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Final Protocol to
guide the assessment
of catheter-based
renal denervation for
treatment-resistant
hypertension

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MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Australian Government Health Minister to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

Purpose of this document

This document is intended to provide a draft decision analytic protocol that will be used to guide the assessment of an intervention for a particular population of patients. The draft protocol that will be finalised after inviting relevant stakeholders to provide input to the protocol. The final protocol will provide the basis for the assessment of the intervention.

The protocol guiding the assessment of the health intervention has been developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

Patients – specification of the characteristics of the patients in whom the intervention is to be considered for use;

Intervention – specification of the proposed intervention

Comparator – specification of the therapy most likely to be replaced by the proposed intervention

Outcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention

Purpose of application

A proposal for an application requesting MBS listing of catheter-based renal denervation for treatment-resistant hypertension was received from Medtronic Australasia Pty Ltd by the Department of Health and Ageing in October 2012. PASC and the Department acknowledge that other devices are available and that the DAP and the subsequent assessment phase should clearly account for all eligible devices. The Department will liaise with the applicant and all device manufacturers to resolve this issue during the assessment process.

This decision analytic protocol has been drafted to guide the assessment of the safety, effectiveness and cost-effectiveness of catheter-based renal denervation for treatment-resistant hypertension in order to inform MSAC's decision-making regarding public funding of the intervention.

Intervention

Description of the medical condition

Hypertension is defined as abnormally high arterial blood pressure. In Australia, an adult systolic blood pressure of ≥ 140 mm Hg or a diastolic blood pressure of ≥ 90 mm Hg is classified as hypertension (National Heart Foundation 2010). Hypertension can be further divided into subcategories depending on systolic and diastolic blood pressure – with increasing grades representing an increase in severity (Table 1).

Table 1 National Heart Foundation classification of hypertension (Heart Foundation 2010)

Diagnostic Category	Systolic (mmHg)	Diastolic (mmHg)
Normal	< 120	< 80
High-normal (prehypertension)	120 - 139	80 - 89
Grade 1 (mild) hypertension	140 - 159	90 - 99
Grade 2 (moderate) hypertension	160 - 179	100 - 109
Grade 3 (severe) hypertension	≥ 180	≥ 110
Isolated systolic hypertension	≥ 140	< 90
Isolated systolic hypertension with widened pulse pressure	≥ 160	≤ 70

The aetiology of hypertension is complex. In most patients hypertension results from a combination of genetic factors such as differences in adrenergic tone (Kamran-Riaz et al 2011) and lifestyle factors such as excess salt intake, smoking, moderate to high alcohol intake, body mass index $>25\text{kg/m}^2$ and physical inactivity (National

Heart Foundation 2010). Hypertension can also be secondary to other disease processes.

Clinical consequences of hypertension

Hypertension is a significant factor influencing the progression of cardiovascular diseases. It is a well-established risk factor for coronary heart disease, stroke, heart failure and chronic kidney disease (National Heart Foundation 2010) with the risk of cardiovascular mortality rising linearly with increases above age-related targets in blood pressure - doubling for every 20 mm Hg (systolic) and 10 mm Hg (diastolic) increase above 115/75 mm (Lewington et al 2002). Additionally, hypertension can result in structural changes to the heart such as left ventricular hypertrophy (LVH) and cardiac fibrosis (Levy et al 1996). These alterations lead to poor cardiac function - LVH is well-established as prognostic for poor cardiovascular outcomes (Devereux et al 2004; Pierdomenico et al 2010).

Data from the Australian Institute of Health and Welfare (AIHW) indicate that high-blood pressure is a significant public health issue for Australians. For example:

- In 1999-2000, 32 per cent of men and 27 per cent of women aged 25 years and over had high blood pressure (AIHW 2004).
- When compared to other risk factors, hypertension contributes to more years of lost 'healthy life' due to disability and disease from cardiovascular disease (Begg et al 2007).
- In 2003, high blood pressure was responsible for almost 8% of the burden of disease in Australia (Begg et al 2007).
- In 2007, cardiovascular disease was recorded as the primary cause of death for 46,623 Australians (AIHW, 2010). Half of these deaths (22,727) were due to coronary heart disease and 8,623 to stroke (AIHW, 2010) – both linked to hypertension as a major causative risk factor.
- In terms of contributing causes of death, hypertensive diseases were ranked 6th and 5th for men and women, respectively (AIHW 2011).
- Coronary heart disease and stroke are linked to hypertension as a major causative risk factor. In 2004/05 these were the most costly cardiovascular diseases accounting for \$2.36 billion per year (AIHW 2010).

Current treatments for hypertension

In Australia, the treatment for hypertension is advised by the Heart Foundation guidelines (National Heart Foundation 2010, summarised in Figure 1). The first treatment option is to implement lifestyle changes including limiting alcohol and salt intake and promoting exercise and weight loss. Patients who do not respond to these changes, or who have grade 3 hypertension, isolated systolic hypertension, or have a high cardiovascular risk profile will commence drug therapy. The Heart Foundation guidelines recommend starting monotherapy with the lowest tolerated dose of the selected first line agent. If the initial agent is not tolerated, the patient is switched to another drug class starting at the lowest recommended dose. Target blood pressure is usually 140/90 for uncomplicated hypertensive patients (JNC7 2003) and 130/80 for diabetic patients (American Diabetes Association 2004). If target blood pressure levels are not reached, combination therapy is initiated using a second agent from a different drug class at a low dose. This approach minimises adverse events while maximising treatment efficacy. If blood pressure still remains above the target, the dosage of one agent is increased in a stepwise manner, before increasing the dose of the other agent. If combination therapy with two drugs is not effective in reducing blood pressure levels then a combination of three or more antihypertensive drugs from different classes may be required.

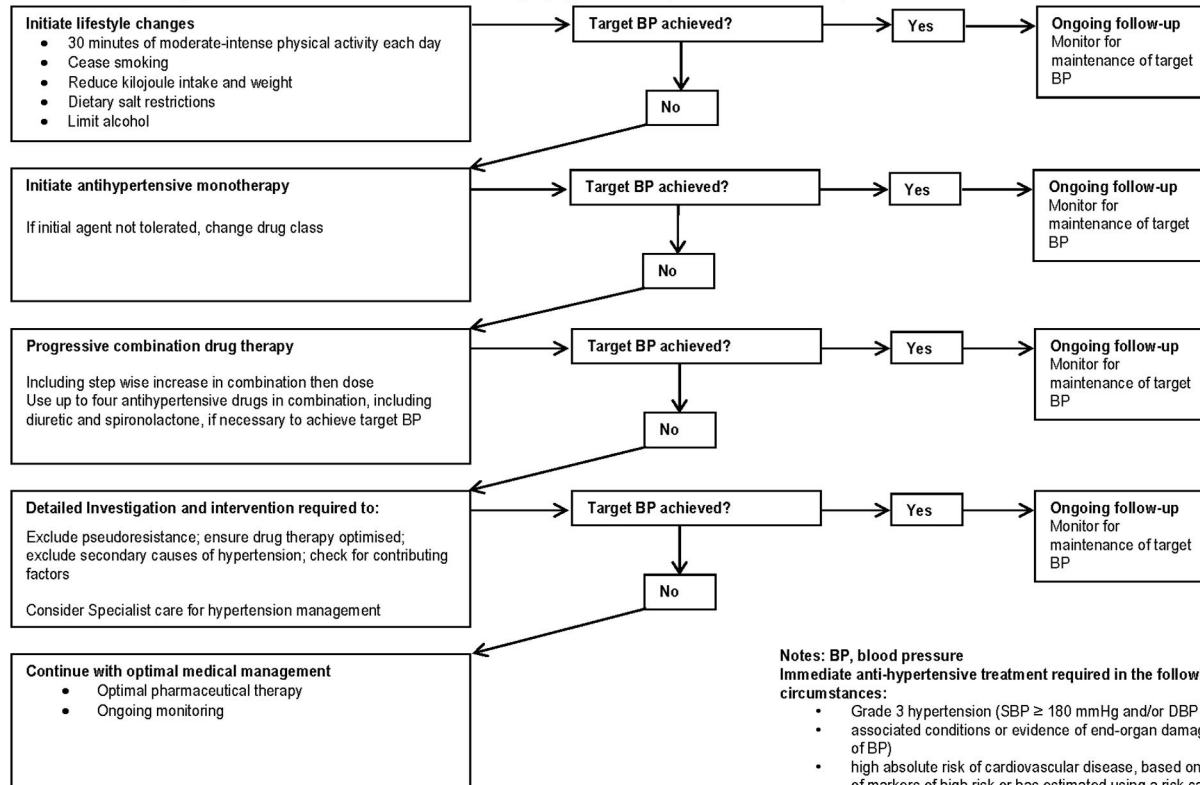
Where blood pressure remains above target levels despite maximal doses of at least two appropriate agents after a reasonable time period, detailed investigation may be required to determine possible causes of suboptimal control of blood pressure. Possible causes include:

