons

	Increment vs DbE	Increment vs SPECT
Costs	-	-
Test (including treatment of AEs and specialist referral)	$308	$180
Cost of revascularisation + OMT+ complications	$10,300	$5,509
Total	**$10,608**	**$5,689**
Testing outcomes	-	-
Total correct diagnoses	–6.7%	–3.1%
Unnecessary revascularisations averted	–14.5%	–7.5%
Revascularisations undertaken with correct diagnosis	7.8%	4.4%
Incremental cost per correct diagnosis	**Dominated**	**Dominated**
Incremental cost per unnecessary revascularisations averted	**Dominated**	**Dominated**
Incremental cost per revascularisations undertaken with correct diagnosis	**$136,002**	**$129,301**

AE = adverse event; DbE = low-dose dobutamine echocardiography; OMT = optimal medical therapy; SPECT = single-photon emission computed tomography

Sensitivity analyses were performed varying the important parameters, and the modelled results were identified to be most sensitive to changes in the accuracy inputs of LGE-CMR.

12. Financial/budgetary impacts

Population One

A market-based approach was used to estimate the financial implications of the introduction of CMR for the diagnosis of CAD. However, as MBS items for the comparator tests are not specific to the population that is proposed to be eligible for CMR, the estimated number of tests has been back-calculated based on the number of ICAs performed in the population who have an intermediate PTP of CAD.

Key assumptions:

- That uptake of CMR for the diagnosis of CAD is low (approximately 10%), because of limited access and low patient acceptability of MRI scanners, due to the high demand in other specialties and indications and the time required to undertake each CMR; and
- That cost offsets for current testing assume that the relative use of the tests across all indications applies to the tests offset by the introduction of CMR.

The financial implications to the MBS resulting from the proposed listing of CMR for the diagnosis of CAD are summarised in Table 6.

Table 6 Total costs to the MBS associated with CMR for diagnosis of CAD

	2016–17	2017–18	2018–19	2019–20	2020–21
CMR					
Number of services	6,763	6,843	6,924	7,004	7,084
Cost to the MBS	$5,173,817	$5,235,202	$5,296,587	$5,357,972	$5,419,357
Tests offset					
Number of services offset	6,763	6,843	6,924	7,004	7,084
Costs offset	$2,352,761	$2,380,676	$2,408,590	$2,436,505	$2,464,420
Net cost to the MBS	**$2,821,055**	**$2,854,526**	**$2,887,997**	**$2,921,467**	**$2,954,938**

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; MBS = Medicare Benefits Schedule

Population Two

A market-based approach was used to estimate the potential number of services eligible for proposed LGE-CMR for myocardial viability assessment. It was assumed that 50% of current utilisation of Db-Echo (Item 55117) and single SPECT (Item 61303) is for myocardial viability assessment, and that LGE-CMR would substitute for 10% of this utilisation.

The financial implications to the MBS resulting from the proposed listing of LGE-CMR for the assessment of myocardial viability are summarised in Table 7.

Table 7 Total costs to the MBS associated with LGE-CMR for the assessment of myocardial viability

	2016–17	2017–18	2018–19	2019–20	2020–21
LGE-CMR					
Number of services	4,444	4,771	5,122	5,499	5,903
Cost to the MBS	$2,644,130	$2,838,646	$3,047,472	$3,271,660	$3,512,341
Tests offset					
Number of services offset	4,444	4,771	5,122	5,499	5,903
Costs offset	$1,914,329	$2,055,157	$2,206,345	$2,368,656	$2,542,906
Net cost to the MBS	**$729,801**	**$783,489**	**$841,127**	**$903,004**	**$969,434**

LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; MBS = Medicare Benefits Schedule

13. Key issues from ESC for MSAC

ESC discussed and summarised the report and provided the following summary for MSAC to consider.

There are two distinct populations to be noted though viability assessment with late gadolinium enhancement (LGE) is common in both, forming a secondary part of the test in Population One and the primary purpose of the test in Population Two.

Population One

CMR was non-inferior in terms of effectiveness but was inferior in safety compared to stress echo.

There are several functional vs anatomical tests available for this indication and it is likely that CMR will become an add-on test as most people would have already had a stress echo. If it is to be considered as a replacement, ESC considered that it will most likely replace SPECT, however, this was not how the assessment group undertook the modelling.

