



Australian Government

Department of Health

MEDICAL SERVICES ADVISORY COMMITTEE

Magnetic resonance imaging of patients with
suspected non-ischaemic cardiomyopathies

Final Protocol for Application 1393

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FINAL

1. Title of application

Magnetic resonance imaging of patients with suspected non-ischaemic cardiomyopathies.

2. Purpose of application

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

Cardiac magnetic resonance imaging (CMRI) is a non-invasive imaging technique that utilises radiofrequency signals to image soft tissues. CMRI affords the ability to measure, in one examination, multiple aspects of heart and vascular structure and function. These include, but are not limited to, assessment of left and right ventricular function, myocardial viability, ischaemia assessment, scar assessment, tissue characterisation, imaging of aorta and great vessels, paediatric and adult congenital abnormality imaging, and imaging of the proximal coronary arteries. All of this is achieved without the use of ionising radiation and nephrotoxic contrast media. The ability of CMRI to provide insight into tissue characterisation offers unique information to assist in the diagnosis of diseases of the myocardium, known as cardiomyopathies. This is not routinely available by means other than myocardial biopsy or autopsy.

CMRI has been adopted into clinical practice in Europe,¹ the United Kingdom and the United States. International guidelines from the American College of Cardiology /American Heart Association have recognised over 17 appropriate indications for CMRI, including the evaluation of suspected myocarditis, arrhythmogenic right ventricular cardiomyopathy, restrictive cardiomyopathy, and hypertrophic cardiomyopathy.² A narrative review by Karamitsos et al (2009) broadly summarises the role of CMRI in determining the underlying aetiology of heart failure due to non-ischaemic cardiomyopathies.³

At present, the availability of CMRI in Australia remains restricted due to the lack of a Medicare rebate, with only a small number of public hospitals able to provide this service. It is proposed that expansion of the current MBS services to include these new indications will allow for more accurate diagnosis and prognosis of patients who are suspected of having non-ischaemic cardiomyopathies.

3. Intervention – proposed medical service

A. Provide a description of the proposed medical service.

MRI utilises strong, uniform magnetic fields to investigate the anatomy, perfusion, tissue characterisation and function of different organs and systems within the human body. When hydrogen protons present in human cells are exposed to this magnetic field, they align along its rotational axis in a uniform plane. In order to generate an image, a sequence of smaller magnetic pulses is targeted towards the area of interest, exciting the protons, which then release radiofrequency signals upon relaxation.⁴ These signals are converted into an image that represents

the concentration of hydrogen protons in tissue, making MRI particularly useful for imaging soft tissues with a high concentration of water.

CMRI can be used to discern anatomical features of the heart that can be used to differentiate between cardiomyopathies of varying aetiology. CMRI uses T1, T2, T2* and delayed contrast enhancement sequences to characterise myocardium.⁵ Anatomical CMRI protocols include single-shot images to provide localisation of cardiac structures within the heart and great vessels using “dark-blood” or “bright-blood” techniques. Additional sequences in which image contrast is weighted by intrinsic magnetic relaxation times (T1, T2, or T2* relaxation times) are also obtained.⁵ Used in combination, CMRI sequences can discern:

- reduced ejection fraction, typically with global dysfunction
- increased ventricular volumes
- relative myocardial wall thinning
- infiltration, iron loading, inflammation and oedema
- myocardial scarring and fibrosis

During the examination, patients are required to lie in either a prone or supine position within the MRI machine, with as little movement as possible. Images are timed to breath holds, as movement during the imaging procedure can blur the pictures.

The magnetic field strength within conventional MRI scanners is either 1.0T (Teslas), 1.5T or 3.0T. The majority of scanners utilise 1.5T fields for CMRI.⁶ The use of higher strength fields allows for images with higher spatial resolution, but also increases the chance of imaging artefacts that may obscure the image.⁴

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

The proposed medical service does not include a specific trademarked health technology.

C. 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.

Medicare-eligible MRI units are available in public hospitals, private hospitals, and outpatient clinics across Australia.⁷ The proposed service will be available in each of these settings, subject to the availability of specialised cardiac software and appropriately qualified and experienced staff.

- D. 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.).*

Service duration and frequency

A CMRI study consists of approximately 10 minutes for intravenous cannulation and patient safety briefing, 60 to 80 minutes of image acquisition time, 15 to 30 minutes of software analysis time, and 15 to 30 minutes of expert reporting time. The Applicant has suggested that the proposed medical service would be utilised initially as a single, one-off test to determine the underlying aetiology of the cardiomyopathy. There may be some need for longitudinal follow-up in a minority of disease subtypes, or in cases where an unexpected pathology is identified during the scan. Patients are likely to require repeat CMRI studies once every two to five years, but not more than once per year. In the vast majority of patients, limiting the use of CMRI to one scan per 12-month period would be sufficient.

Equipment

The proposed medical service can be conducted using standard whole-body MRI systems utilising specialised cardiac software for quantitative analysis, and either abdominal coils, body coils, thoracic coils or specialised cardiac coils. The choice of coil for CMRI is usually informed by the requirements of each MRI machine. Cardiac software may be incorporated within the scanner; however, third party software that is external to the scanner is more common in clinical practice as scanners are typically occupied during analysis. The use of specialised cardiac coils may offer certain advantages over standard body/thoracic coils, including superior spatial and temporal resolution, as well as decreased image acquisition time; however, Health Expert Standing Panel (HESP), Applicant and public consultation feedback suggests CMRI may be conducted sufficiently with thoracic coils.

Co-administered interventions

CMRI investigations that use tissue characterisation and delayed contrast enhancement sequences require the administration of a gadolinium chelate contrast agent, currently listed on the MBS under item number 63491. Delayed contrast-enhanced MRI sequences use a gadolinium-based contrast agent to define the extent of irreversibly damaged myocardium.⁸ The contrast is administered intravenously as a single bolus for tissue characterisation. The total dose is dependent on the type of gadolinium used, and the weight of the patient. In contraindicated patients, the sensitivity for detecting diseases through tissue characterisation would be decreased without the use of a contrast agent. No additional diagnostic tests are considered to be co-administered with CMRI at the time of the scan. General anaesthesia would not commonly be required as part of the proposed service, as patients are required to respond to direction during the imaging.

Referral arrangement

Although general practitioners may refer patients for a limited number of MRI procedures, the Cardiac Society of Australia and New Zealand (CSANZ) recommends that the proposed service should be limited to specialist referral. The proposed service is intended to be used to determine the underlying aetiology of heart failure, which is typically a specialist field. Similarly, specialist referral is required for comparator tests, such as computed tomography coronary angiography (CTCA) (MBS items 57360, 57361), as well as existing CMR services (MBS item 63385). The Applicant further suggests that specialist referral is appropriate given the complexity of the test and the level of understanding required to interpret the test results.

Specialist referral is recommended in the guidelines of the National Heart Foundation and the CSANZ for the management of patients with chronic heart failure.⁹ Similarly, guidelines on acute and chronic heart failure produced by the National Institute for Health and Care Excellence (NICE) recommend specialist referral for patients with heart failure and previous myocardial infarction.^{10, 11} PASC input recommends the list of specialists available to refer patients for CMRI services be open to discussion, but should, as a minimum, include cardiothoracic surgeons and cardiologists.

Service provider and accreditation

The Applicant suggests that the proposed service should not be considered a standard radiological procedure due to the complexity of the test in defining cardiac pathologies. Although sufficiently accredited radiologists or cardiologists may report on CMRI images, the proposed service is intended to be utilised primarily by cardiologists. Data from the Euro CMRI registry suggests that only a minority of CMRI scans are reported by radiologists alone (~3%) and that the majority are reported by either cardiologists alone (~75%) or cardiologist / radiologist teams (~20%).¹ It is the intention of the Applicant that the radiologist or cardiologist trained in CMRI be personally available to attend all examinations.

Current legislative requirements stipulate that Medicare-eligible MRI items must be reported on by a trained and credentialed specialist in diagnostic radiology. In order to satisfy the Chief Executive of Medicare, the specialist must be a participant in the Royal Australian and New Zealand College of Radiologist's (RANZCR) Quality and Accreditation Program (Health Insurance Regulation 2013 – 2.5.4 – Eligible Providers).¹² Legislative changes would be required to allow cardiologists to report on CMRI scans, and there would need to be support from the sector for this change to occur.

In line with the required legislative changes, the CSANZ recommends consideration towards the development of a Conjoint Accreditation Committee for accreditation of specialists to undertake diagnostic interpretation of CMRI, analogous to the Conjoint Committee for CTCA.¹³ CSANZ would recommend collaboration on this development between CSANZ, RANZCR and the Department. The level of specialist accreditation for CMRI procedures recommended by the Applicant is equivalent to at least Society for Cardiovascular Magnetic Resonance (SCMR) level 2 training.¹⁴ These guidelines are broadly applicable, and are consistent with Australian practice. A specific training document for the provision of CMRI services has been developed for Australia by the CSANZ's Imaging Council.

Funding for the proposed service in rural or remote areas should only be provided if suitable MRI hardware and software is available, along with a properly trained and credentialed provider, and appropriately trained radiography staff.

E. Describe any potential risks to the patient.

MRI is a non-invasive imaging technique that carries a low risk of complications and adverse events. As MRI utilises magnetic fields to image anatomy and function, patients are not exposed to ionising radiation. The primary cause of direct harm associated with MRI sequencing for cardiomyopathies includes claustrophobia, adverse reactions to contrast agents and patient discomfort due to the noise of the machine. As with all MRI procedures, patients with implantable medical devices that contain metal may be contraindicated for CMRI. However, recent guidelines suggest that CMRI may be performed in patients with implantable cardiac pacing and resynchronisation devices when strict safety protocols are followed.^{15, 16}

The incidence of adverse events caused by CMRI procedures was evaluated in the 2009 pilot phase of the European Cardiovascular Magnetic Resonance (EuroCMR) Registry. From a total of 11,040 consecutive CMRI patients, 124 reported mild adverse events, of which 94 were caused by reactions to adenosine and dobutamine stress perfusion agents, 27 were allergic reactions to a contrast agent, and two were unspecified. Five severe complications were reported, including non-sustained ventricular tachycardia, ventricular fibrillation, overt heart failure, and unstable angina. All severe complications were related to the administration of adenosine and dobutamine stress perfusion agents, which are not required for CMRI sequences for cardiomyopathies.⁶

Beyond the direct risks associated with the scan, the main risks associated with the proposed service include physical harms from follow-up testing, and false negative and false positive test results. Estimates of the risks associated with test accuracy will be informed by the assessment.

4. Population and medical condition eligible for the proposed medical services

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

The term 'cardiomyopathy' encompasses a diverse range of diseases of the myocardium that lead to structural and functional impairments in its ability to contract or relax, and which are not caused by coronary artery disease (CAD), hypertension, valvular disease or congenital heart disease.¹⁷ These impairments can cause subsequent heart failure, rhythm disturbances and death. The natural history and prognosis of cardiomyopathies varies depending on the underlying aetiology of the disorder.¹⁷ Cardiomyopathies can be broadly characterised into five key sub-groups, all of which may benefit from the use of CMRI:

Dilated cardiomyopathy (DCM): DCM is reportedly the most common phenotype of cardiomyopathy. It is defined as left ventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions (i.e. hypertension, valve disease) or CAD significant enough to cause global systolic impairment.¹⁷ Systolic dysfunction caused by DCM often presents as fatigue, angina or chronic heart failure. Autosomal dominant inheritance is believed to be the most common cause of DCM, occurring in approximately 20% to 35% of cases.¹⁸ Other causes include, but are not limited to, infection, inflammation (i.e. myocarditis), toxins and auto-immune disorders.¹⁷ The prevalence of DCM is currently unknown, although evidence from the United States estimates the disease to be prevalent in approximately one in every 2,500 individuals.¹⁹

Hypertrophic cardiomyopathy (HCM): Traditional definitions of HCM differentiate thickening of the ventricle wall caused by myocyte hypertrophy from thickening caused by interstitial infiltration or intracellular accumulation of metabolic substrates observed in restrictive cardiomyopathies. In clinical practice, non-invasive imaging techniques and myocardial biopsy are often unable to accurately make this distinction, prompting a revision of the definition of HCM to simply: *“Increased ventricular wall thickness or mass in the absence of loading conditions (hypertension, valve disease) sufficient to cause the observed abnormality”*.¹⁷ The increase in wall thickness may cause left ventricular (LV) outflow obstruction, arrhythmias, vasovagal syncope or abnormal peripheral vascular response.²⁰ Patients with HCM often have few presenting symptoms. Thus, a diagnosis of HCM is often incidental. The most common presenting symptoms include shortness of breath (dyspnea) and chest pain on exertion, but a few patients may also present with syncope or pre-syncope. It is estimated that HCM has a prevalence of approximately one in 500 adults, and 0.5 in 100,000 children.^{20, 21} HCM is the most common cause of sudden cardiac death in young people.²²

Restrictive cardiomyopathy (RCM): Although restrictive ventricular abnormalities may have several causes, RCM can be broadly defined as *“restrictive ventricular physiology in the presence of normal or reduced diastolic volumes (of one or both ventricles), normal or reduced systolic volumes, and normal ventricular wall thickness”*.¹⁷ Impaired myocardial relaxation is a characteristic trait of RCM, leading to inadequate diastolic filling in one or both ventricles. Systolic function is often normal, or near normal. RCM may be inherited, idiopathic or due to a systemic disorder. Common subtypes of RCM include iron overload cardiomyopathy (hemochromatosis), sarcoidosis, amyloidosis, and endocardial disorders.¹⁷ Patients with RCM often present with heart failure symptoms, and will eventually need a heart transplant due to the limited availability of effective therapeutic interventions. The prevalence of RCM is currently unknown, but it is believed to be the least common subtype of cardiomyopathy.¹⁷