- Pseudoresistance: non-adherence to therapy; hypertension only in a clinical setting ("white coat hypertension")
- Sub-optimal drug therapy
- Secondary hypertension resulting from an undiagnosed underlying condition
- Use of medication that can increase blood pressure; poor lifestyle; continued high alcohol intake; unrecognized high salt intake; sleep apnoea

Where blood pressure remains elevated, with target blood pressure not reached at 3 months after initiating drug therapy – despite adjusting treatment – the Heart Foundation guidelines recommend that specialist care should be considered (National Heart Foundation 2010).

Figure 1: Flowchart summarising the Heart Foundation Guidelines for managing hypertension (Heart Foundation 2010)

Figure 1: Flowchart summarising the Heart Foundation Guidelines for managing hypertension (Heart Foundation 2010)



Treatment-resistant hypertension

Despite adherence to multiple anti-hypertensive medications, a small subset of hypertensive patients will continue to experience blood pressure above target levels. This condition is termed treatment-resistant hypertension, and typically describes uncontrolled, elevated blood pressure, despite treatment with optimal doses of three or more anti-hypertensive medications (including a diuretic) (Calhoun et al 2008). Treatment-resistant hypertension may also be used to describe patients whose blood pressure is controlled but require four or more antihypertensive medications (Calhoun et al 2008). There are several potential causes of treatment-resistant hypertension (Calhoun et al 2008). For example:

- heavy alcohol intake, continued intake of drugs that raise blood pressure (e.g. liquorice, cocaine, glucocorticoids, non-steroidal anti-inflammatory drugs)
- untreated obstructive sleep apnoea
- irreversible or scarcely reversible renal damage
- volume overload due to inadequate diuretic therapy, progressive renal insufficiency, high sodium intake or hyperaldosteronism

The kidneys contribute to the long-term regulation of arterial blood pressure through maintaining sodium and water volume, renin modulation and renal-sympathetic neuronal interaction (DiBona 2002). Renal dysfunction is beginning to be appreciated as a pre-requisite for the development of hypertension. Of particular importance, an emerging pathological contributor to hypertension is thought to result from increased sympathetic nerve activity which lies within and immediately adjacent to the walls of the renal arteries (Katholi et al 2010). Increased renal reabsorption of sodium and water within the nephron, vasoconstriction, renin and norepinephrine release and vascular resistance accompanied by a decrease of glomerular filtration rate and renal blood flow which stem from increased sympathetic activity all act to increase blood pressure (DiBona 2002). If left uncontrolled, these interactions are not only detrimental to the kidneys, but also the positive feedback interactions may lead to the development of greater hypertension and additional injury (Navar & Hamm 1999).

Cohort data from the United States of America suggests that approximately 16.2 per cent of hypertension patients meet the definition of treatment resistant hypertension

(blood pressure remains uncontrolled despite being on more than three medications) (Egan et al 2009). No Australia-specific data were identified.

Clinical consequences of treatment-resistance hypertension

Treatment-resistant hypertension is considered the most severe and high-risk group amongst all hypertension categories (Doumas et al 2010) as the uncontrolled high blood pressure increases the risk of cardiovascular and kidney morbidity. Daugherty et al (2012) reported a 50 per cent increase in cardiovascular events in patients with treatment-resistant hypertension when compared to patients whose blood pressure had been controlled on three medications.

Expert clinical input has confirmed that apart from drug therapy there are no other proven therapies for treatment-resistant hypertension beyond the proposed service.

Description and proposed delivery of proposed new intervention

Catheter-based renal denervation in managing treatment-resistant hypertension

Based on the role of the sympathetic nervous system in hypertension, renal denervation utilises ablative technology to selectively disrupt the renal sympathetic nervous system in a localised and minimally invasive manner at the level of the kidney using an endovascular approach. This technology is developing in a rapid manner and includes radiofrequency-based systems and ultrasound-based systems. Due to the fact that this DAP is based on an application regarding a radiofrequency ablation device, the examples in this DAP relate to this particular group of devices. However, the proposed MBS descriptor is sufficiently broad to include consideration of any TGA-approved catheter-based renal denervation system.

Currently available radiofrequency renal denervation systems share similar components such as:

- An ablation catheter
- Radiofrequency ablation generator

It is important to note that each radiofrequency ablation device differs. For example, the Boston Scientific Vessix™ Vascular V2 and Covidien OneShot™ are balloon catheters with multiple electrodes. The St Jude Medical EnligHTN™ catheter has an expandable electrode basket with four ablation electrodes. The Medtronic Symplicity® catheter has a single electrode at the tip.

Additional consumable items such as an introducer sheath, disposable guide catheter and dispersive electrodes are general items used for many endovascular procedures. The procedure is performed in a catheterisation laboratory, using standard endovascular intervention techniques similar to those used in renal angioplasty or stenting. The ablation catheter is localised via the femoral artery to the renal arteries. The efferent and afferent nerves adjacent to the artery are ablated through the arterial wall. During the procedure, both renal arteries are treated. Following this service, optimal medical management must be continued.

Renal denervation is thought to improve blood pressure levels by reducing sympathetically-mediated kidney function (Katholi et al 2010). Animal and human studies suggest this occurs by reducing renin release and sodium retention, improving renal blood flow and facilitating normal arterial pressure (Katholi et al 2010).

Other catheter-based renal denervation technologies include ultrasound devices.

CardioSonic Ltd. TIVUS™ (Therapeutic IntraVascular UltraSound) is a high-intensity, nonfocused ultrasonic (US) catheter system for renal denervation. The first-in-man TIVUS I clinical study included participants at the Royal Perth Hospital (Western Australia). The TIVUS II trial (NCT01835535) is currently underway.

ReCor Medical, Inc. PARADISE™ (Percutaneous Renal Denervation System) is a nonfocused ultrasound system for performing renal denervation. The first-in-man study (REDUCE) was undertaken in South Africa, and the ACHIEVE study, started in February 2013, includes a number of European centres (NCT01789918).