ESC noted that the populations in the key comparative trial (CECaT) were hospital based out-patients and may not reflect real life scenarios to be faced in the intended population in Australia.

ESC noted that:

- the negative predictive value for SP-CMR + LGEis lower for Population One when compared to CTCA.
- in terms of Positive Predictive Value, the strength of the results appears relevant: If the result is strongly positive, it may lead to ICA, however, if the result is indeterminate, it will more likely lead to other additional tests.

Population Two

ESC advised that the assessment of viability has limited evidence but LGE-CMR could possibly be a replacement test. It was noted that CSANZ suggests that newer studies may provide significant evidence. As such, ESC advised that MSAC may consider deferring to

allow for further evaluation of these data. The existing data do not appear sufficient for a full cost utility analysis.

Other information for MSAC

ESC also advised that MSAC may want to consider additional issues in relation to accessibility given the position of MRI licensing arrangements and real-life referral patterns where GPs can request other comparators (Ex-ECG, stress-Echo, SPECT) but not the full range of MRI tests.

It was noted that this test delivers similar accuracy to other tests without radiation exposure, however given the target population is for older Australians, minimising radiation exposure is less of a concern than it would be for a younger patient cohort.

There is some question over the population applicability of the CECaT trial to the general population, due to the hospital based nature of the trial.

ESC advised that it is unclear whether current guidelines are strictly followed in practice, for example, the European Society of Cardiology guideline suggests transthoracic echo as an initial investigation for assessment of LV ejection fraction as a means of risk stratification, but it is not clear that this occurs.

ESC asked MSAC to consider whether there is merit in undertaking further analysis for the subpopulation of patients who cannot have a CTCA where the decision to progress to ICA is not justified, noting the limitations/restrictions of CTCA (such as contrast allergy, high coronary artery calcium scores).

Finally, ESC noted that there may be significant out-of-pocket expenses.

14. Other significant factors

International guidelines for the use of CMR indicate that there is still some uncertainty around using this test in both Populations One and Two, as data are still emerging. For all types of non-invasive imaging, recommendations highlight the use of imaging only in cases of genuine clinical uncertainty.

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

In our original rebuttal to the review we stated that the assessment performed was flawed and is not fit for the purpose of informing MSAC in regard to cardiac MRI. We believe that the assessment group were poorly advised in their choice of relevant trials in the literature. Landmark trials such as the CeMARC study were dismissed. Much of the assessment and calculations were focused upon the older CECaT study. The entire protocol in CECaT, from the patient group, to scanner type / location, to sequences used, to acquisition, to analysis, is fundamentally different to the techniques in our proposal. We even provided a letter from the corresponding author of the CECaT stating that, although they were immensely proud of the trial, it was not appropriate to use that data to inform decisions on our proposal.

MSAC stated that invasive coronary angiography is the reference standard for confirming or ruling out coronary artery disease (CAD) but this technique is recognised as being unreliable to define the significance of coronary lesions. In the setting of chest pain assessment, it is the presence of a functionally significant stenosis, rather that the simple presence of CAD, which

is more relevant. A patient may have a 50% coronary stenosis, that is not responsible for their chest pain as it does not limit flow down the artery. Fractional flow reserve (FFR) (or quantitative coronary angiography) would be more appropriate comparators for a functional test such as MRI.

As data from inappropriate trials was used for the analysis, all the subsequent calculations and statements (from number of indeterminate studies to positive and negative predictive values), to the economic consequences) are simply not relevant to the proposal.

References:

1. Lancet. 2012 Feb 4;379(9814):453-60. doi: 10.1016/S0140-6736(11)61335-4

2. Greenwood JP, Herzog BA, Brown JM, Everett CC, Nixon J, Bijsterveld P, Maredia N, Motwani M, Dickinson CJ, Ball SG, Plein S. Ann Intern Med. 2016 May 10. doi: 10.7326/M15-1801.

3. Walker S1, Girardin F, McKenna C, Ball SG, Nixon J, Plein S, Greenwood JP, Sculpher M. Heart. 2013 Jun;99(12):873-81

16. Further information on MSAC

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