Arrhythmogenic right ventricular cardiomyopathy (ARVC): Also known as arrhythmogenic right ventricular dysplasia (ARVD), ARVC presents as *“the progressive replacement of right ventricular myocardium with adipose and fibrous tissue”*.¹⁷ Patients with ARVC are commonly asymptomatic, but may present with cardiac arrhythmias that can cause sudden cardiac death. Biventricular heart failure is a late-stage symptom caused by diffuse disease, and is therefore not typically a presenting symptom of ARVC.²³ ARVC is a familial condition, with both autosomal dominant and autosomal

recessive inheritance. Although the estimated prevalence of ARVC is low (1 in 5000), it is a common cause of sudden cardiac death in young athletes.¹⁷

Unclassified cardiomyopathies: There are two key subtypes of unclassified cardiomyopathies, including left ventricular non-compaction cardiomyopathy—a rare condition that shares similar diagnostic features as DCM—and takotsubo cardiomyopathy, also referred to as transient left ventricular apical ballooning syndrome. Takotsubo cardiomyopathy is defined as “transient regional systolic dysfunction involving the left ventricular apex and/or mid-ventricle in the absence of obstructive coronary disease on coronary angiography”.¹⁷ Apical ballooning typically causes chest pain that mimics angina, often prompting an investigation into suspected CAD. Symptoms typically resolve spontaneously within two weeks of presentation if left untreated.²⁴ The cause of takotsubo cardiomyopathy is currently unclear, but it appears to demonstrate post-menopausal female predominance, and often follows an acute emotional or physical stress episode.²⁴ The exact prevalence of takotsubo cardiomyopathy is currently unknown, but it is estimated to occur in 2% of patients presenting with an acute coronary syndrome in the United States and Europe.²⁵ It is estimated that between 4% and 7% of patients with a suspected acute coronary event will have had a myocardial infarct in the absence of significant coronary stenosis.²⁶

Incidence and prevalence of cardiomyopathies in Australia

The true prevalence of cardiomyopathies in Australia is unknown, as data for cardiomyopathies and heart failure are reported coincidentally. Estimates from the National Health Survey suggest that heart failure was prevalent in 1.3% of Australians in 2007-2008, with female gender predominance.²⁷ By extrapolating from international findings, it has been estimated that heart failure presents in 30,000 new cases in Australia each year. In 2007-2008, heart failure or cardiomyopathy accounted for 10% of all hospitalisations for cardiovascular disease.²⁷ Most patients who were hospitalised were aged 65 years and older, and nearly 90% of deaths occurred in adults over the age of 75.

As discussed, some forms of cardiomyopathy, particularly ARVC and HCM, may cause cardiac arrhythmias prior to heart failure, resulting in sudden cardiac death. Estimates from the Australian Bureau of Statistics indicate that a total of 3,849 patients died from heart failure in 2012 (10th most common cause of death) and 1,720 died from cardiac arrhythmia (19th most common cause of death);²⁸ However, it is impossible to determine what proportion of heart failure or arrhythmia deaths were directly related to non-ischaemic cardiomyopathies.

Australian Institute of Health and Welfare (AIHW) principal diagnosis data cubes indicate that there were 4,845 hospital separations for cardiomyopathies in 2011-12.²⁹ A large proportion of reported separations were either unspecified (1,222 separations), or labelled “Other” (828 separations). Although the reported hospital diagnoses provide an estimate of the annual Australian incidence of each disease, they carry two key limitations: first, **they do not reflect the number of individuals that were investigated for each disorder**, and second, **CMRI will not be necessary for every case of suspected cardiomyopathy as the diagnosis and aetiology may be clear from prior testing.**

A summary of the estimated prevalence for each subtype of cardiomyopathy is provided in Table 1, although these estimates should be used with caution due to limitations in the epidemiological data

and AIHW hospital statistics. Discussions with the Protocol Advisory Sub Committee (PASC) suggest the Australian hospital separations listed in Table 1 are likely to provide an upper estimate for the likely utilisation of CMRI for investigating DCM. Conversely, HCM is grossly underestimated by hospital data, as the majority of patients will be managed in outpatient clinics.

Table 1: Estimated prevalence of cardiomyopathy subtypes derived from peer-reviewed literature, and total number of reported Australian hospital separations by aetiology

Indication	Estimated prevalence from literature	Estimated Australian prevalence	Australian hospital separations, 2011-12 [†]
DCM	1 in 2,500 ¹⁹	7,160*	2,066
HCM	1 in 500 ^{20, 21}	35,804*	506
RCM	Unknown ^{17**}	Unknown	25
ARVC	1 in 5,000 ³⁰	3,580*	Not reported
Takotsubo cardiomyopathy	2% of ACS patients ²⁵	1,398 ^{††}	Not reported
Acute myocarditis	Unknown	Unknown	213

ACS=acute coronary syndrome, ARVC=Arrhythmogenic right ventricular cardiomyopathy, DCM=dilated cardiomyopathy, HCM=hypertrophic cardiomyopathy, RCM=restrictive cardiomyopathy.

*Prevalence estimates are based on the Australian population aged 18 and older as of 30 June 2012, reported to be 17,902,257 in total.³¹

**While the prevalence of restrictive cardiomyopathy is unknown, it is estimated to be the least common subtype of cardiomyopathy.¹⁷

[†]Data sourced from the Australian Institute of Health and Welfare's principal diagnosis data cubes, 2011-12.²⁹

^{††}Estimate based on 69,900 heart attack events in Australians over the age of 25 in 2011.³²

B. 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.

Cardiomyopathies are a disparate group; however, the clinical presentations of these patients are broadly similar. There is also considerable phenotypic overlap between the different types of cardiomyopathy. The Applicant has suggested that five cardiomyopathy sub-populations will benefit from the use of CMRI. Through consultation with the PASC, populations one to three include an additional subgroup of asymptomatic first-degree relatives. The proposed patient populations include:

1. Patients presenting with heart failure symptoms, in whom echocardiography is inconclusive or suggests a dilated cardiomyopathy, and in whom further diagnostic clarification is required.
 - i. Asymptomatic individuals with a family history of non-ischaemic dilated cardiomyopathy in a first-degree relative.
2. Patients in whom echocardiography suggests increased wall thickness, and in whom a hypertrophic or restrictive cardiomyopathy is suspected and further diagnostic clarification is required.

- i. Asymptomatic individuals with a family history of hypertrophic or restrictive cardiomyopathy in a first-degree relative.
3. Patients in whom arrhythmogenic right ventricular cardiomyopathy is suspected on the basis of International Task Force Criteria.
 - i. Asymptomatic individuals with a family history of arrhythmogenic right ventricular cardiomyopathy in a first-degree relative.
4. Patients with troponin-positive chest pain, electrocardiography changes suspicious of an acute coronary syndrome, and no culprit lesion identified on coronary angiography.
5. Asymptomatic individuals with a family history of sudden cardiac death or aborted sudden cardiac death in a first-degree relative, excluding channelopathies and arrhythmia.

C. 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.

At least two systematic reviews have investigated the use of CMRI for the investigation of patients with suspected non-ischaemic cardiomyopathies, e.g. Kuruvilla et al (2014),³³ Green et al (2012).³⁴ Similarly, a number of narrative reviews exist outlining the clinical efficacy of CMRI for various subtypes of cardiomyopathy e.g. Leong et al (2012),³⁵ To et al (2011),³⁶ Srinivasan et al (2013),³⁷ Dickerson et al (2013).³⁸

There is evidence that CMRI is a cost effective and clinically effective intervention for patients presenting with heart failure. Assomull et al (2011) demonstrated that using CMRI as a gatekeeper to invasive coronary angiography (ICA) was a cheaper diagnostic strategy in a decision tree model when United Kingdom-based costs were assumed.³⁹ For CMRI the sensitivity (100%), specificity (96%), and diagnostic accuracy (97%) were equivalent to ICA (sensitivity, 93%; specificity, 96%; and diagnostic accuracy, 95%). Hence CMRI proved to be a safe, clinically effective, and potentially economical gatekeeper to ICA in patients presenting with heart failure of uncertain aetiology. CMRI has proven cost effectiveness for the diagnosis of CAD and this may be relevant for patients presenting with ischaemic heart failure. Relevant recent papers include Walker et al (2013)⁴⁰ and Boldt et al (2013).⁴¹

The European CMR registry is a pivotal, multi-national study with over 27,000 enrolled patients from 57 centres in 15 countries.¹ The study included patients with DCM (population 1), HCM (population 2) and ARVC (population 3). The authors reported a demonstrated impact of CMRI on patient management in 62% of cases, including a new diagnosis not suspected before the CMRI in 9% of cases, and a change in therapeutic management in 53% of cases. Additional studies reporting surrogate outcomes of effectiveness of CMRI in each population are outlined below:

Dilated Cardiomyopathy

1. **Change in Management:** McCrohon et al (2003) investigated the use of CMRI in 90 patients with heart failure due to DCM. The findings suggest that using coronary angiography as the arbiter for the presence of LV dysfunction caused by CAD, may lead to an incorrect assignment of the cause of DCM in 13% of patients.⁴²

2. **Cost effectiveness / diagnostic accuracy:** Assomull et al (2011) assessed the diagnostic accuracy of CMRI as a non-invasive gatekeeper to coronary angiography in 120 consecutive patients with heart failure of unknown aetiology.³⁹ The authors demonstrated that using CMRI as a gatekeeper to invasive coronary angiography (ICA) was a cheaper diagnostic strategy in a decision tree model when United Kingdom–based costs were assumed, and the sensitivity (100%), specificity (96%), and diagnostic accuracy (97%) of CMRI were equivalent to that of ICA (sensitivity 93%, specificity 96%, diagnostic accuracy 95%).
3. **Prognosis:** In a recent study conducted by Leong et al (2012) the presence of late gadolinium enhancement (LGE) on CMRI was the only independent predictor of medical therapy failure (i.e. lack of LVEF improvement at follow up) in newly presenting DCM patients when considered with other clinical, echocardiographic and ECG criteria.³⁵ Leyva et al (2012) demonstrated that LGE on CMRI was an independent predictor of both morbidity and mortality following cardiac resynchronisation therapy.⁴³ Gulati et al (2013) conducted a prognostic study of 472 consecutive patients with DCM. The authors concluded that CMRI of midwall fibrosis was a predictor of death and cardiovascular hospitalisation, and improved risk stratification beyond left ventricular ejection fraction.⁴⁴ A systematic review and meta-analysis of the literature demonstrates that late gadolinium enhancement on CMRI predicts adverse cardiovascular outcomes in non-ischemic cardiomyopathy.³³

Hypertrophic cardiomyopathy/restrictive cardiomyopathy

1. **Diagnostic accuracy:** In 2004 Moon et al reported 10 patients with the apical variant of HCM, 8 of whom had prior echo examinations which were reported as normal.⁴⁵ CMRI is key in differentiating HCM from "phenocopies" or hearts with similar morphology but profoundly different etiology,⁴⁶ such as amyloid or Anderson-Fabry disease,⁴⁷ or amyloidosis. Austin et al (2009) conducted a study of 47 consecutive patients with suspected cardiac amyloidosis. Sensitivity (88%) and specificity (90%) of CMRI was confirmed by myocardial biopsy. At one year follow-up CMRI was a predictor of mortality.⁴⁸
2. **Change in management:** Rickers et al (2005) compared the ability of CMRI and echocardiography to detect increased wall thickness in 48 patients with suspected HCM.⁴⁹ CMRI was able to detect increased segmental wall thickness in three patients (6%) unidentified by echocardiography, leading to a change in diagnosis and management for a minority of patients.
3. **Change in management:** The EuroCMR myocarditis / cardiomyopathy population included patients with HCM.¹ This registry suggested an impact upon patient management (new diagnosis and/or therapeutic consequence) in 55% of these patients. In some cases the suggestion of a restrictive cardiomyopathy relate to myocardial infiltration, such as from iron overload.
4. **Change in management:** Valente et al (2013) reported that CMRI can identify abnormally thick myocardium in approximately 10% of HCM mutation carriers shown to have normal wall thickness by echocardiography.⁵⁰ This is an important study, as the included patients (n=40) were already known to be carriers of an HCM gene. In the Australian setting, where most patients will not have the opportunity to undergo genetic testing for HCM, the

identification of subtle phenotypic abnormalities makes the difference between missing the disease and making the appropriate diagnosis.

5. **Prognosis:** Two recent papers from the US and UK showed that a new CMRI technique of T1 mapping (a marker of myocardial infiltration and expansion of extracellular volume) was an independent predictor of mortality in systemic Amyloidosis.^{51, 52}

Arrhythmogenic right ventricular cardiomyopathy

1. **Change in management:** Taylor et al (2013) investigated the use of CMRI in 732 patients for the investigation of cardiac tumours (n=34), cardiomyopathy (n=488), ARVC (n=118) or viability (n=92). Following the CMRI scan, 37% of patients with a planned implantable device or cardiac surgery based on prior testing did not undergo the intervention.⁵³
2. **Change in management:** Borgquist et al (2014) evaluated the agreement between CMRI and echocardiography for the investigation of suspected ARVC. The findings indicate that up to 50% of ARVC patients would have missed diagnosis if CMRI was not utilised and they had been assessed by echocardiography alone.⁵⁴

Takotsubo cardiomyopathy

1. **Change in management:** Gerbaud et al (2012) studied 130 patients with troponin-positive chest pain, abnormal ECG changes and no culprit lesion identified by angiography. CMRI enabled a diagnosis in 100 of 130 patients (77%),⁵⁵ including 37 (28.5%) with acute myocardial infarction, 34 (26.1%) with myocarditis, 28 (21.5%) with apical ballooning syndrome and one (0.8%) with hypertrophic cardiomyopathy. CMRI provided a formal diagnosis in 69% of patients in which the clinical diagnosis was uncertain between at least two possibilities, and corrected a wrong diagnosis in 8% of patients. The CMRI-suggested diagnosis led to a modification of therapy in 42 patients (32%).
2. **Change in management:** In very recent Australian data (currently unpublished, submitted for peer-review), of 125 consecutive patients presenting to a tertiary centre between 2010 and 2014 with cardiac chest pain, elevated troponin and unobstructed coronaries, CMR provides a definite diagnosis in 87% of these patients. The authors used a panel of three experienced (> 5 years) consultant cardiologists unaware of the CMR diagnosis and blinded to each other's assessment, who each provided a clinical diagnosis based on clinical, biochemical, ECG, echocardiographic and angiographic findings. A consensus panel diagnosis was defined as two or more cardiologists sharing the same clinical diagnosis. In this study, there was only moderate level of agreement between the three cardiologists (k=0.466, p<0.01) and a poor level of agreement between the consensus panel and CMRI (k=0.38, p<0.01) with the most disagreement seen in patients with non-ST segment elevation myocardial infarction (NSTEMI) diagnosed on CMRI. Hence, CMRI led to a change in management in these patients.