Note for Intervention:

Purpose-designed ablation systems for the renal artery should be included.

Historically, MSAC prefers to consider generic devices, rather than distinguish between different brands.

- Where possible the primary approach to the Intervention should group similar technologies together. For example, information regarding all RFA devices should be provided together; information regarding all ultrasound devices

should be provided together etc.

However, there are instances where MSAC and Medicare have distinguished between different brands due to varying evidence and clinical profiles.

- PASC recognises that each branded device for catheter-based renal denervation is quite distinct from other similar technologies (e.g. number and size of ablation probes, use of balloon, use of cooling fluid) and may have a different clinical safety and effectiveness profile. Therefore, evidence regarding each individual device should be provided separately to enable MSAC to determine whether devices are equivalent in their clinical utility. The MBS item may be modified to allow for MSAC's final recommendation.

Administration, dose, frequency of administration, duration of treatment

The provision of this service may vary between different types of radiofrequency ablation, or other ablative devices, due to differences between brands in terms of technology and delivery of ablation.

Referral for catheter-based renal denervation can come from hypertension specialists or other specialists (e.g. cardiologists, renal physicians) involved in the management of patients who are not meeting target blood pressure levels, despite optimal medical management. The threshold for referrals can vary depending on the particular co-morbidities being managed in addition to hypertension (e.g. diabetes, coronary heart disease etc.).

Before undertaking renal denervation, duplex renal ultrasound is used to assess renal vascular anatomy and appropriateness for the intervention. Imaging of renal artery anatomy is currently commonly undertaken in patients with treatment-resistant hypertension as part of standard patient work-up to establish reasons for uncontrolled blood pressure, although these images may not have provided the required detail to determine eligibility to renal artery denervation, or may be too old to establish the current eligibility of the patient to the service. The ideal anatomical features are the presence of a single renal artery supplying each kidney (20mm in length and 4mm diameter), without stenosis, free of major lesions and has not been

subjected to angioplasty or stenting and is available via percutaneous femoral access.

Renal denervation may be provided by a range of specialists including interventional cardiologists, interventional radiologists, vascular surgeons and interventional nephrologists.

Prior to the procedure, the patient should receive appropriate systemic anticoagulation and local anaesthesia. The catheter is percutaneously introduced via the femoral artery and positioned to the distal region of the renal artery (close to the renal hilum) under angiographic guidance. At this point, the generator is activated and radiofrequency energy is delivered to the artery wall. For certain devices (e.g. Symplicity®) blood flow cools the endothelium, minimising injury to adjacent tissue. For other devices, (e.g. those with balloon catheters), a cooled fluid circulation is used to minimise injury. The energy released during the ablations may cause visceral pain, justifying sedation or analgesia with opiates or narcotics. For certain devices (e.g. Symplicity®) the ablation process needs to be repeated to treat the required area of the renal artery. For these devices a series of 4-6 ablations per renal artery is required depending on renal artery length. For other devices, multiple electrodes mean that only 1-2 ablations are required per artery. The procedure is repeated in the opposite renal artery.

At the end of the procedure, an angiogram of the renal arteries should be used to check for the presence of renal artery dissection or infarct. It should be noted that some irregularities can be observed after renal denervation that are not pathologically significant (Aziz et al 2012).

Apparently healthy renal arteries may be fragile because they have been exposed to high blood pressure levels for a long time before denervation. There is therefore a risk of renal artery dissection. The centre should therefore have emergency stenting equipment.

Ablation is estimated to take between 30-50 minutes (Aziz et al 2012). The average total procedural time is approximately 60 minutes, including time for angiography. The ablation time may vary due to issues such as renal artery anatomy, spasms, patient discomfort. It may also vary depending on the type of device used.

The procedure should be carried out exclusively at specialist centres with appropriate catheterisation laboratory and emergency stenting facilities. Clinicians should have sufficient experience in catheterisation and angioplasty of renal arteries and have the necessary technical resources available for the management of any immediate complications such as artery dissection. Training for the delivery of renal denervation involves proctoring by clinicians experienced in delivering this procedure. Feedback from all manufacturers has informed that training in the use of all devices would be provided with manufacturer support and proctoring from an experienced service provider. The applicant suggests a short learning curve for the technique with the applicant covering the costs of supervision.

The applicant has indicated that there are limited periprocedural risks.

For morning cases, most patients would be discharged at the end of the day, with approximately 10 per cent of cases remaining for an overnight stay. For afternoon cases, most patients would remain hospitalised overnight for post-procedure management and monitoring.

Expert clinical input has suggested that there are very few circumstances where it would be helpful to repeat the therapy, although this could be undertaken. For example, if there was an excellent response at the initial procedure and the blood pressure rebounded some years later, it would be reasonable to consider repeating the treatment. However, due to the lack of current evidence, PASC suggests this treatment should only be offered as a one-off service unless evidence to the contrary becomes available.

Co-administered interventions

Duplex renal ultrasounds are used most commonly in the current Australian clinical setting to assess renal vascular anatomy and appropriateness for intervention. Appropriate prior images of the renal vasculature may be available from the standard work-up of patients with treatment-resistant hypertension. In these cases, additional imaging to assess eligibility for the service would not be required.

The main co-administered intervention is angiographic imaging of the renal arteries to guide the renal denervation procedure. Expert clinical input has suggested that multiple angiography runs are undertaken to document the position of the catheter, and that digital subtraction angiography is often used to minimise contrast usage. It

would be common to use more than 20 angiography runs per case. Angiography is also performed at the end of each procedure to confirm the absence of damage to the renal artery. Expert clinical input suggests that previous safety studies have documented that later complications following the procedure are rare and as a consequence routine imaging after the index procedure is not necessary. Current MBS items for angiography include items 60024-60033. PASC has concluded that as angiography is an integral part of the proposed service that angiography costs should be included as part of the proposed fee.

Although the procedure is uncomfortable, the service is commonly provided by the specialist (interventional cardiologist, interventional radiologist, vascular surgeon, interventional nephrologist) performing the procedure without the need for general anaesthesia. This is consistent with other endovascular procedures.

In some cases initial angiography prior to providing renal denervation may identify a previously unknown renal artery stricture that requires the application of a stent. Expert clinical advice suggests that this may be provided during the same procedure as part of the renal denervation service, and that it is common for patients who are to undergo renal artery denervation to be asked to sign consent forms for the insertion of a renal artery stent. Alternatively, the stent may be provided during the initial procedure with renal artery denervation provided at a later date. The relevant MBS item number for stent implantation is 35309.

Patient monitoring equipment and general endovascular procedure consumables would be commonly available in a catheterisation facility. Medications commonly used during the procedure include anxiolytic/amnestic medication, anticoagulation, pain medication and vasodilation. However, in each procedure medication is tailored to individual patient circumstances as determined by the treating clinician.

Optimal medical management (including anti-hypertension medication and ongoing monitoring) will continue after the intervention.