Investigation of asymptomatic patients with a family history of sudden cardiac death

This is a diverse range of patients in whom a first degree relative has died suddenly from a presumed arrhythmia. As such, the group includes patients with a family history that could include HCM, ARVD or DCM, but the exact nature of the underlying abnormality has not been determined in the proband. As it is not clinically feasible to perform genetic testing for each variant of all these conditions, identifying any subtle phenotypic characteristics of mutation carriers is important. Therefore studies considering the utility of CMRI in mutation carriers for these diseases are relevant.

1. Valente et al (2013) showed that CMR can identify abnormally thick myocardium in approximately 10% of HCM mutation carriers who were thought to have normal wall thickness on echocardiography.⁵⁰ This is an important study, as the included patients were already known to be carriers of a HCM gene but judged normal on other testing.
2. In 2013, te Riele et al demonstrated the incremental value of CMRI in arrhythmic risk stratification of ARVC-associated desmosomal mutation carriers.⁵⁶ Sixty-nine patients with ARVC-associated mutations but had not sustained ventricular arrhythmias were included. Sixty one per cent presented with electrical abnormalities on the basis of electrocardiography and Holter monitoring, of whom 20 (48%) had abnormal results on CMRI. Eleven patients (16%) experienced sustained ventricular arrhythmias, exclusively in patients with both electrical abnormalities (electrocardiography and/or Holter monitoring) and abnormal CMRI results.
3. Mavrogeni et (2013) all applied CMRI to patients with a family history of sudden cardiac death and recent ventricular tachycardia and found the CMR identified abnormalities and provided a diagnosis in 22/25 patients.⁵⁷

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

Initial uptake of the service will be limited due to the availability of CMRI equipment and staff with suitable training and qualifications. Conventional MRI services are available in private and public facilities across Australia. There are 350 (171 full and 179 partial) Medicare-eligible MRI units in Australia.⁵⁸ The capacity for CMRI is currently unknown, however, as there are no mechanisms for registering the number of MRI machines equipped with specialised cardiac software. The requirement for a minimum level of training for radiologists is encouraged by the Department. This will have an impact on the initial availability of CMRI services, however, as it is presumed that few Australian radiologists have attained these qualifications to date. Based on the limited use of CMRI in State-based and private hospitals, the Applicant estimates that there are 20 to 25 sites in Australia that have dedicated cardiac software, and technologists and physicians with the requisite experience to conduct CMRI scans. This is likely to be a limiting factor in the initial uptake of the proposed service.

Due to the uncertain incidence and prevalence of cardiomyopathies in the Australian population, it is difficult to accurately estimate the likely uptake of the proposed service in the context of available MRI machines and suitably qualified staff. In addition, the number of patients with heart failure symptoms who are contraindicated for CMRI due to an implantable cardiac defibrillator is also difficult to estimate.

4.1 Population One

Population One includes two subgroups of patients with suspected dilated cardiomyopathy:

- i. Patients presenting with heart failure symptoms, in whom echocardiography is inconclusive or suggests a dilated cardiomyopathy, and in whom further diagnostic clarification is required.
- ii. Asymptomatic individuals with a family history of non-ischaemic dilated cardiomyopathy in a first-degree relative in whom echocardiography is inconclusive.

Clinical claim for the proposed intervention

CMRI in patients with suspected DCM provides information regarding left ventricular morphology and tissue characterisation. It is recognised as providing more accurate information than echocardiography in the assessment of left ventricular structure and function. In addition, CMRI may help identify the aetiology of the DCM through tissue characterisation with late gadolinium enhancement (LGE). LGE is able to demonstrate different patterns of myocardial scarring for different aetiologies of DCM. For example, a sub-endocardial pattern on LGE indicates scarring from a prior myocardial infarction, showing that the cardiomyopathy relates to CAD. Current standard practice employs a coronary angiogram as the main method to identify patients for whom CAD was the culprit for LV dysfunction. Published CMRI data has shown, however, that using the coronary angiogram as the arbiter for the presence of LV dysfunction caused by CAD could have led to an incorrect assignment of the cause of DCM in 13% of patients.⁴² The detection of mid-wall fibrosis—present in approximately 30% of DCM patients—has a role in the risk stratification of patients, as fibrosis is a predictor of all-cause mortality and cardiovascular hospitalisation. Mid-wall LGE also predicts ventricular tachycardia and sudden cardiac death.⁴⁴

Data from the pilot phase of the EuroCMR registry demonstrates the potential impact that CMRI may have on patient management,¹ showing that 55% of patients undergoing CMRI for suspected cardiomyopathy or myocarditis had a change in diagnosis or therapy.¹ In 16% of cases the final diagnosis based on CMRI was different to the diagnosis before CMRI. Identifying the correct underlying aetiology is likely to improve patient outcomes and reduce downstream costs.

There are benefits of CMRI in terms of diagnostic accuracy compared to comparators. For example the 13% of patients with a previously unrecognized ischaemic cardiomyopathy may benefit from revascularization and medications for secondary prevention of coronary atherosclerosis. Family members of patients with a defined cause of DCM, such as ischaemic cardiomyopathy, myocarditis, and sarcoid, would not require screening for DCM.

Beyond the diagnostic accuracy for identifying DCM, a key benefit of CMRI is the ability to define the aetiology and hence alter patient management. It is challenging to define how frequently this might occur and how patient management might change following the CMRI scan. Yoshida et al (2013) performed a direct comparison of the diagnostic capability of cardiac magnetic resonance and endomyocardial biopsy (EMB) in patients with heart failure.⁵⁹ From a group of 1034 patients with heart failure of unknown aetiology, 180 patients underwent both CMRI and EMB. The utility of CMRI in identifying new cardiac diagnosis is demonstrated by the identification of patients from this DCM group who would be classified into other populations (HCM, ARVC) for this proposal. Importantly, all of the patients who received accurate diagnoses with EMB alone were also correctly diagnosed using the combined diagnosis with clinical data, echocardiogram, plus CMRI. In this group, 26% of patients (n=36) were diagnosed with hypertrophic cardiomyopathy, with 15 cases in the dilated phase of HCM. Cardiac MRI identified 13 cases of sarcoidosis, five cases of ARVD, one case of myocarditis and three cases of amyloidosis.⁵⁹

The benefits of CMRI in terms of any potential change in management compared to comparators can be difficult to quantify, particularly if the MRI results in a new diagnosis. Eligibility for an implantable defibrillator provides one such example. In patients with a left ventricular ejection fraction less than 30%, (or less than 35% depending upon the aetiology and guideline) an implantable cardiac defibrillator (ICD) is indicated. The study by Joshi et al (2012) reviewed the potential clinical impact of cardiovascular magnetic resonance assessment of ejection fraction compared to echo ejection fraction (EF) on eligibility for ICD implantation.⁶⁰ Among patients with an echocardiographic EF of between 25% and 40%, they found that 41% were reclassified by CMRI. In addition, echocardiography identified only one of the six patients with left ventricular thrombus noted on CMRI. The presence of LV thrombus would usually require anticoagulation in a newly diagnosed cardiomyopathy patient, although the situation is less clear for chronic DCM patients. However, left ventricular thrombus may be of greater clinical importance in ICD patients, as defibrillation threshold testing following implantation would generally be avoided due to the risk of embolisation. At the EF threshold of 35%, CMRI reclassified 11 of 52 (21%) of patients with respect to eligibility for ICD. In 10 of the 11 instances of reclassification, CMRI found the EF to be below 35% making the patient potentially ICD-eligible, although one patient would avoid unnecessary ICD implantation.⁶⁰

The change in management for a new diagnosis post-CMRI would depend upon the exact nature of the new diagnosis. Assuming that myocarditis, sarcoidosis and amyloidosis are potentially treatable if identified early, using the data from Yoshida's study, 12.5% of patients (17/136) would have a treatable cause of DCM identified.⁵⁹ Appropriate therapy could reverse the cardiomyopathy and avoid the need for family screening.

The benefits of the change in management to patient health outcomes is similarly difficult to define. Considering the patients with a new diagnosis that may be treatable, cardiac MRI has the potential to be lifesaving. Cardiac amyloid typically causes increased wall thickness and so is considered in the HCM section of this protocol, but and also present as a DCM. In amyloid light-chain (AL) amyloidosis, the commonest form of amyloid, cardiac involvement is frequent and is the cause of death in most of patients. Effective treatments for AL amyloidosis are available, but treatment options are limited

when the myocardial disease is advanced. It is expected that CMRI will identify the majority of cardiac amyloid patients and some of those will be amenable to treatment. Importantly, the identification of cardiac amyloid may allow the patient to avoid other therapies and investigations, such as ICD (when their prognosis is grim due to advanced disease).

In summary, the proposed benefits of CMRI in patients with suspected DCM include:

- i. Increased diagnostic sensitivity compared to the current non-invasive techniques of investigating and differentiating DCM.
- ii. Increased safety compared to invasive coronary angiography, myocardial perfusion scans or CTCA including the avoidance of ionising tests (radiation) and subsequent cancers.
- iii. Potential change in patient management in more than 50% of patients. This may be due to increased diagnostic sensitivity, leading to a change in diagnosis and treatment pathway. In around one in seven patients from the Euro CMR registry, CMRI resulted in a different final diagnosis.¹
- iv. Potential avoidance of invasive coronary angiography or CTCA.

Comparator(s)

The main comparators that CMRI will potentially replace, i.e. tests that would otherwise be used to investigate patients with an abnormal echocardiography result, but in whom further information is required to confirm the aetiology of the disease, include:

1) Invasive coronary angiography with or without left ventricular angiogram (MBS Items 38215-38246)

Invasive coronary angiography (ICA) is currently the gold standard used to rule out ischaemic causes of DCM. In this regard, ICA is used in Population One to discount CAD as the primary source of a patient's heart failure symptoms. Due to its invasiveness, ICA is only recommended in patients with stable symptoms, and only when non-invasive testing provides inadequate information to determine the likelihood of a cardiac event as a result of CAD.⁶¹

2) Computed tomography coronary angiography (CTCA) (MBS Items 57360, 57361)

CTCA utilises intravenous contrast to visualise the lumen of coronary arteries, enabling diagnosis of ischaemic causes of left ventricular dilation. The primary use in Population One is to rule out ischaemic causes of DCM. The use of CT to image coronary arteries may avoid the use of invasive coronary catheterisation, however, the use of CTCA is not recommended in patients who are obese, cannot hold a breath, have high calcium scores (e.g. Agatston score > 400), or a regular heart rate greater than 65 beats per minute.⁶¹ CTCA is primarily indicated for patients who have a low intermediate pre-test probability of CAD (15-45%).⁶²

3) Exercise or pharmacologic (adenosine or dobutamine) single-photon emission computed tomography (SPECT) (MBS Items 61302, 61303, 61306, 61307, 61651, 61652, 61653, 61654)

SPECT utilises technetium-99m or thallium-201 radiopharmaceutical tracers to visualise regional myocardial blood flow and perfusion.⁶¹ Regional areas affected by myocardial ischaemia are identified by monitoring tracer uptake under peak stress (either pharmacological or exercise) compared to baseline uptake during rest. In Population One, SPECT is used to rule-out ischaemic causes of DCM.

4) Watchful waiting

The Applicant suggests that in current clinical practice the majority of patients with suspected DCM will proceed directly to medical therapy with follow-up monitoring on the basis of clinical history, ECG and echocardiography results. In such cases, the aetiology of the disease may be unknown, and medical treatment may be ineffective if the cause of DCM is unclear. First degree relatives of the DCM patient should undergo screening if an inherited cause cannot be excluded.

Reference standard(s)

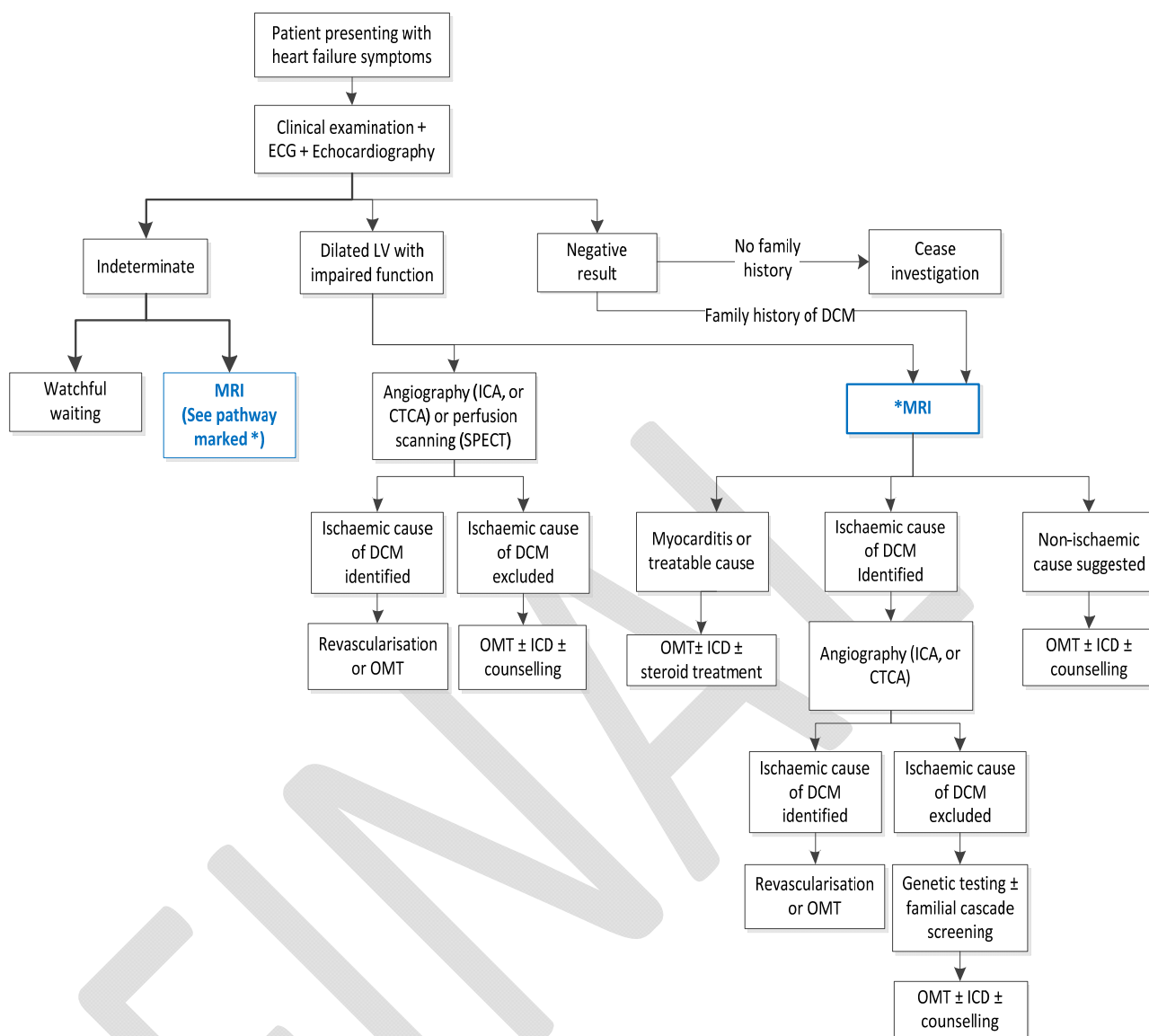
The reference standard for differentiating non-ischaemic DCM from an ischaemic DCM would be invasive coronary angiography, although SPECT and CT coronary angiography would sometimes be utilised. Once coronary artery disease has been excluded, aetiology of a non-ischaemic DCM can be sought by either myocardial biopsy or genetic testing, depending on the suspected aetiology of the disease. In Australian clinical practice, a diagnosis of familial DCM is often confirmed by the presence of DCM in patients with a family history in two first-degree relatives, or through genetic testing for known mutations.⁶³ PASC recognises that for DCM these reference standards are imperfect.

Clinical pathway

In this population, CMRI is primarily intended to be used as an adjunct diagnostic tool to clinical examination, chest x-ray and echocardiography. Echocardiography would typically be expected to show impaired LV function with a dilated left ventricle. CMRI would then be requested to further clarify the diagnosis, and in some cases also inform prognosis and the investigation of first degree relatives (see Figure 2). For example, in a patient with a dilated LV with poor systolic function identified on echocardiography, CMRI could show typical changes of an acute myocarditis, post myocarditis fibrosis, unsuspected ischaemic damage, or alternatively indicate an idiopathic/familial pattern of fibrosis. The investigation of first degree relatives would be triggered by the second finding but prevented by the first. Echocardiography alone would be unable to distinguish between these diagnoses.

In addition to adjunct diagnosis, CMRI has the potential to act as a gatekeeper to invasive coronary angiography, as discussed earlier.³⁹ The clinical pathway for suspected DCM is informed by the European Society of Cardiology's clinical practice guidelines for the diagnosis and treatment of acute and chronic heart failure.⁶⁴

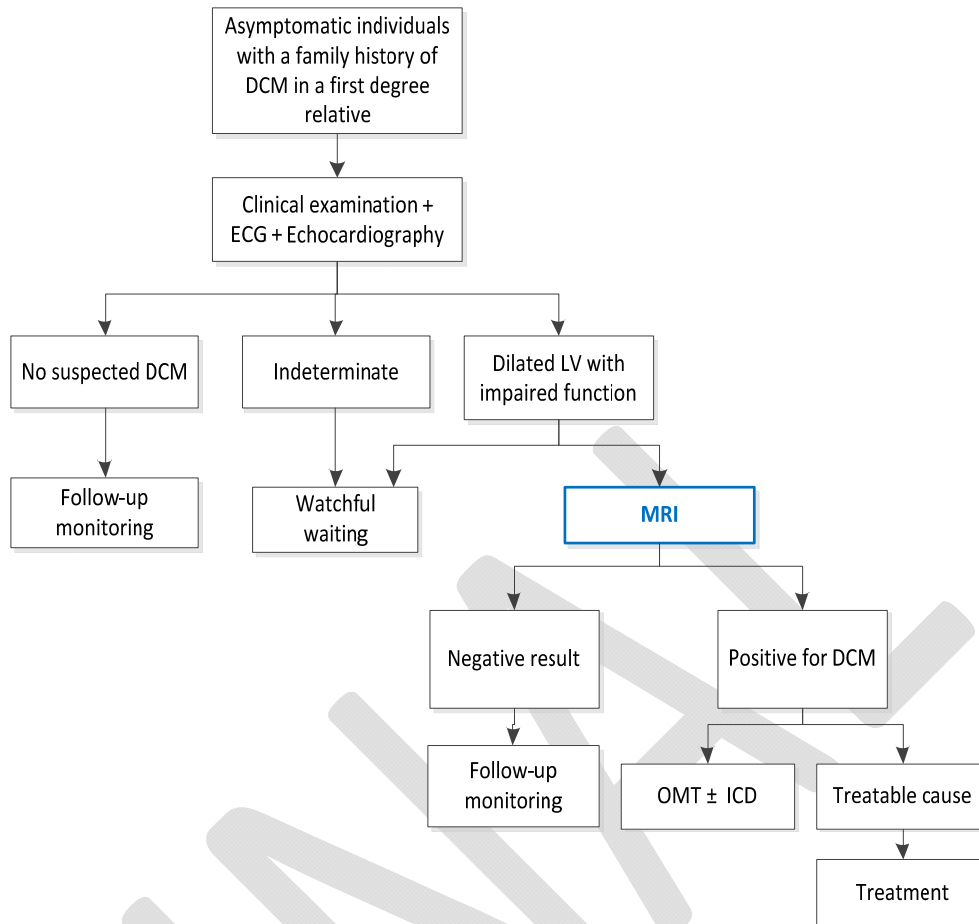
Figure 1: Proposed clinical practice algorithm for the investigation of suspected DCM



CTCA=computed tomography coronary angiography, DCM=dilated cardiomyopathy, ECG=electrocardiography, ICA=invasive coronary angiography, ICD=implantable cardioverter defibrillator, MRI=magnetic resonance imaging, OMT=optimal medical therapy, SPECT=single-photon emission computed tomography.

Population One also includes a subgroup of asymptomatic patients with a family history of DCM in a first-degree relative. In this population, CMRI is intended to be used as an adjunct diagnostic tool to confirm the diagnosis and establish the aetiology of DCM. The pathway for the investigation of first degree relatives of patients with DCM is informed by clinical practice guidelines published by CSANZ.⁶³

Figure 2: Proposed clinical practice algorithm for the investigation of asymptomatic patients with a family history of DCM in a first-degree relative.



DCM=dilated cardiomyopathy, ECG=electrocardiography, ICD=implantable cardioverter defibrillator, MRI=magnetic resonance imaging, OMT=optimal medical therapy.

Health outcomes

Relevant health outcomes for the investigation of CMRI in patients with suspected DCM are outlined in Table 2.

Economic evaluation

The economic evaluation for the proposed service is informed by the following clinical claims:

- Superior safety and non-inferior effectiveness compared to invasive coronary angiography.
- Superior safety and superior effectiveness compared to CTCA.
- Non-inferior safety and superior effectiveness compared to medical management without further testing.

In this context, the economic evaluation of the proposed service will be a cost-effectiveness analysis/cost-utility analysis.

Summary of PICO criteria**Table 2: Summary of PICO to define the research question(s) for Population One**

PICO Criteria	Comments
Patients	<ol style="list-style-type: none"> 1. Patients presenting with heart failure symptoms, in whom echocardiography is inconclusive or suggests a dilated cardiomyopathy, and in whom further diagnostic clarification is required. 2. Asymptomatic individuals with a family history of non-ischaemic dilated cardiomyopathy in a first-degree relative in whom echocardiography is inconclusive.
Intervention	MRI assessment of myocardial structure and function, including tissue characterisation
Comparator	<ol style="list-style-type: none"> 1. Angiography (MBS Items 38215-38246) 2. CTCA (MBS Items 57360, 57361) 3. SPECT (MBS Items 61302, 61303, 1306, 61307, 61651, 61652, 61653, 61654) 4. Watchful waiting in the context of optimal medical therapy
Outcomes	<p><u>Safety</u></p> <ul style="list-style-type: none"> • Gadolinium contrast adverse reaction • Claustrophobia • Physical harms from follow-up testing • Other adverse events arising from CMRI <p><u>Effectiveness</u></p> <p>Health outcomes</p> <ul style="list-style-type: none"> • Cardiac disease-specific mortality • Survival • Cardiac hospitalisation • Adverse cardiac event over defined period • Quality of life scores <p>Diagnostic accuracy</p> <ul style="list-style-type: none"> • Sensitivity, specificity (confirmed by reference standard) • Positive predictive value, negative predictive value (confirmed by reference standard) • Positive likelihood ratio, negative likelihood ratio (confirmed by reference standard) • ROC curves • Unsatisfactory or uninterpretable test results <p>Patient management</p> <ul style="list-style-type: none"> • Change in clinical diagnosis • Change in treatment pathway (initiated, ceased, modified, avoided) • Patient compliance with, preference for imaging • Time to initial diagnosis • Time from diagnosis to treatment • Rates of re-intervention <p><u>Cost-effectiveness</u></p> <ul style="list-style-type: none"> • Cost • Cost per quality adjusted life year or disability adjusted life year • Incremental cost-effectiveness ratio
Prior tests	<ol style="list-style-type: none"> 1. Clinical examination 2. Echocardiography (MBS Items 55113, 55115) 3. ECG (MBS Items 11700, 11701, 11702)
Reference test	Myocardial biopsy (MBS Item 38275) or genetic testing.

Research question for assessment: In patients with a family history of DCM in whom echocardiography is inconclusive, or in patients with heart failure symptoms in whom echocardiography is inconclusive or suggests a DCM and in whom further diagnostic clarification is required; what is the safety, effectiveness and cost-effectiveness of CMRI compared to invasive coronary angiography, SPECT, CTCA or watchful waiting in the context of optimal medical therapy?

4.2 Population Two

Population Two includes two subgroups of patients with suspected hypertrophic or restrictive cardiomyopathies:

- i. Patients in whom echocardiography suggests increased wall thickness, a hypertrophic or restrictive cardiomyopathy is suspected, and in whom further diagnostic clarification is required.
- ii. Asymptomatic patients with a family history of hypertrophic or restrictive cardiomyopathy in a first-degree relative.

Clinical claim for the proposed intervention

Increased LV wall thickness may be physiological (in response to pressure loading such as hypertension or aortic stenosis) or pathological (such as abnormal LV hypertrophy or myocardial infiltration). Hypertrophic and restrictive cardiomyopathies have been combined in Population 2 due to difficulty in differentiating between these two phenotypes of cardiomyopathy by echo and clinical assessment. In patients with suspected HCM or RCM, CMRI provides information regarding the patient's left ventricular morphology and tissue characterisation. This information can help differentiate physiological hypertrophy from pathologically increased LV wall thickness. It may also help differentiate infiltration from HCM and may provide further information on the type of infiltration. This may have an impact on patient management and the need for the investigation of first degree relatives. CMRI can identify myocardial scarring, which is a contributory risk factor for sudden cardiac arrest, and can allow for more appropriate use of an ICD with suspected HCM. CMRI is capable of identifying regions of LV hypertrophy not readily recognised by echocardiography and can be solely responsible for diagnosis of the HCM phenotype in an important minority of patients.^{49,}

⁶⁵ Due to improved visualisation of the myocardium when compared to echocardiogram, CMRI can identify otherwise undetected areas of wall thickening in the anterolateral LV free wall resulting in a diagnosis of HCM that could otherwise be missed. In this regard, the Applicant suggests that CMRI be recommended even if the echocardiography result is negative, in the context of a positive family history. This principle is also important when testing family members suspected of having HCM.

There are benefits of CMRI in terms of diagnostic accuracy compared to comparators such as echocardiography, as specified in section 4C. In summary, the proposed benefits of CMRI in patients with suspected HCM or RCM include:

- i. Increased ability to differentiate between HCM and RCM, due to increased diagnostic sensitivity compared to the current non-invasive techniques of investigating RCM.

- ii. Potential change in patient management due to increased diagnostic sensitivity, leading to a change in diagnosis and treatment pathway.

Comparator(s)

In Australian clinical practice, in the absence of CMRI a diagnosis of HCM or RCM is most commonly established through watchful waiting in combination with conventional therapy.