Summary box for Intervention:

Following discussions and clinical input, PASC agrees that the base case scenarios should be as follows:

- An assistant would usually not be required.
- The service would normally be provided under conscious sedation. Clinical judgement is required as the procedure can be painful. The economic modelling should allow for the use of general anaesthesia in the sensitivity analysis.
- Anaesthetist attendance is required for the delivery of conscious sedation in some jurisdictions. The assessment phase should determine anaesthetist requirement on a state-by-state basis. This information should be reflected in the economic model. The sensitivity analysis should allow for any uncertainty in anaesthetist attendance.
- A previous image of the renal vasculature (e.g. Doppler, MRI, CT, MRA, CTA) is commonly available as part of standard hypertension clinical management. Therefore an additional image to identify eligibility for the service would normally not be required. The economic modelling should allow for the requirement of an additional duplex renal ultrasound in the sensitivity analysis.
- Previous imaging studies taken as part of standard clinical management and available to determine patient eligibility should accurately identify appropriate renal artery anatomy. However, the sensitivity analyses should allow for rare cases where intra-procedural angiography identifies inappropriate anatomy and an inability to provide the ablation therapy.
- As above, previous imaging studies to determine patient eligibility should accurately identify appropriate renal artery anatomy. However, the sensitivity analyses should allow for rare cases where intra-procedural angiography identifies the need for a renal artery stent.
- Detailed imaging after the service has been completed would not be required.
- Expert clinical opinion advises that catheter-based renal denervation can be provided as a day procedure. However, an overnight stay is required when a service is provided in the afternoon.
- Any evidence regarding variability between devices in terms of technical issues (for example number of ablations, ablation time, procedure time, use of anaesthesia and so on) should be provided.

Background

Current arrangements for public reimbursement

There is currently no MBS item for catheter-based renal denervation. Hypertension is most commonly managed with pharmaceutical intervention, and there are many medications approved for this use on the Pharmaceutical Benefits Schedule. There are no other effective management options for treatment-resistant hypertension.

Current use of catheter-based renal denervation in Australia

Catheter-based renal denervation has previously received funding for treatment-resistant hypertension patients through the Victorian Department of Health as a result of a Victorian Policy Advisory Committee on Technology (VPACT) assessment from 2011-2013. Queensland Department of Health has also provided funding for the service as a result of a Queensland Policy and Advisory Committee on New Technology (QPACT) assessment although the current status of this support is not known.

The Baker IDI Heart and Diabetes Institute, Melbourne receives research funding from the National Health and Medical Research Council (NHMRC) for Catheter-based renal denervation for uncontrolled hypertension (NHMRC reference 1034397). The NHMRC have also provided research funding for Catheter-based renal denervation for chronic kidney disease and end-stage renal disease (NHMRC references 1046594 and 1052470, respectively).

Australian Hospitals are taking part in the Global Symplicity[®] Registry (Clinicaltrials.gov Identifier: NCT01534299) (The Alfred Hospital St. Vincent's Hospital in Melbourne; Geelong; John Hunter Hospital in Newcastle; the St George and Royal Prince Alfred Hospitals in Sydney; Princess Alexandra Hospital in Brisbane; and the Royal Perth Hospital and Sir Charles Gairdner Hospital in Perth).

Boston Scientific's Vessix[™] renal denervation system has been trialled at multiple international sites including in Australia (REDUCE HTN, NCT01541865) at St. Vincent's Hospital (New South Wales), The Prince Charles Hospital (Queensland), Royal Adelaide Hospital and Flinders Medical Centre (South Australia) and Monash Cardiovascular Research Centre (Victoria).

Australian centres have participated in all of St Jude Medical’s EnligHTN™ system’s clinical trials (EnligHTN 1 NCT01438229, EnligHTN II NCT01705080, EnligHTN III NCT018362146). These are the Royal Adelaide Hospital, Flinders Medical Centre, St Andrew’s Hospital (South Australia), Monash Heart, Monash University, St. Vincent’s Hospital (Victoria).

Regulatory status

A number of radiofrequency ablation devices are listed on the ARTG (Table 2). Of these the devices by St. Jude, Pacific Clinical Research Group, Covidien and Medtronic are specifically listed to denervate the human kidney. Pacific Clinical Research Group’s Vessix Vascular V2 is the only ARTG listed device listed explicitly for treatment-resistant hypertension. Devices from Medtronic, Covidien, St. Jude and Pacific Clinical Research Group (Boston Scientific) have all commenced clinical trials.

The Vessix Vascular V2 system is classified under ‘catheter, angioplasty, radiofrequency, thermal. All other devices are classified under ‘generator, lesion, radiofrequency’.

Currently no ultrasound-based renal denervation device is listed on the ARTG.

Table 2 Australian regulatory status of catheter-based ablative devices for use in the renal arteries

ARTG no.	Sponsor	Item Description	Product Category
186730	Medtronic Australasia Pty Ltd	Ardian Symplicity® Catheter System is intended to deliver low-level radiofrequency energy through the wall of the renal artery to denervate the human kidney . The System may consist of a generator (to deliver the controlled radiofrequency energy at specific power, temperature and time settings) with its power cord, a foot pedal and an extension cable.	Medical Device Class IIb
198986	Medtronic Australasia Pty Ltd	Symplicity® Catheter System is intended to deliver low-level radiofrequency energy through the wall of the renal artery to denervate the human kidney . The System may consist of a generator (to deliver the controlled radiofrequency energy at specific power, temperature and time settings) with its power cord, a foot pedal and an extension cable.	Medical Device Class IIb
198985	Medtronic Australasia Pty Ltd	Symplicity® Catheter System is intended to deliver low-level radiofrequency energy through the wall of the renal artery to denervate the human	Medical Device Class IIb

ARTG no.	Sponsor	Item Description	Product Category
		kidney.	
170236	Medtronic Australasia Pty Ltd	The Symplicity® System is intended to deliver low-level radiofrequency energy through the wall of the renal artery to denervate the human kidney.	Medical Device Class IIb
200781	Covidien Pty Ltd	The generator delivers low-level radiofrequency energy through the wall of the renal artery to denervate the human kidney. The System may consist of a generator (to deliver the controlled radiofrequency energy) with its AC power cord.	Medical Devices Class I
201773	Covidien Pty Ltd	The generator delivers low-level radiofrequency energy through the wall of the renal artery to denervate the human kidney. The System may consist of a generator (to deliver the controlled radiofrequency energy) with its AC power cord.	Medical Devices Class IIb
198878	St Jude Medical Australia Pty Ltd	The RF Ablation Generator is intended to deliver RF energy to the Renal Artery Ablation Catheter	Medical Device Class IIb
197340	St Jude Medical Australia Pty Ltd	The ablation catheter is indicated for use in renal denervation procedures for the treatment of hypertension.	Medical Device Class IIb
200215	Pacific Clinical Research Group Pty Ltd	The Vessix Vascular V2 Renal Denervation System is intended to be used to treat patients with medication-resistant hypertension. The Vessix Vascular V2 Catheter is NOT intended for use in any artery other than the renal artery and is designed and intended to be used ONLY with the Vessix Vascular V2 Generator.	Medical Device Class IIb

Patient population

Catheter-based renal denervation is proposed for patients with elevated, uncontrolled systolic blood pressure (above target levels), despite compliance with three or more antihypertensive drugs, including a diuretic.

Compliance with prescribed antihypertensive drug regime will be confirmed and secondary causes of hypertension and possible contributing factors will be excluded before the patient is classified as treatment-resistant hypertension and considered potentially eligible for renal denervation, where treatment is consistent with Heart Foundation Guidelines (2010). PASC acknowledges that it may be impossible to rule out non-compliance to specific aspects of previous treatment (such as weight loss or adherence to lifestyle changes). However, by the time that a patient is considered to be 'treatment resistant' in line with current guidelines they will have realistically failed all current therapy, and all possible causes of uncontrolled blood pressure

should be addressed as part of the current hypertension management guidelines. In addition, PASC recognises that patients who are unable to adhere to medication due to intolerance or cognitive difficulties could also benefit from the proposed service.

In terms of further tests to more accurately define the eligible population, other tests (such as the MSNA and spill-over tests) are not simple to perform and are restricted to a few research centres. Therefore the patients who would respond best to the procedure are those simply with high blood pressure readings in whom other causes of hypertension have been excluded and who are unresponsive to treatment.

The following population has currently been excluded from consideration for the proposed service in this DAP:

- Patients whose blood pressure is controlled but requires at least four antihypertensive medications.

PASC acknowledges that patients with renal impairment (eGFR < 45ml/min/1.73m²) were excluded in the published trials. However, when applied with clinical discretion catheter-based renal denervation may be able to provide an option in this population. Any evidence regarding the use of renal nerve denervation in this population should be provided separately.

Proposed MBS listing

Table 3: Proposed MBS item descriptor for catheter-based renal denervation for treatment-resistant hypertension

Category 3 – Therapeutic Procedures	
MBS XXXXX	Endovascular ablation of renal sympathetic nerves under image guidance (angiography) in patients with treatment-resistant hypertension who have been investigated and treated according to hypertension management guidelines. Includes angiography. One service only. (Anaes.) Fee: \$2098.45

Notes regarding the MBS listing:

- The proposed listing is broad and includes any approved endovascular ablative device.
- This treatment is to be offered as a once-in-a-lifetime service, unless evidence to the contrary becomes available. It has been established that assistant services are not required, and anaesthetist services may be required.
- The applicant has suggested a total time for the proposed service as approximately 2-2:15 hours, including 45 minutes pre-service, 60 minutes for the procedure, and 15-30 minutes post-service. The assessment phase should provide evidence regarding the mean times for the ablation, for the procedure and for the service.
- The applicant has suggested MBS item 38287 (ablation of arrhythmia circuit or focus or isolation procedure involving one atrial chamber) as an existing item which closely resembles the proposed service in terms of complexity and time. Item 38287 was the basis for the fee for the proposed item. PASC agrees that this is an appropriate item from which to consider the proposed service.
- As the procedure of renal denervation requires the use of angiography as part of the service delivery, this item and the associated fee should include the angiography component.
- A fit-for-purpose input-based assessment of this fee should be undertaken. This should include both the provision of catheter-based renal denervation and angiography. As a result the fee may vary from that shown above.
- An Explanatory Note may need to be provided to elaborate on the MBS item descriptor, for example to provide a clear definition of treatment-resistant hypertension.

Clinical place for proposed intervention

Hypertension can lead to significant health problems. Hypertension plays a major role in the aetiology of many cardiovascular diseases such as stroke, ischemic heart disease, chronic kidney disease and heart failure (National Heart Foundation 2010, Dubow & Fink 2011).

The 1999–2000 Australian Diabetes, Obesity and Lifestyle Study estimated that around 3.7 million Australian over the age of 25 had high blood pressure or were on medication for the condition (AIHW 2010). Self-reports from the Australian Bureau of Statistics Nation Health Survey (NHS) of 2004–05 estimated this number to be 2.1 million, corresponding to 11 per cent of the population (ABS 2006). It should be noted that self-reported data typically underestimates disease prevalence (Knox 2008). Most recent, the results from a National Blood Pressure Screening Day determined the prevalence of hypertension was approximately 34% (Carrington et al. 2010). Among indigenous Australians aged ≥ 35 years the rate of hypertension was found to be 22% (ABS 2006) and a study of general practice activity in Australia showed that high blood pressure is the most common problem managed by a general practitioner (6%) (AIHW 2010).

The 2004–05 NHS found that the prevalence rates for hypertensive disease increased with age, with 14% of those aged 45–54 years reporting the disease compared to 41% for those aged 75 years and over (ABS 2006). Every year 3% of the adult population develops hypertensive disease with the risk increasing from 1% for those aged between 25 and 34 years to 8% for those aged between 65 and 74 years (ABS 2006).

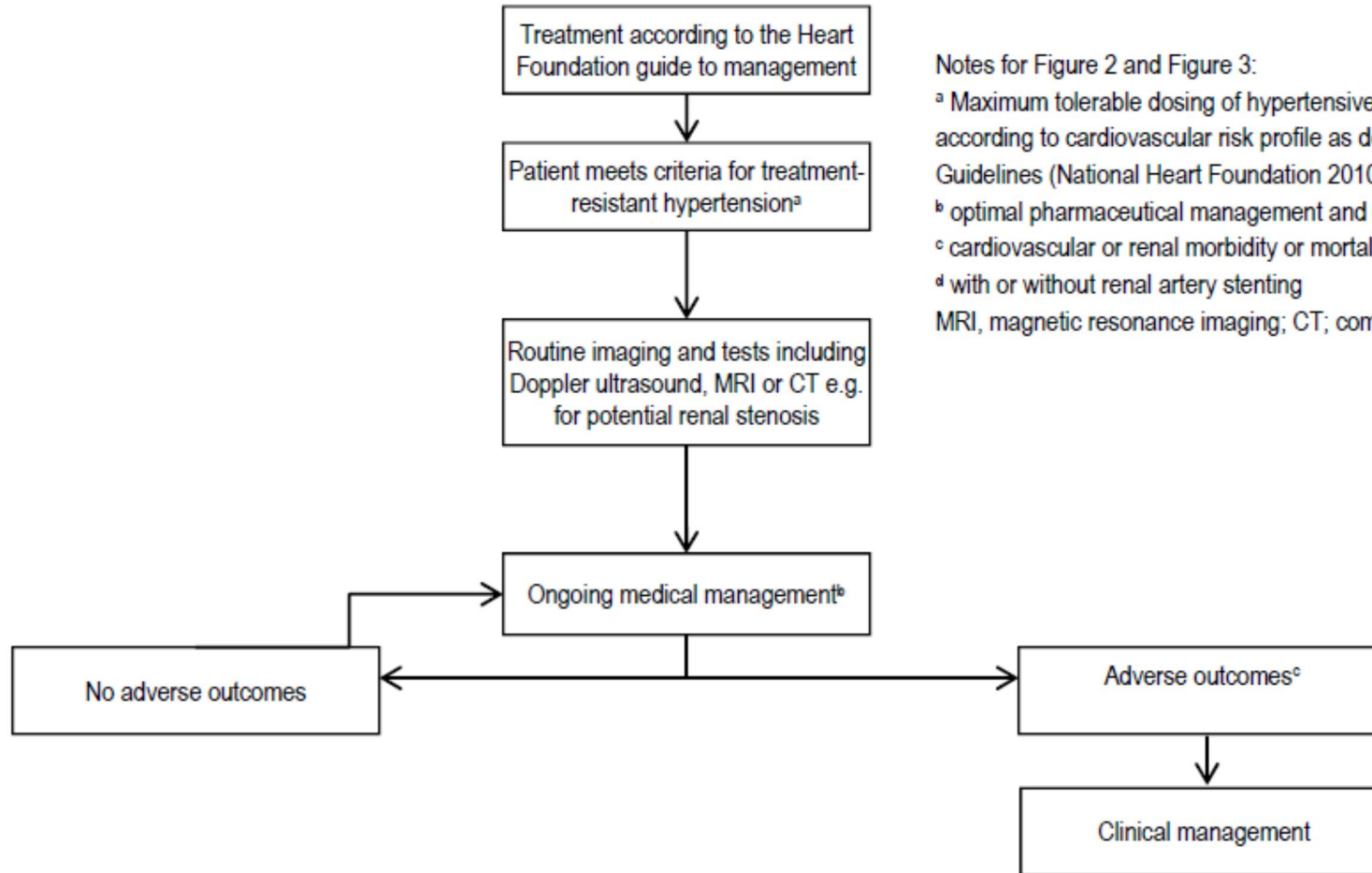
The prevalence of resistant hypertension overall is not well understood. Estimates range from as little as 5% in general practice to 50% in nephrology clinics (Kaplan 2005). At present it is believed 15 – 30% of all treated hypertensive patients may be treatment-resistant (Pimenta & Calhoun 2012). Cohort data from the United States of America suggests that approximately 16.2 per cent of hypertension patients meet the definition of treatment resistant hypertension (blood pressure remains uncontrolled despite being on more than three medications) (Egan et al 2009).