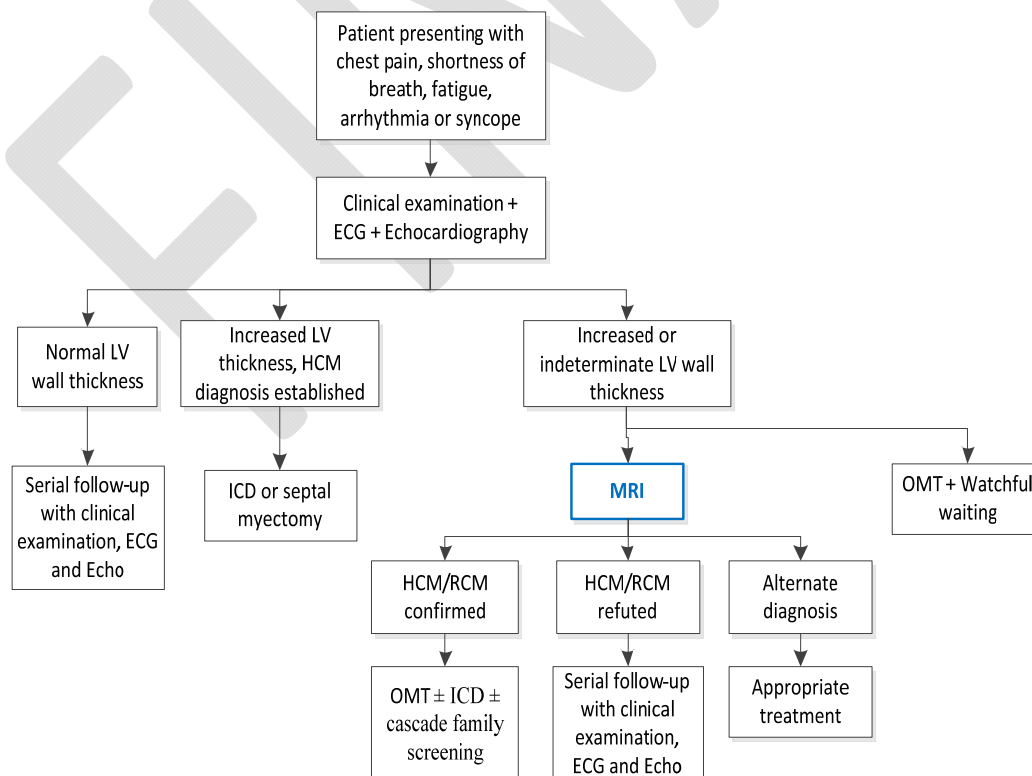
Reference standard(s)

The current reference standard for RCM is right ventricular biopsy,⁶⁶ however, as noted previously, this technique is seldom used in clinical practice due to its invasiveness and risk of sampling error.³⁸ The reference standards for HCM are myocardial biopsy or genetic testing, depending on the aetiology of the condition.²¹ Both of these tests are considered to be imperfect reference standards.

Clinical pathway

The diagnosis of HCM is often established on the basis of family history, clinical assessment, biochemistry and non-invasive testing (including clinical assessment, ECG, echocardiography and CMRI).⁶⁷ The primary use of CMRI in population Two is as an adjunct diagnostic tool in conjunction with echocardiography, ECG and clinical examination. Device therapy (i.e. ICD) is the most important therapy for these patients, rather than medical treatment. The clinical pathway for suspected HCM/RCM (Figure 3) has been informed by the European Society of Cardiology’s clinical practice guidelines for the diagnosis and treatment of hypertrophic cardiomyopathy.²¹

Figure 3: Proposed clinical practice algorithm for the diagnosis of suspected HCM/RCM

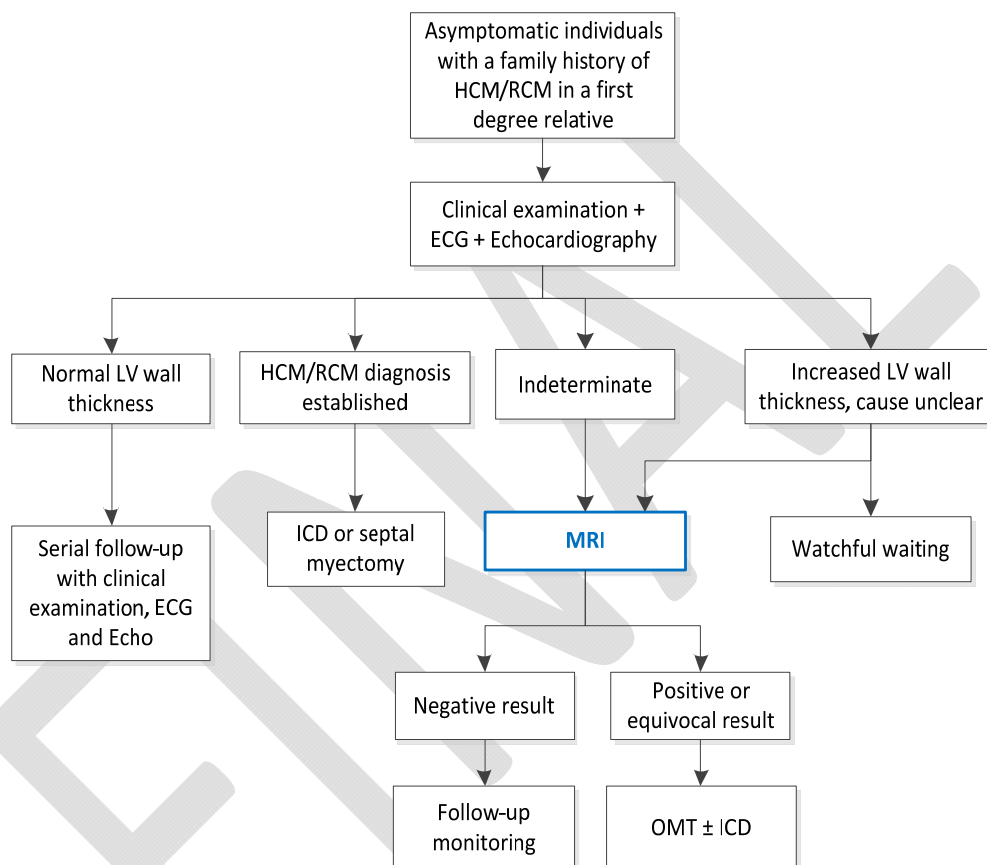


ECG=electrocardiography, HCM=hypertrophic cardiomyopathy, ICD=implantable cardioverter defibrillator, LV=left ventricle, MRI=magnetic resonance imaging, OMT=optimal medical therapy, RCM=restrictive cardiomyopathy.

Final Protocol

In asymptomatic patients with a family history of HCM or RCM, CMRI is primarily intended to be used as an adjunct to conventional testing (including clinical assessment, ECG and echocardiography). In patients with a suspected pathology based on conventional testing, CMRI will provide additional information on the aetiology of the disease, leading to potential changes to therapeutic management. In the absence of CMRI, patients are typically managed with follow-up monitoring. The clinical pathway for the investigation of patients with a family history of HCM/RCM in a first degree relative is presented in Figure 4.

Figure 4: Proposed clinical practice algorithm for the investigation of asymptomatic patients with a family history of HCM/RCM in a first-degree relative



ECG=electrocardiography, HCM=hypertrophic cardiomyopathy, ICD=implantable cardioverter defibrillator, LV=left ventricle, MRI=magnetic resonance imaging, OMT=optimal medical therapy, RCM=restrictive cardiomyopathy.

Relevant health outcomes for the investigation of CMRI in patients with suspected HCM/RCM are outlined in Table 3.

Economic evaluation

The economic evaluation for the proposed service is informed by the following clinical claims:

- Superior safety and non-inferior effectiveness compared to myocardial biopsy
- Non-inferior safety and superior effectiveness compared to genetic testing
- Non-inferior safety and superior effectiveness compared to non-invasive testing

In this context, the economic evaluation of the proposed service will be a cost-effectiveness analysis/cost-utility analysis.

Summary of PICO criteria**Table 3: Summary of PICO to define the research question(s) for Population Two**

PICO Criteria	Comments
Patients	<ol style="list-style-type: none"> Patients in whom echocardiography suggests increased wall thickness, a hypertrophic or restrictive cardiomyopathy is suspected, and in whom further diagnostic clarification is required. Asymptomatic patients with a family history of hypertrophic or restrictive cardiomyopathy in a first-degree relative.
Intervention	MRI assessment of myocardial structure and function, including tissue characterisation
Comparator	Watchful waiting in the context of conventional therapy
Outcomes	<p><u>Safety</u></p> <ul style="list-style-type: none"> Gadolinium contrast adverse reaction Claustrophobia Physical harms from follow-up testing Harms associated with the investigation of first degree relatives Other adverse events arising from CMRI <p><u>Effectiveness</u></p> <p>Health outcomes</p> <ul style="list-style-type: none"> Cardiac disease-specific mortality Survival Cardiac hospitalisation Adverse cardiac event over defined period Quality of life scores <p>Diagnostic accuracy</p> <ul style="list-style-type: none"> Sensitivity, specificity (confirmed by reference standard) Positive predictive value, negative predictive value (confirmed by reference standard) Positive likelihood ratio, negative likelihood ratio (confirmed by reference standard) ROC curves Unsatisfactory or uninterpretable test results <p>Patient management</p> <ul style="list-style-type: none"> Change in clinical diagnosis Change in treatment pathway (initiated, ceased, modified, avoided) Patient compliance with, preference for imaging Time to initial diagnosis Time from diagnosis to treatment Rates of re-intervention <p><u>Cost-effectiveness</u></p> <ul style="list-style-type: none"> Cost Cost per quality adjusted life year or disability adjusted life year Incremental cost-effectiveness ratio
Prior tests	<ol style="list-style-type: none"> Clinical examination Echocardiography (MBS Items 55113, 55115, 55118) ECG (MBS Items 11700, 11701, 11702)
Reference standard(s)	Myocardial biopsy (MBS Item 38275) and genetic testing (MBS Item 73317 for hemochromatosis, no other items identified).

Research question for assessment: In asymptomatic patients with a family history of HCM or RCM, or in patients in whom echocardiography suggests increased LV wall thickness, a HCM or RCM is suspected, and in whom further diagnostic clarification is required; what is the safety, effectiveness and cost-effectiveness of CMRI compared to watchful waiting in the context of conventional therapy.

4.3 Population Three

Population Three includes two subgroups of patients with suspected arrhythmogenic right ventricular cardiomyopathy:

- i. Patients in whom arrhythmogenic right ventricular cardiomyopathy is suspected on the basis of other International Task Force Criteria.
- ii. Asymptomatic patients with a family history of arrhythmogenic right ventricular cardiomyopathy in a first-degree relative.

Clinical claim for the proposed intervention

The primary use of CMRI in Population Three is as an adjunct diagnostic tool in conjunction with a number of tests outlined in the International Task Force Criteria for diagnosing ARVC.²³ In accordance with the Criteria, prior non-invasive tests may include ECG (including Holter monitoring, resting ECG, or signal-averaged ECG) or echocardiography. International guidelines state that MRI is an accepted part of the assessment of patients with suspected ARVC, and is not intended to replace other tests. CMRI can contribute both major and minor criteria towards the diagnosis of ARVC. Beyond RV dilation, CMRI adds regional RV akinesia, dyskinesia, or aneurysm.²³ These abnormalities are often not revealed adequately by echocardiography. A study by Borgquist et al (2014) indicates that up to 50% of patients with ARVD would have been missed had they been assessed only by echocardiography and if CMRI was not utilised.⁵⁴ The diagnosis of ARVC can be made based on either two major, or one major and two minor criteria, or four minor criteria from different categories. Thus, the use of MRI may avoid the need for invasive testing, such as myocardial biopsy, RV angiography or electrophysiological studies if enough diagnostic criteria can be established with non-invasive imaging tests.⁶⁸

There are benefits of CMRI in terms of diagnostic accuracy compared to comparators particularly with an increase in diagnostic information leading to an alternate diagnosis. In the study by Liu et al (2014) CMRI was performed upon 968 patients with suspected ARVC.⁶⁹ CMRI identified alternative cardiac diagnoses in 9.2% of patients, and in 43 patients (4.4%) of the diagnoses were clinically significant mimics of ARVC, including cardiac sarcoidosis, congenital heart disease, right ventricular (RV) volume overload conditions, and other cardiomyopathies. Similarly a New Zealand study by Looi et al (2012) of 92 patients with suspected ARVC found that CMRI detected important, previously undiagnosed pathology, including partial anomalous pulmonary venous drainage (2%) and dilated left ventricle (3%), left ventricular dysfunction (6%) and other minor abnormalities (5%).⁷⁰ No patients had ARVC based upon the 1994 Task Force Criteria (TFC) prior to CMRI, but four met proposed Modified TFC. The CMRI scans revealed nine patients (10%) who had findings consistent with ARVC. Two patients met one major TFC whereas seven met one or two minor criteria.⁷⁰

Final Protocol

In terms of any potential change in patient management, when compared to comparators or no MRI, this evidence would suggest that approximately 10% of these patients would have a new cardiac diagnosis that ought to lead to a change in their therapy.

The benefits of the change in management to patient health outcomes are in two groups; those patients in whom the MRI makes the diagnosis of ARVC when other criteria have been inconclusive and those in whom the MRI identifies another diagnosis. Specific examples of the latter would include those with sarcoid, who could receive immunosuppression and avoid progressive cardiac disease, those with congenital heart disease who could undergo corrective surgery, those with amyloid from a treatable condition (such as myeloma) who could undergo therapy, etc.

An estimate for the size of the effect of these claims (supported by references above) would be as follows:

- 10% to 50% of ARVC patients, who would otherwise have been missed, would be diagnosed with ARVC following CMRI. Due to the high risk of sudden arrhythmic death in this condition some would be eligible for ICD implantation that should abort sudden death in most cases. The identification of these patients could also lead to appropriate screening of family members and avoidance of sudden death in these relatives too.
- 10% of patients with significant alternate cardiac diagnosis would be identified. In those with congenital heart disease (at least 2%) corrective surgery could be performed. This may avoid ICD implantation but more importantly will avoid progressive right heart failure and premature death. Their relatives would not need any investigations for ARVC.

The primary benefits of CMRI for Population Three therefore include:

- i. Increased safety compared to existing invasive diagnostic testing options.
- ii. Potential avoidance of invasive diagnostic testing (including myocardial biopsy, angiography and electrophysiologic studies) due to earlier establishment of required criteria to confirm a diagnosis of ARVC.
- iii. Improved diagnostic sensitivity and specificity for identifying International Task Force Criteria.

Comparator(s)

As MRI is intended to be used as an adjunct to existing diagnostic imaging modalities, the appropriate comparator to MRI for Population Three is watchful waiting in the context of optimal medical therapy.