At present, it is difficult to determine the proportion of Australians with treatment-resistant hypertension eligible for renal denervation. In the Symplicity HTN-2 trial 44 per cent of treatment-resistant hypertension patients were excluded for reasons including non-compliance, unsuitable anatomy, patient preference, and other reasons (Symplicity HTN-2 Investigators 2010). Similarly, Savard et al (2012) determined from a patient cohort admitted to hospital for hypertension only 7.4% met the criteria for treatment-resistant hypertension with only 1.2% deemed eligible renal denervation.

Two clinical decision pathways are provided. Figure 2 shows the current clinical management algorithm. Figure 3 shows the proposed clinical management algorithm. Issues that have informed the algorithms include:

- Doppler ultrasound is the most common imaging to determine renal artery anatomy and eligibility for the service.
- Other recent images may commonly be available (e.g. as part of standard patient assessment for hypertension). This may include Doppler ultrasound, MRI, CT, MRA or CTA. In these cases additional imaging for eligibility for the service is not required.
- The algorithm allows for rare cases where initial angiography during service delivery shows that renal artery anatomy is not appropriate for renal nerve denervation. In this case the MBS item for abandoned surgery could be claimed (item 30001).
- The algorithm allows for rare cases where due to previously unrecognised renal artery stenosis a renal artery stent may be applied as part of the renal denervation service. This is also considered to be a rare event as appropriate renal artery anatomy would have usually been clearly established through previous imaging studies.
- Ongoing medical management would include standard care for hypertension.
- Clinical management for adverse outcomes would include hospitalisation for stroke, heart failure, other emergency procedures and recovery.

Figure 2: Current clinical management algorithm for treatment-resistant hypertension



Notes for Figure 2 and Figure 3:

^a Maximum tolerable dosing of hypertensive drug therapy with patient managed according to cardiovascular risk profile as described in the Heart Foundation Guidelines (National Heart Foundation 2010) on hypertension management.

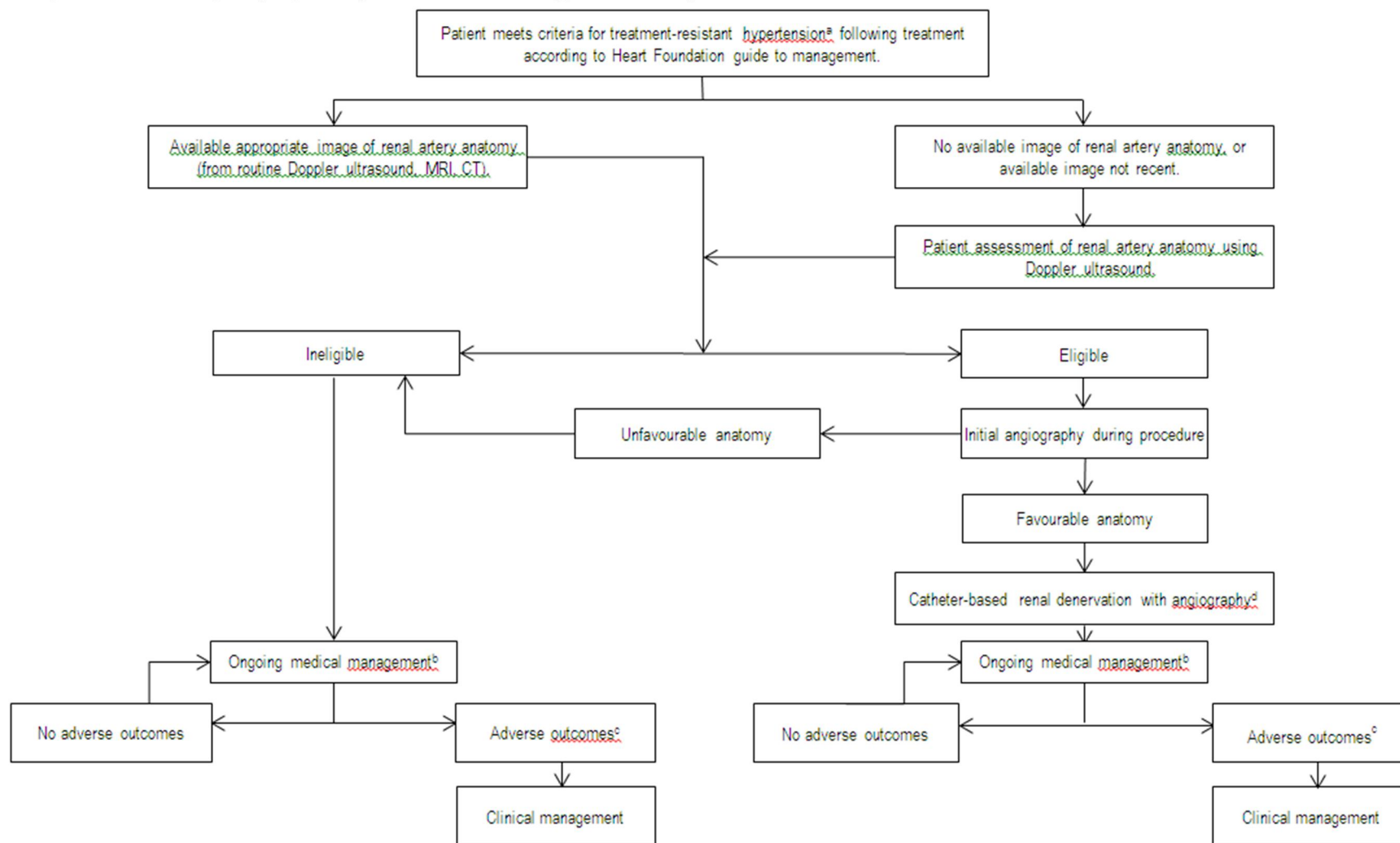
^b optimal pharmaceutical management and ongoing monitoring

^c cardiovascular or renal morbidity or mortality

^d with or without renal artery stenting

MRI, magnetic resonance imaging; CT; computed tomography

Figure 3: Proposed clinical management algorithm for treatment-resistant hypertension



Comparator

Optimal medical management, including:

- Pharmaceutical management with different classes of anti-hypertensive medication.
- Ongoing monitoring.

The Heart Foundation guidelines recommend ACE inhibitors (ACEI) or angiotensin II receptor blockers (ARB), dihydropyridine calcium channel blockers, and low dose thiazide diuretics. The most effective combination is ACE inhibitor with calcium channel blocker (National Heart Foundation 2010). Expert clinical input has confirmed that the most common medications used by patients with treatment-resistant hypertension are ACEI, ARB, calcium channel blockers, beta blockers and diuretics.

Clinical claim

Denervation combined with optimal medical management is superior to optimal medical management alone in reducing elevated blood pressure. Improving blood pressure to target levels will improve patient's quality of life by avoiding morbidity related to stroke, coronary heart disease, heart failure and chronic kidney disease.