Reference standard(s)

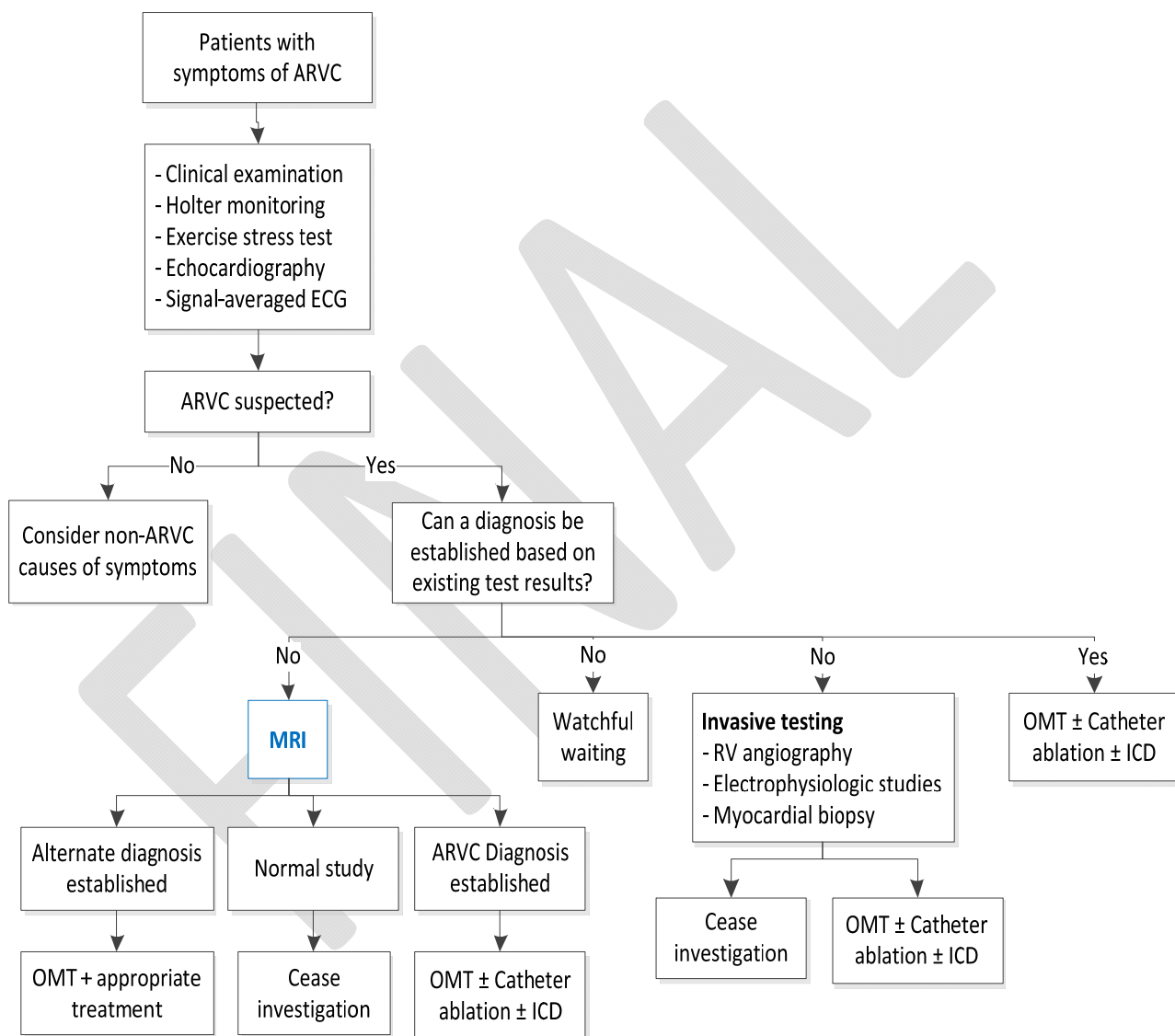
There is currently no single test that represents the reference standard for diagnosing ARVC. A diagnosis of ARVC is confirmed based on International Task Force Criteria, and is defined by the presence of either:

- i. Two major criteria; or
- ii. One major and two minor criteria; or
- iii. Four minor criteria.²³

Clinical pathway

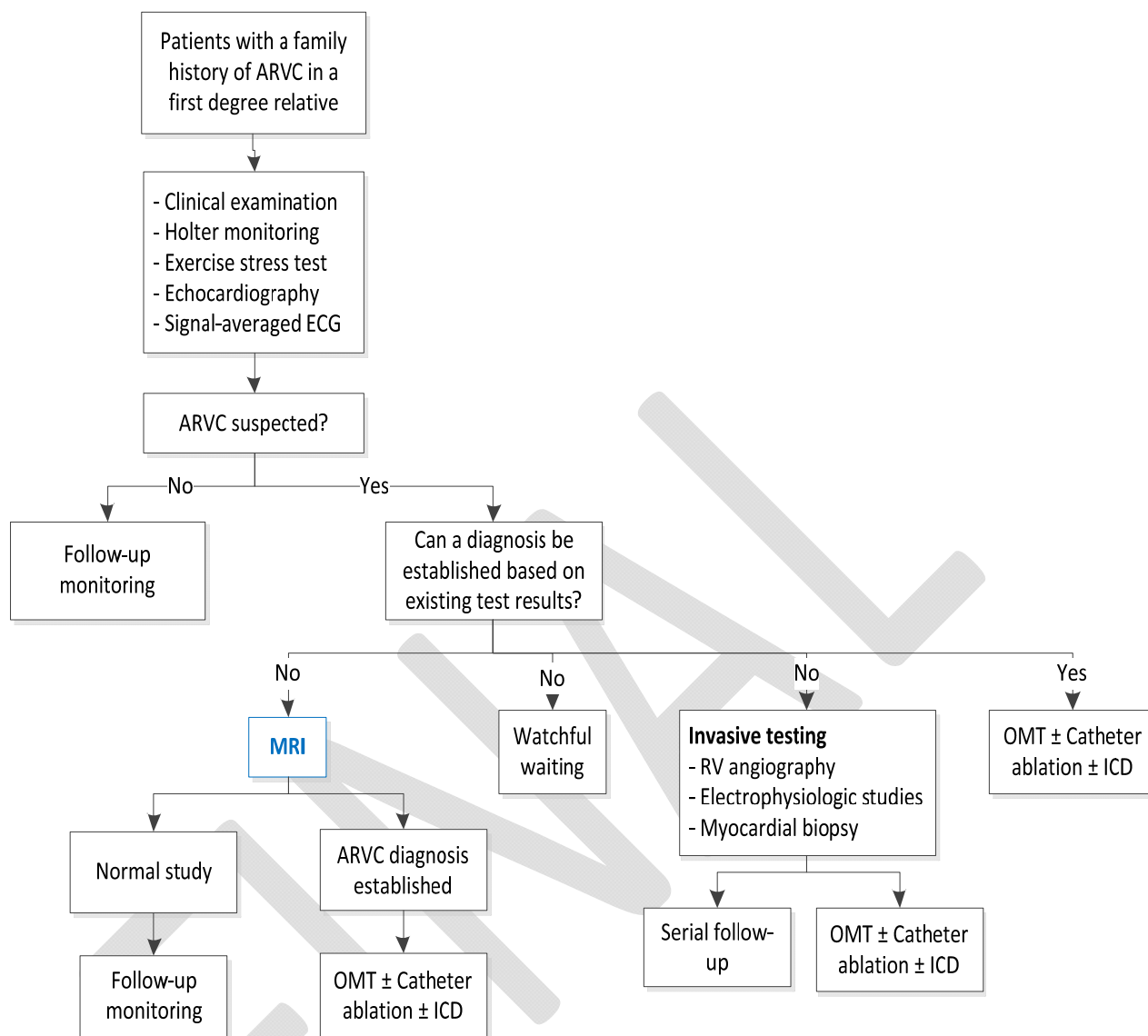
CMRI is an established tool used in the workup for establishing a diagnosis of ARVC. The clinical management algorithm for the evaluation of patients with suspected ARVC is informed by the International Task Force Criteria,²³ and a published diagnostic algorithm by Anderson (2006).⁶⁸ The primary difference between the clinical pathways for symptomatic (Figure 5) and asymptomatic patients (Figure 6) is the decision to proceed to either follow-up monitoring or further diagnostic testing if ARVC is not suspected following non-invasive testing.

Figure 5: Proposed clinical practice algorithm for the diagnosis of suspected ARVC



ARVC=arrhythmogenic right ventricular cardiomyopathy, ECG=electrocardiography, ICD=implantable cardioverter defibrillator, MRI=magnetic resonance imaging, OMT=optimal medical therapy, RV=right ventricle.

Figure 6: Proposed clinical practice algorithm for investigating patients with a family history of ARVC in a first degree relative



ARVC=arrhythmogenic right ventricular cardiomyopathy, ECG=electrocardiography, ICD=implantable cardioverter defibrillator, MRI=magnetic resonance imaging, OMT=optimal medical therapy, RV=right ventricle.

Health outcomes

Relevant health outcomes for the investigation of CMRI in patients with suspected ARVC are outlined in Table 4.

Economic evaluation

The economic evaluation for the proposed service is informed by the following clinical claims:

- Non-inferior safety and superior effectiveness compared to non-invasive testing.
- Superior safety and non-inferior effectiveness compared to invasive testing.

In this context, the economic evaluation of the proposed service will be a cost-effectiveness analysis/cost-utility analysis.

Summary of PICO criteria**Table 4: Summary of PICO to define the research question(s) for Population Three**

PICO Criteria	Comments
Patients	Patients in whom arrhythmogenic right ventricular cardiomyopathy is suspected on the basis of other International Task Force Criteria
Intervention	MRI assessment of myocardial structure and function
Comparator	Watchful waiting with optimal medical therapy
Outcomes	<p><u>Safety</u></p> <ul style="list-style-type: none"> • Gadolinium contrast adverse reaction • Claustrophobia • Physical harms from follow-up testing • Harms associated with the investigation of asymptomatic individuals with a family history of ARVC • Other adverse events arising from CMRI <p><u>Effectiveness</u></p> <p>Health outcomes</p> <ul style="list-style-type: none"> • Cardiac disease-specific mortality • Survival • Cardiac hospitalisation • Adverse cardiac event over defined period • Quality of life scores <p>Diagnostic accuracy</p> <ul style="list-style-type: none"> • Sensitivity, specificity (confirmed by reference standard) • Positive predictive value, negative predictive value (confirmed by reference standard) • Positive likelihood ratio, negative likelihood ratio (confirmed by reference standard) • ROC curves • Unsatisfactory or uninterpretable test results <p>Patient management</p> <ul style="list-style-type: none"> • Change in clinical diagnosis • Change in treatment pathway (initiated, ceased, modified, avoided) • Patient compliance with, preference for imaging • Time to initial diagnosis • Time from diagnosis to treatment • Rates of re-intervention <p><u>Cost-effectiveness</u></p> <ul style="list-style-type: none"> • Cost • Cost per quality adjusted life year or disability adjusted life year • Incremental cost-effectiveness ratio
Prior test(s)	<ol style="list-style-type: none"> 1. Clinical examination 2. Transthoracic echocardiography (MBS Items 55113, 55115) 3. Holter monitoring (MBS Item 11709) 4. Signal-averaged ECG (MBS Item 11713) 5. Exercise stress testing (MBS Item 11712)
Reference standard(s)	International Task Force Criteria

Research question for assessment: In patients with a family history of ARVC, or in whom ARVC is suspected on the basis of other International Task Force Criteria, what is the safety, effectiveness and cost-effectiveness of CMRI compared to watchful waiting in the context of optimal medical therapy?

4.4 Population Four

Population Four includes patients with troponin-positive chest pain, ECG changes suspicious of acute coronary syndrome (ACS), and no culprit lesion identified on coronary angiography.

Clinical claim for the proposed intervention

Identifying the underlying aetiology in troponin-positive patients who do not have ACS is important for ensuring that treatment pathways are appropriate. Establishing an alternate diagnosis with CMRI can spare patients lifelong medical therapy for the secondary prevention of CAD, and spare multiple further investigations such as transoesophageal echocardiography to identify a paradoxical embolism. Without MRI, the default diagnosis will often be ACS secondary to CAD, even though non-obstructive or normal coronary arteries have been reported in up to 10% of ST-elevation myocardial infarction and 12% of non-ST elevation myocardial infarction.^{71, 72} Such patients would undergo needless life-long medical therapy and follow-up for CAD. In contrast, patients with myocarditis often will need only follow-up investigation to determine the aetiology of the myocardial inflammation, and medication for a short period.

The benefits of MRI in this population include:

- i. Increased sensitivity and specificity for correctly identifying the underlying aetiology of symptoms compared to watchful waiting.
- ii. Change in patient management compared to watchful waiting, which in certain patients will lead to avoidance of unnecessary treatment and follow-up monitoring.

Comparator(s)

In Population Four, CMRI will potentially replace watchful waiting in the context of optimal medical therapy. The Applicant suggests that in current clinical practice patients suspected of having an acute coronary event, but in whom no culprit lesion is identified, may proceed to medical therapy without further investigation. These patients may receive a lifetime of unnecessary, PBS-sponsored medication if the underlying diagnosis is not CAD (i.e. is acute myocarditis or takotsubo/stress cardiomyopathy). Furthermore, an incorrect diagnosis of ACS in this situation may also impact adversely on the patient in terms of future employment and/or insurance.