A table summarising the economic evaluation to be presented is shown below (Table 4).

Table 4: Classification of an intervention for determination of economic evaluation to be presented

		Comparative effectiveness versus comparator				
		Superior		Non-inferior	Inferior	
Comparative safety versus comparator	Superior	CEA/CUA		CEA/CUA	Net clinical benefit	CEA/CUA
					Neutral benefit	CEA/CUA*
					Net harms	None^
	Non-inferior	CEA/CUA		CEA/CUA*	None^	
	Inferior	Net clinical benefit	CEA/CUA	None^	None^	
		Neutral benefit	CEA/CUA*			
Net harms		None^				

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

The modelling should account for base case and sensitivity analyses as shown in the DAP.

Other relevant literature

The following section provides a summary of some relevant literature that was available during the initial drafting of this DAP. Please note that a comprehensive review, including a critique of studies and relevance to the Australian context, will be undertaken as part of the assessment phase.

A horizon scanning prioritising summary in 2010 by HealthPACT concluded that 'renal denervation may be a viable option for the treatment of resistant hypertension'. However, a recommendation was made for the device to be reviewed in 24 months' time due to the lack of randomised control trials (Department of Health and Aging 2010).

The National Institute of Health and Clinical Excellence in the United Kingdom recently published recommendations with regards to the catheter-based renal denervation. They recommend patient selection should be carried out by a multidisciplinary team including a physician with expertise in hypertension and a specialist in endovascular interventions, giving considerations to the number of antihypertensive drugs that have failed to control the patient's blood pressure and the anatomical suitability of their renal arteries. The procedure should only be done by specialists who are experienced in endovascular interventions and with facilities for emergency stenting in case this is required. They also suggest that there is inadequate evidence on efficacy in the long term; this is particularly important for a procedure aimed at treating resistant hypertension. The limited evidence suggests a low incidence of serious periprocedural complications, but there is inadequate evidence on long-term safety. Therefore this procedure should only be used with

special arrangements for clinical governance, consent, and audit or research (NICE 2012).

The French Scientific Society (Cardiology, Radiology and Hypertension) proposed to limit renal denervation to patients with uncontrolled hypertension who are receiving four or more anti-hypertensives with at least one diuretic or spironolactone. Additionally, patient's office and ambulatory blood pressure measurement must be greater than 160/100 mm Hg and 135/85 mm Hg with correct renal artery function and anatomy. Optimal medical management must not be interrupted during recovery from renal denervation because its effects can be delayed up to 3 months. Patients' blood pressure, renal function and anatomy should be monitored for 12-36 months after the procedure. The society cautioned that in the absence of long term safety data the efficacy of the procedure remains to be determined. The society also noted that 10% of patients who underwent the Symplicity HTN-2 trials showed no benefit from renal denervation and for the majority of participants, their anti-hypertensive medications had not decreased (Pathak et al 2012).

Outcomes and health care resources affected by introduction of proposed intervention

Outcomes

Primary outcomes include:

- Clinical outcomes of cardiovascular or renal disease (e.g. stroke; heart failure)
- Systolic and diastolic blood pressure (including initial and final blood pressure, and change in blood pressure). The means by which blood pressure is measured needs to be reported: e.g. whether this is ambulatory blood pressure monitoring or office blood pressure monitoring
- Quality of life
- Mortality

Secondary outcomes include:

- Failure rate
- Repeat or additional procedures
- Cardiac function (e.g. central hemodynamics, left ventricular hypertrophy)
- Change in medication

- Change in health care resources (e.g. visits to specialists for ongoing monitoring or for co-morbidities)
- Renal function (such as estimated glomerular filtration rate (eGFR), serum creatinine, urinary protein excretion)
- Hospitalisations
- Stent insertion

Adverse events

- Including but not limited to:
- Pseudoaneurysm
- Backpain
- Renal artery dissection
- Hypotension
- Mortality

The main outcome for modelling purposes should be any change in cardiovascular disease. The change in blood pressure is an appropriate surrogate for this main clinical outcome. The modelling should allow for uncertainty regarding this outcome.

The assessment will need to record the following information relevant to resource use:

- Number of runs of digital subtraction angiography used per procedure.
- The type of imaging (e.g. digital subtraction angiography) used immediately following the procedure and during service provision to confirm the absence of damage to the renal artery.
- Any requirement of an assistant.
- The presence or absence of a radiographer to determine patient suitability and to assist guiding the catheter.
- Use of an anaesthetist; use and type of anaesthesia.
- Time of the ablation.
- Time of the entire procedure.
- The proportion of patients who receive the service as a day procedure compared to patients who remain in hospital overnight.

Health care resources

The health care resources required to provide the service include:

- The diagnostic tests confirming resistant hypertension (base case is that these resources remain unchanged compared to current care)
- Specialist to provide the intervention
- Possible use of an assistant (noting that the base case is that an assistant is not required)
- Possible requirement of general anaesthesia (noting that the base case is for the use of conscious sedation)
- Possible use of an anaesthetist (noting that some jurisdictions require the attendance of an anaesthetist for conscious sedation)
- Nursing staff to assist before, during and after the procedure
- Hypertension specialist/clinician to provide ongoing optimal medical management (remain unchanged compared to current care)
- Diagnostic tests (renal function, blood pressure, central hemodynamics, left ventricular hypertrophy) (remain unchanged compared to current care)
- Standard angiography laboratory equipment.

The procedure has been reported to cost between \$8,000 and \$10,000 per patient according to an interview with Professor Robert Whitbourn of St Vincent's Public Hospital, Melbourne (Australian Broadcasting Corporation 2011).

A list of resources associated with the intervention and comparator is shown in Table 5. Note that this list may not be comprehensive. PASC acknowledges that hospital-based diagnostic and pathology services would not be required as an additional resource following the proposed intervention. These tests would be part of standard care to all patients with treatment-resistant hypertension.

Table 5: List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Number of units of resource per relevant time horizon per patient receiving resource	Source of information of number of units*
<u>Resources provided to identify the eligible population that would vary from current clinical practice (from Step 2, e.g., diagnostic and other investigative medical services, prior therapeutic interventions).</u>				
- No additional resources required (see Heart Foundation Guidelines)	n/a	n/a	n/a	n/a

	Provider of resource	Setting in which resource is provided	Number of units of resource per relevant time horizon per patient receiving resource	Source of information of number of units*
- Imaging to assess renal vascular anatomy (duplex ultrasound). This may or may not be an additional resource (previous appropriate images may be available)	MBS	-	1 service	-
Resources provided in association with the proposed medical service to deliver the proposed intervention (from Step 1, e.g., pre-treatments, co-administered interventions).				
- Patient monitoring	Private or Public Hospital	Catheterization laboratory	Equipment for monitoring blood pressure, heart rate & oxygenation	-
- Nursing and technician support	Private or Public Hospital	Catheterization laboratory	Nursing and technician support for duration of renal denervation procedure	-
- Medication	Private or Public Hospital	Catheterization laboratory	Medication and dosage during the procedure is tailored to individual patient circumstances, but likely to include anxiolytic and amnestic medication; anticoagulants; pain medication and vasodilators	-
- Consumables	Private or Public Hospital	Catheterization laboratory	1 set of consumables, including renal denervation catheter and other disposables required for endovascular procedures.	-
- Radiology (angiography)	MBS	Catheterization laboratory	1 service which should be included as part of the fee for the proposed service	-
- Anaesthetist	MBS	Catheterization laboratory	Attendance varies according to jurisdictional guidelines and requirement of general anaesthetic	-
- Renal artery stent	Private or Public Hospital	Catheterization laboratory	Possible 1 service; MBS 35309	-
- Hospitalisation for procedure, including pre-procedure admission and post-procedure overnight stay	Private or Public Hospital	Private or Public Hospital	1 inpatient episode (overnight stay) or day case	-
- Diagnostic and pathology services (including tests for urea (66500), electrolytes, full blood exam)	MBS	Private or Public Hospital	1 service for each required test	-