Reference standard(s)

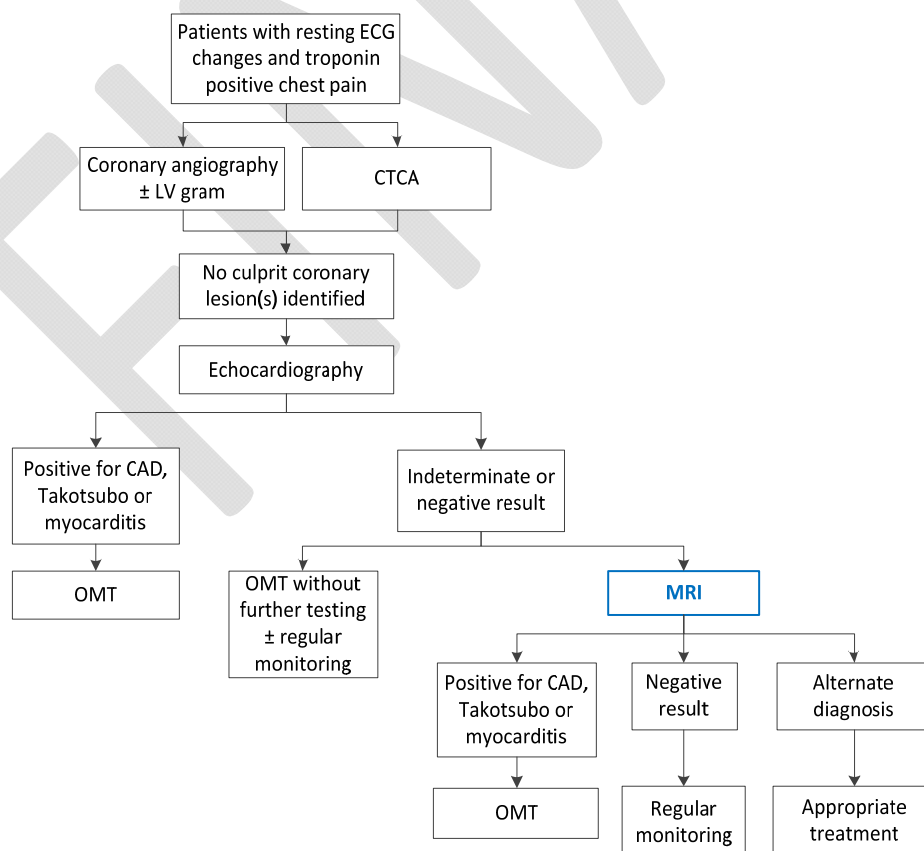
There is currently no definitive reference standard for confirming a diagnosis of takotsubo cardiomyopathy. In the absence of a suitable reference test, clinical follow-up provides the best confirmation of a diagnosis of takotsubo cardiomyopathy. The reference standard for diagnosing

myocarditis is myocardial biopsy.⁷³ However, as noted previously, this technique is seldom used in clinical practice due to its invasiveness and risk of sampling error. As with the other populations, CMRI can identify alternate diagnoses including HCM or infiltrative cardiomyopathy who would otherwise be missed. The study by Assomull et al (2007) suggests that a cardiomyopathy would be identified in ~4% of patients, a myocardial infarct would be the diagnosis in 12% and 50% of patients would have myocarditis.⁷⁴ In 35% the MRI was inconclusive. The change in management therefore depends upon the presumptive diagnosis prior to MRI. If it is assumed that all these patients are treated as an ACS (NSTEMI) then MRI would change management in more than 50% of patients. The majority would not require lifelong statin therapy, ACE inhibitor therapy, aspirin therapy or 12 months of clopidogrel. If the presumptive diagnosis was myocarditis then the diagnosis would be changed in 15% so that appropriate therapy could be delivered. Considering the ACS subgroup, this could reduce recurrent presentation and ischaemic events by more than 40%.

Clinical pathway

The primary use of CMRI in Population Four is as an adjunct diagnostic tool in conjunction with ECG, biochemistry, angiography and echocardiography. In these patients the diagnosis is often unclear, but primarily includes CAD, acute myocarditis or takotsubo cardiomyopathy.⁵⁵ The current clinical management pathway was established by the Assessment Group in consultation with the Applicant.

Figure 7: Proposed clinical practice algorithm for the diagnosis of patients with troponin-positive chest pain, ECG changes suspicious of ACS, and no culprit lesion identified on angiogram.



CAD=coronary artery disease, CTCA=computed tomography coronary angiography, ECG=electrocardiography, ICD=implantable cardioverter defibrillator, LV=left ventricular, MRI=magnetic resonance imaging, OMT=optimal medical therapy.

Health outcomes

Relevant health outcomes for the investigation of CMRI in patients with troponin-positive chest pain, ECG changes suspicious of ACS, and no culprit lesion identified on angiogram are outlined in Table 5.

Economic evaluation

The economic evaluation for the proposed service is informed by the following clinical claims:

- Non-inferior safety and superior effectiveness compared to echocardiography.
- Non-inferior safety and superior effectiveness compared to directed medical therapy without further testing.
- Superior safety and superior effectiveness compared to myocardial biopsy.

In this context, the economic evaluation of the proposed service will be a cost-effectiveness analysis/cost-utility analysis.

Summary of PICO criteria

Table 5: Summary of PICO to define the research question(s) for Population Four

PICO Criteria	Comments
Patients	Patients with troponin-positive chest pain, ECG changes suspicious of ACS, and no culprit lesion identified on coronary angiography.
Intervention	MRI assessment of myocardial structure and function, including tissue characterisation
Comparator	Watchful waiting in the context of optimal medical therapy
Outcomes	<p><u>Safety</u></p> <ul style="list-style-type: none"> • Gadolinium contrast adverse reaction • Claustrophobia • Physical harms from follow-up testing • Other adverse events arising from CMRI <p><u>Effectiveness</u></p> <p>Health outcomes</p> <ul style="list-style-type: none"> • Cardiac disease-specific mortality • Survival • Cardiac hospitalisation • Adverse cardiac event over defined period • Quality of life scores <p>Diagnostic accuracy</p> <ul style="list-style-type: none"> • Sensitivity, specificity (confirmed by reference standard) • Positive predictive value, negative predictive value (confirmed by reference standard) • Positive likelihood ratio, negative likelihood ratio (confirmed by reference standard) • ROC curves • Unsatisfactory or uninterpretable test results <p>Patient management</p> <ul style="list-style-type: none"> • Change in clinical diagnosis • Change in treatment pathway (initiated, ceased, modified, avoided) • Patient compliance with, preference for imaging

PICO Criteria	Comments
	<ul style="list-style-type: none"> • Time to initial diagnosis • Time from diagnosis to treatment • Rates of re-intervention <p><u>Cost-effectiveness</u></p> <ul style="list-style-type: none"> • Cost • Cost per quality adjusted life year or disability adjusted life year • Incremental cost-effectiveness ratio
Prior tests	<ol style="list-style-type: none"> 1. ECG (MBS Items 11700, 11701, 11702) 2. Clinical examination 3. Invasive coronary angiography (MBS Item 38215-38246) or CTCA (MBS Items 57360, 57361) 4. Echocardiography (MBS Items 55113, 55115)
Reference standard	Myocardial biopsy (MBS Item 38275)

Research question for assessment: In patients with troponin-positive chest pain, ECG changes suspicious of ACS, and no culprit lesion identified on coronary angiography, what is the safety, effectiveness and cost-effectiveness of CMRI compared to watchful waiting in the context of optimal medical therapy?

4.5 Population Five

Population Five includes asymptomatic individuals with a family history of sudden cardiac death or aborted sudden cardiac death in a first-degree relative, excluding channelopathies and arrhythmia.

Clinical claim for the proposed intervention

The primary use of CMRI in Population 5 is as an adjunct diagnostic tool. CMRI is intended to be used as an additional test to determine the presence of underlying disease in patients with a family history of sudden cardiac death or aborted sudden cardiac death in a first degree relative. For some patients, sudden death may be the first manifestation of cardiomyopathy. CMRI provides additional information beyond standard testing in regard to an assessment of LV structure and function, and can also provide information on tissue characterisation. Pre-symptomatic disease usually can be identified by echocardiography in patients with a family history of sudden cardiac death. Patients for whom the CMRI examination would be most useful include those with equivocal echocardiography findings, or those who have an affected relative with abnormal CMRI findings.

The proposed benefits of CMRI in this population include:

- Earlier identification of disease in an affected first-degree relative.
- Increased sensitivity and specificity for identifying cardiomyopathy subtypes compared to comparator tests.

Comparator(s)

In the absence of CMRI, asymptomatic patients with a family history of sudden cardiac death are managed through watchful waiting with regular follow-up. Therefore, the appropriate comparator to CMRI for Population Five is watchful waiting.

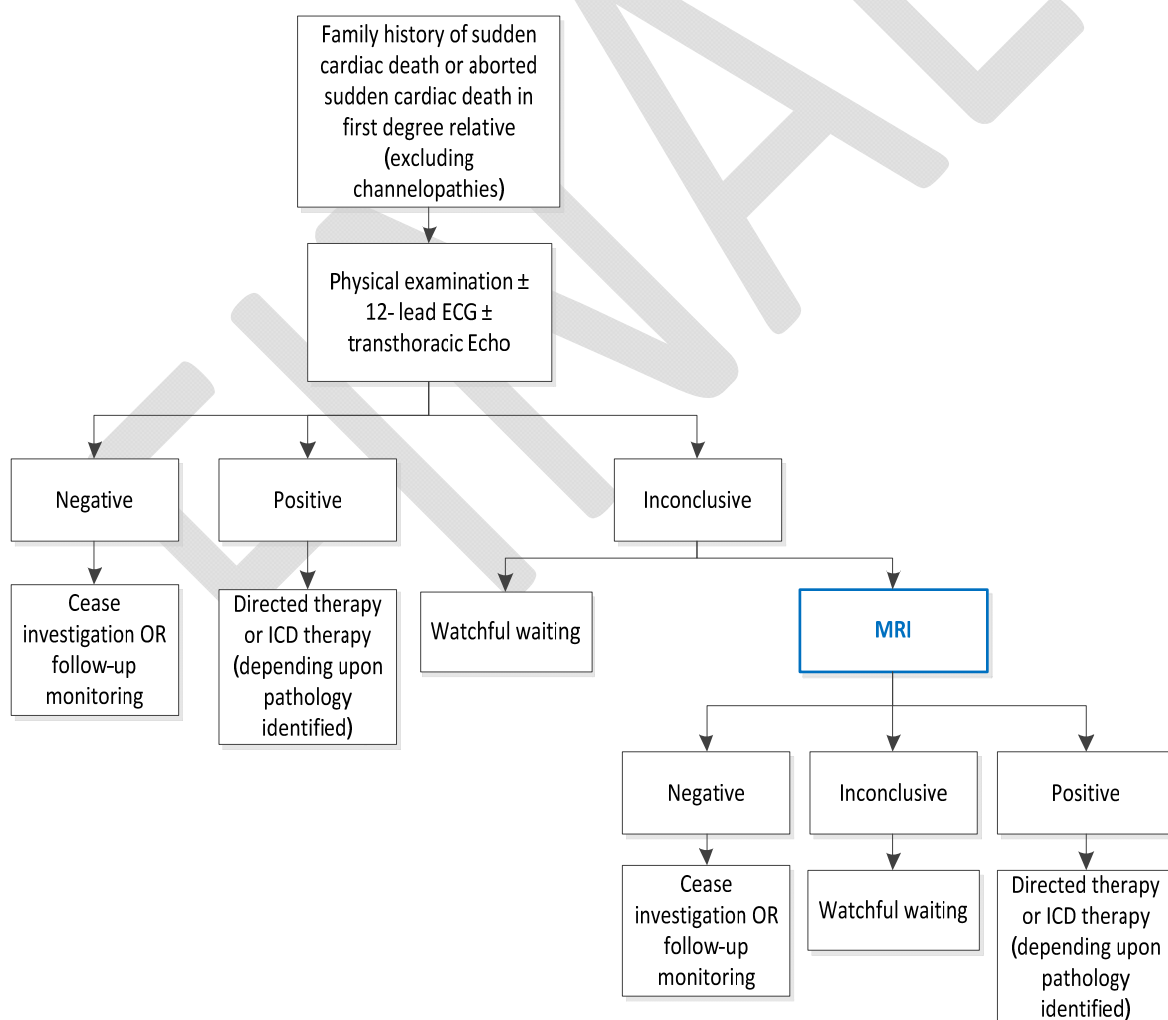
Reference standard(s)

There are currently no available diagnostic tests that can act as a reference test for sudden cardiac death. In the absence of diagnostic testing, watchful waiting with possible repeat evaluation every few years, dependent upon the pathology, is considered to be the imperfect reference standard.

Clinical pathway

In asymptomatic individuals with a family history of sudden cardiac death, CMRI is intended to be used as an adjunct diagnostic test to clinical evaluation, ECG, and transthoracic echocardiography. Other tests may depend upon the exact type of pathology being investigated. For example, holter monitors may also be applied. In the absence of clinical practice guidelines, the proposed clinical management algorithm for patients with a family history of sudden cardiac death was developed by the Assessment Group in consultation with the Applicant, and is presented in Figure 8.

Figure 8: Proposed clinical management algorithm for asymptomatic individuals with a family history of sudden cardiac death or aborted sudden cardiac death in a first-degree relative.



ECG=electrocardiography, Echo=echocardiography, ICD=implantable cardioverter defibrillator, MRI=magnetic resonance imaging.

Health outcomes

Relevant health outcomes for the investigation of CMRI in asymptomatic individuals with a family history of sudden cardiac death or aborted sudden cardiac death in a first-degree relative are outlined in Table 6.

Economic evaluation

The economic evaluation for the proposed service is informed by the following clinical claims:

- Non-inferior safety and superior efficacy compared to non-invasive testing.

In this context, the economic evaluation of the proposed service will be a cost-effectiveness analysis/cost-utility analysis.

Summary of PICO criteria

Table 6: Summary of PICO to define the research question(s) for Population Five

PICO Criteria	Comments
Patients	Asymptomatic individuals with a family history of sudden cardiac death or aborted sudden cardiac death in a first-degree relative, excluding channelopathies and arrhythmia.
Intervention	MRI assessment of myocardial structure and function, including tissue characterisation
Comparator	Watchful waiting
Outcomes	<p><u>Safety</u></p> <ul style="list-style-type: none"> • Gadolinium contrast adverse reaction • Claustrophobia • Physical harms from follow-up testing • Other adverse events arising from CMRI <p><u>Effectiveness</u></p> <p>Health outcomes</p> <ul style="list-style-type: none"> • Cardiac disease-specific mortality • Survival • Cardiac hospitalisation • Adverse cardiac event over defined period • Quality of life scores <p>Diagnostic accuracy</p> <ul style="list-style-type: none"> • Sensitivity, specificity (confirmed by reference standard) • Positive predictive value, negative predictive value (confirmed by reference standard) • Positive likelihood ratio, negative likelihood ratio (confirmed by reference standard) • ROC curves • Unsatisfactory or uninterpretable test results <p>Patient management</p> <ul style="list-style-type: none"> • Change in clinical diagnosis • Change in treatment pathway (initiated, ceased, modified, avoided) • Patient compliance with, preference for imaging • Time to initial diagnosis • Time from diagnosis to treatment

PICO Criteria	Comments
	<ul style="list-style-type: none"> Rates of re-intervention <u>Cost-effectiveness</u> <ul style="list-style-type: none"> Cost Cost per quality adjusted life year or disability adjusted life year Incremental cost-effectiveness ratio
Prior tests	Clinical evaluation, ECG, transthoracic echocardiography. Other tests may depend upon the exact type of pathology being investigated. For example, holter monitors may also be applied.
Reference standard	Watchful waiting with possible repeat evaluation every few years dependent upon the pathology.

Research question for assessment: In patients with a family history of sudden cardiac death or aborted sudden cardiac death in a first-degree relative, excluding channelopathies and arrhythmia; what is the safety, effectiveness and cost-effectiveness of CMRI compared to watchful waiting.

5. Fee for the proposed medical service

A. Explain the type of funding proposed for this service.

The current application requests the listing of five new 'Category 5 – Diagnostic Imaging Services' Items on the MBS (Table 7) to include subtypes of cardiomyopathy. The proposed items are intended to be co-claimed with modifying item 63491 (fee: \$44.80), which covers the cost of administering a contrast agent for eligible MRI scans.

Table 7: Proposed MBS Item for the investigation of suspected cardiomyopathies with CMRI

Category 5 – Diagnostic Imaging Services
<p>MBS [item number (Note: this will be assigned by the Department if listed on the MBS)]</p> <p>NOTE: Benefits are payable for each service included by Subgroup ## on one occasion only in any 12 month period</p> <p>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 cardiovascular system for:</p> <p>(a) assessment of myocardial structure and function, including tissue characterisation; and</p> <p>(b) the request for the scan identifies that the patient presents with:</p> <p>(i) heart failure symptoms, in whom echocardiography is inconclusive or suggests a dilated cardiomyopathy, and in whom further diagnostic clarification is required; or</p> <p>(ii) a family history of non-ischaemic dilated cardiomyopathy in a first-degree relative in whom echocardiography is inconclusive.</p> <p>(Contrast)</p> <p>Fee: \$855.20 Benefit: 75% = \$641.40 85% = \$726.90</p>

<p>Category 5 – Diagnostic Imaging Services</p> <p>MBS [item number (Note: this will be assigned by the Department if listed on the MBS)]</p> <p>NOTE: Benefits are payable for each service included by Subgroup ## on one occasion only in any 12 month period</p> <p>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 cardiovascular system for:</p> <p>(a) assessment of myocardial structure and function, including tissue characterisation; and</p> <p>(b) the request for the scan identifies that the patient presents with:</p> <ul style="list-style-type: none"> (i) echocardiography results suggesting increased left ventricular wall thickness, a hypertrophic or restrictive cardiomyopathy is suspected, and in whom further diagnostic clarification is required; or (ii) a family history of hypertrophic or restrictive cardiomyopathy in a first degree relative. <p>(Contrast)</p> <p>Fee: \$855.20 Benefit: 75% = \$641.40 85% = \$726.90</p>
<p>Category 5 – Diagnostic Imaging Services</p> <p>MBS [item number (Note: this will be assigned by the Department if listed on the MBS)]</p> <p>NOTE: Benefits are payable for each service included by Subgroup ## on one occasion only in any 12 month period</p> <p>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 cardiovascular system:</p> <p>(a) assessment of myocardial structure and function; and</p> <p>(b) the request for the scan identifies that the patient presents with:</p> <ul style="list-style-type: none"> (i) symptoms consistent with arrhythmic right ventricular cardiomyopathy on the basis of task force criteria; or (ii) a family history of arrhythmic right ventricular cardiomyopathy in a first degree relative. <p>(Contrast)</p> <p>Fee: \$855.20 Benefit: 75% = \$641.40 85% = \$726.90</p>
<p>Category 5 – Diagnostic Imaging Services</p> <p>MBS [item number (Note: this will be assigned by the Department if listed on the MBS)]</p> <p>NOTE: Benefits are payable for each service included by Subgroup ## on one occasion only in any 12 month period</p> <p>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 cardiovascular system for:</p> <p>(a) assessment of myocardial structure and function, including tissue characterisation; and</p> <p>(b) the request for the scan identifies that the patient presents with troponin-positive chest pain, electrocardiography changes suspicious of acute coronary syndrome, and no culprit lesion identified on coronary angiography.</p> <p>(Contrast)</p> <p>Fee: \$855.20 Benefit: 75% = \$641.40 85% = \$726.90</p>

Category 5 – Diagnostic Imaging Services

MBS [item number (Note: this will be assigned by the Department if listed on the MBS)]

NOTE: Benefits are payable for each service included by Subgroup ## 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 consultant physician and where the request for the scan specifically identifies the clinical indication for the scan - scan of cardiovascular system for:

(a) assessment of myocardial structure and function, including tissue characterisation; and

(b) the request for the scan identifies that the patient presents with a family history of sudden cardiac death or aborted sudden cardiac death in a first degree relative, excluding channelopathies and arrhythmia.

(Contrast)

Fee: \$855.20 Benefit: 75% = \$641.40 85% = \$726.90

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

The total estimated cost of conducting one CMRI scan on one patient for suspected cardiomyopathies is estimated to range between \$1,100 and \$1,200. This estimated cost was suggested by the RANZCR, and is supported by the CSANZ. However, there is a high degree of variability and uncertainty in how the total cost is estimated, as it may be influenced by a range of factors relating to the time and labour resources, consumable resources, and capital resources used to perform the service.

Consumable resources

Consumable resources required to undertake a CMRI scan cost approximately \$100 including the cost of gadolinium-based contrast. The consumable costs include:

- Linen = \$5.00
- Cannula = \$1.52
- ECG electrodes = \$2.52
- Gadolinium contrast = ~\$50
- Connecting tubing = \$30.50
- Dual Syringe = \$28
- Valves x 2 = \$10.20

Time and labour resources

The time to perform the scan is a significant factor in determining the overall cost of the service, which may vary significantly depending on the setting in which the scan is performed. In an efficient, high volume centre with highly trained and experienced CMRI staff, a scan for suspected cardiomyopathies may take 50 to 60 minutes. In a lower volume centre with less experience conducting CMRI, which is likely to be more common in private practice, CMRI scans take longer to perform. In low-volume centres, the time taken to conduct CMRI ranges between 60 to 80 minutes on average, as suggested by RANCR and supported by CSANZ; however, it is common for a scan for suspected ARVC to take in excess of 90 minutes. In such cases there will be additional costs in terms of time for radiographers and supervising clinicians.

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Another factor that can significantly affect the cost of the scan is whether or not specialist oversight is required during image acquisition. Although the application does not advocate for specialist oversight as a technical *requirement* for conducting CMRI in the proposed populations, Applicant experience suggests that specialist oversight may be necessary during the first five years of operation while the CMRI team is familiarising with the technique. Specialist oversight during image acquisition may also be required in a minority of challenging cases, even in experienced teams.

A summary of the time and labour resource costs associated with CMRI in Australian private practice are presented in Table 8. The resource costs should be confirmed during the assessment phase.

Table 8 Estimated human resource costs associated CMRI in Australian private practice

Resource	Nurse/Receptionist	Radiographer	Radiologist/Cardiologist
Average Estimated Time			
<i>Pre-scan patient briefing</i>	10 mins	10 – 15 mins	-
<i>Image acquisition</i>	-	60 – 80 mins	60 – 80 mins†
<i>Software analysis</i>	-	15 – 30 mins	-
<i>Specialist reporting</i>	-	-	15 – 30 mins
<i>Post-scan patient briefing</i>	10 mins	-	-
Total time	20 mins	85 – 125 mins	75 – 110 mins
Estimated Rate	\$25 per hour	\$49 per hour*	\$300 per hour**
Total cost	\$8	\$70-\$100	\$375-\$550

†While it is not a fixed requirement that a cardiologist/radiologist be present during a CMRI scan for cardiomyopathies, Applicant feedback suggests this is common in clinical practice - particularly while radiographers are being trained in CMRI.

*Estimate based on NSW state award rate for Level 3, Grade 1 Year 1 radiographers.

**Estimate based on Applicant feedback, but may be highly variable.

Capital resources

It is difficult to estimate the capital costs associated with conducted CMRI, as MRI units often used for a range of indications; however, the Applicant has emphasised that some MRI units are utilised exclusively for cardiac indications overseas. The capital costs associated with operating a MRI unit include:

- MRI scanner \$1-1.5 million for 1.5T, \$1.7-2.5 million for 3T magnet purchase
- Fit-out \$150-200,000
- Resuscitation equipment – cost unknown
- Picture Archiving Communication System (PACS) and Radiology Information System (RIS) – cost unknown
- Workstation \$100,000
- 3rd party Cardiac software \$20,000
- Maintenance and upgrades – 1.5 T or 3T \$140-160,000 per year, quarterly service

As MRI units in Australia are most often used for a range of indications, the opportunity costs associated with conducting CMRI should also be accounted for when estimating the overall cost of the service. The MRI costs relevant to this application should be confirmed during the assessment phase.

C. Provide details of the proposed fee.

The proposed fee in the original application was \$700 for CMRI in patients with suspected cardiomyopathies (inclusive of the \$44.80 fee for item 63491). Feedback from the RANZCR and private CMRI specialists suggests that patients will be required to pay a significant gap payment at the proposed fee level, depending on where the scan is performed. There are two key scenarios in which CMRI may be used that will affect the cost of the service:

1. In a high volume centre with expertise in CMRI and relatively fast scan acquisition times, a fee of \$655.20 for the proposed service, plus an additional \$44.80 for co-claimed item 63491, might be adequate (**\$700 total fee**).
2. In a lower volume centre, including smaller private practice clinics, a fee of \$855.20 for the proposed service, plus an additional \$44.80 for co-claimed item 63491, would be more appropriate (**\$900 total fee**).

Expert advice suggests that many private practices will not cover costs with a \$700 total fee for standard cardiac scans. One of Australia's largest private hospitals charges \$750 for a private CMRI scan without any stress agent (equivalent to the types of MRI scan performed in this protocol). This scan is allocated for one hour, and is run at a loss. In other private practices with less experienced technicians the scans take between 90-120 mins. It is suggested that a \$900 total fee for a cardiomyopathy scan (i.e. CMRI with Gadolinium contrast but without a stress agent) would minimise gap payments.

The proposed fees are considered to be a conservative estimate compared to the existing rebate for CTCA (MBS Item 57360, fee \$700), a comparator test that involves the use of machines that are less expensive than MRI, and require less time for image acquisition, software analysis and reporting.

6. Healthcare resources

A. Using Table 8, 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.

See Table 8 below.

7. Questions for public funding

A. Please list questions relating to the safety, effectiveness and cost-effectiveness of the service / intervention relevant to this application, for example:

- *Which health / medical professionals provide the service*
- *Are there training and qualification requirements*
- *Are there accreditation requirements*

The primary questions for public funding are listed in section 4, following the PICO table for each proposed population. In addition to the primary questions relating to the safety, effectiveness and cost-effectiveness of the service, the assessment phase should aim to answer the following secondary questions:

1. What proportion of operational time are eligible MRI units likely to be used for CMRI?

FINAL

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 Item	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
Resources provided to identify eligible population										
General Practice consultation	GP	Outpatient	100	TBD						TBD
Specialist consultation	Specialist	Outpatient	100	TBD						TBD
ECG	GP or Specialist	Outpatient or inpatient	100	TBD	11700 11701 11702					TBD
Echocardiography	GP or Specialist	Outpatient or inpatient	100	TBD	55113 55115 55118					TBD
Resources provided to deliver proposed intervention										
Magnetic Resonance Scanner	Specialist	Outpatient or inpatient	100	TBD						TBD
CMRI workstation and software	Specialist	Outpatient or inpatient	100	TBD						TBD
Gadolinium	Radiographer	Outpatient or inpatient	90-100	TBD	63491					TBD
Linen	Radiographer	Outpatient or inpatient	100	TBD						TBD
Dual Syringe	Radiographer	Outpatient or inpatient	90-100	TBD						TBD

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	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 Item	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
Cannula	Radiographer	Outpatient or inpatient	90-100	TBD						TBD
Connecting tubes	Radiographer	Outpatient or inpatient	90-100	TBD						TBD
ECG Electrodes	Radiographer	Outpatient or inpatient	TBD	TBD						TBD
Resources provided in association with proposed intervention										
TBD										TBD
Resources provided to deliver comparator tests										
Myocardial biopsy	Specialist	Outpatient or inpatient	TBD	TBD	38275					TBD
Invasive coronary angiography	Specialist	Outpatient or inpatient	TBD	TBD	38215-38246					TBD
CTCA	Specialist	Outpatient or inpatient	TBD	TBD	57360 57361					TBD
SPECT	Specialist	Outpatient or inpatient	TBD	TBD	61302 61303 61306 61307 61651 61652 61653					TBD

Final Protocol

	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 Item	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
					61654					
Genetic testing	Specialist	Outpatient or inpatient	TBD	TBD	73317					TBD
Echocardiography	Specialist	Outpatient or inpatient	TBD	TBD	55113 55115 55118					TBD
Signal-averaged ECG	Specialist	Outpatient or inpatient	TBD	TBD	11713					TBD
Holter monitoring	Specialist	Outpatient or inpatient	TBD	TBD	11709					TBD
Exercise stress testing	Specialist	Outpatient or inpatient	TBD	TBD	11712					TBD
Resources provided in association with comparator tests										
TBD										TBD
Resources associated with patient management following diagnosis										
Medical therapy	Specialist	Outpatient or inpatient	TBD	TBD						TBD
Implantable cardiac defibrillator (insertion and monitoring)	Specialist	Outpatient or inpatient	TBD	TBD	11727 21941 38212 38213 38384					TBD

Final Protocol

	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 Item	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
					38387					
Heart transplant	Specialist	Outpatient or inpatient	TBD	TBD						TBD
Specialist consultation	Specialist	Outpatient or inpatient	TBD	TBD						TBD

CMRI=cardiac magnetic resonance imaging, CTCA=computed tomography coronary angiography, ECG=electrocardiography, GP=general practitioner, MBS=medical benefits schedule, SPECT=single-photon emission computed tomography, TBD=to be determined.

* Includes costs relating to both the standard and extended safety net.

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