	Provider of resource	Setting in which resource is provided	Number of units of resource per relevant time horizon per patient receiving resource	Source of information of number of units*
- Emergency procedures in adverse events	?	?	?	-
Resources provided to deliver the comparator to deliver the current intervention (from Step 4, e.g., pre-treatments, co-administered interventions).				
Clinician consultation	MBS	Private or Public Hospital; General Practice; out-patient clinic (setting will vary depending on patient co-morbidities and required clinical management)	;	;
- Anti-HTN drug therapy	PBS	Out-patient	Drug regimen, including dosage and number of therapies, determined by clinician	PBS
- Diagnostic and pathology services	MBS, Medicare	Private or Public Hospital; out-patient clinic	;	;
Resources provided following the proposed intervention with the proposed medical service (from Step 8, e.g., resources used to monitor or in follow-up, resources used in management of adverse events, resources used for treatment of down-stream conditions conditioned on the results of the proposed intervention).				
Healthcare resources listed below apply to the ongoing management of hypertension				
Clinician consultation (for blood pressure monitoring)	MBS	Private or Public Hospital; General Practice; out-patient clinic (setting will vary depending on patient co-morbidities and required clinical management)	Frequency of consultations likely to depend on co-morbidity type and symptom severity	
- Anti-HTN drug therapy	PBS	Out-patient	Drug regimen, including dosage and number of therapies, determined by clinician	PBS
- Diagnostic and pathology services	MBS, Medicare	Private or Public Hospital; out-patient clinic	-	-
Healthcare resources listed below apply to the management of cardiovascular and renal morbidity				
- Hospital or community-based treatment, which may include: surgical	-	-	-	-

	Provider of resource	Setting in which resource is provided	Number of units of resource per relevant time horizon per patient receiving resource	Source of information of number of units*
therapy +/- prostheses (e.g. coronary stents); drug therapies; physiotherapy; kidney dialysis (hospital; home or dialysis – satellite – clinic)				
- Diagnostic and pathology services	-	-	-	-
Clinician consultation	-	-	-	-
- Rehabilitation services	-	-	-	-
- Community based services (residential care; allied health; home nursing; carers; ambulance etc.)	-	-	-	-
Resources provided following the comparator to deliver the current intervention (from Step 7, e.g., resources used to monitor or in follow-up, resources used in management of adverse events, resources used for treatment of down-stream conditions conditioned on the results of the proposed intervention).				
Healthcare resources listed below apply to the ongoing management of hypertension,				
Clinician consultation	MBS	Private or Public Hospital; General Practice; out-patient clinic (setting will vary depending on patient co-morbidities and required clinical management)	Frequency of consultations likely to depend on co-morbidity type and symptom severity	-
- Anti-HTN drug therapy	PBS	Out-patient	Drug regimen, including dosage and number of therapies, determined by clinician	PBS
- Diagnostic and pathology services	MBS, Medicare	Private or Public Hospital; out-patient clinic	-	-
Healthcare resources listed below apply to the management of cardiovascular and renal morbidity:				
Hospital or community-based treatment, which may include: surgical therapy +/- prostheses (e.g. coronary stents); drug therapies; physiotherapy; kidney dialysis (hospital; home or	-	-	-	-

	Provider of resource	Setting in which resource is provided	Number of units of resource per relevant time horizon per patient receiving resource	Source of information of number of units*
dialysis – satellite – clinic)				
Diagnostic and pathology services	-	-	-	-
Clinician consultation	-	-	-	-
Rehabilitation services	-	-	-	-
Community based services (residential care; allied health; home nursing; carers; ambulance etc.)	-	-	-	-

Issues associated with resources:

- From the Pharmaceutical Benefits Schedule anti-hypertension medication range in cost from \$49.11 to \$106.82 for three anti-hypertensive medications, one of which is a diuretic. These costs will be dependent on whether the medications are needed daily, weekly or monthly.
- The majority of cases could be performed without the requirement of general anaesthesia.
- Some jurisdictions require the attendance of an anaesthetist for conscious sedation. This requirement should be confirmed during the assessment.
- Expert clinical input has confirmed that only one specialist clinician would normally be involved with providing the ablation service.
- Expert clinical input has suggested that renal complications as a result of the procedure are rare and of low severity. Stenting may be required in the event of a dissection.
- For morning cases, most patients would be discharged at the end of the day. For afternoon cases, most patients would remain hospitalised overnight for post-procedure management and monitoring. The evidence regarding hospital stay should be provided.
- On-going management and standard care with various specialists would continue for both intervention and comparator arms.

- Healthcare resources associated with the clinical management of: stroke; coronary heart disease; heart failure; chronic kidney disease and end-stage renal disease would include:
 - Hospital or community-based treatment, which may include: surgical therapy +/- prostheses (e.g. coronary stents); drug therapies; physiotherapy; kidney dialysis (hospital; home or dialysis – satellite – clinic)
 - Hospital or community based rehabilitation
 - Hospital or community based diagnostic and pathology services
 - Hospital or community based clinical consultations
 - Community-based services (residential care, allied health, home nursing, carer support; ambulance etc.)

Proposed structure of economic evaluation (decision-analytic)

Table 6 summarises the population, intervention, comparator and outcomes of catheter-based renal denervation for treatment-resistant hypertension.

Table 6: Summary of extended PICO to define research question that assessment will investigate

Population	Intervention	Comparator	Outcomes
<p>Patients with confirmed treatment-resistant hypertension (uncontrolled, elevated blood pressure, despite treatment with 3 or more anti-hypertensive medications (including a diuretic) in whom other causes of hypertension have been excluded).</p> <p>Sub-population:</p> <ul style="list-style-type: none"> Any evidence regarding the use of renal denervation in patients with eGFR < 45ml/min/1.73m² should be provided separately. <p>Excluded:</p> <ul style="list-style-type: none"> Patients whose blood pressure is controlled but requires at least four antihypertensive medications. 	<p>Catheter-based renal denervation in addition to optimal medical management</p> <p>Included:</p> <ul style="list-style-type: none"> Any ablative device designed for use in the renal arteries. <p>Evidence regarding different types of devices (e.g. RFA-based, ultrasound-based) should be provided in a generic manner where possible.</p> <p>However, PASC recognises that each device is quite distinct from other similar technologies and may have a different clinical safety and effectiveness profile.</p> <p>Due to the differences between devices and brands, the assessment must provide evidence regarding the safety and effectiveness of each catheter separately to enable MSAC to determine whether devices are equivalent in their clinical utility. Any evidence regarding the equivalence of safety and effectiveness of one catheter to another should be presented.</p>	<p>Optimal medical management</p>	<p>Clinical outcomes of cardiovascular or renal disease</p> <p>Systolic and diastolic blood pressure</p> <p>Quality of life</p> <p>Mortality</p> <p>Also secondary and safety outcomes as listed in 'Outcomes' section above</p>

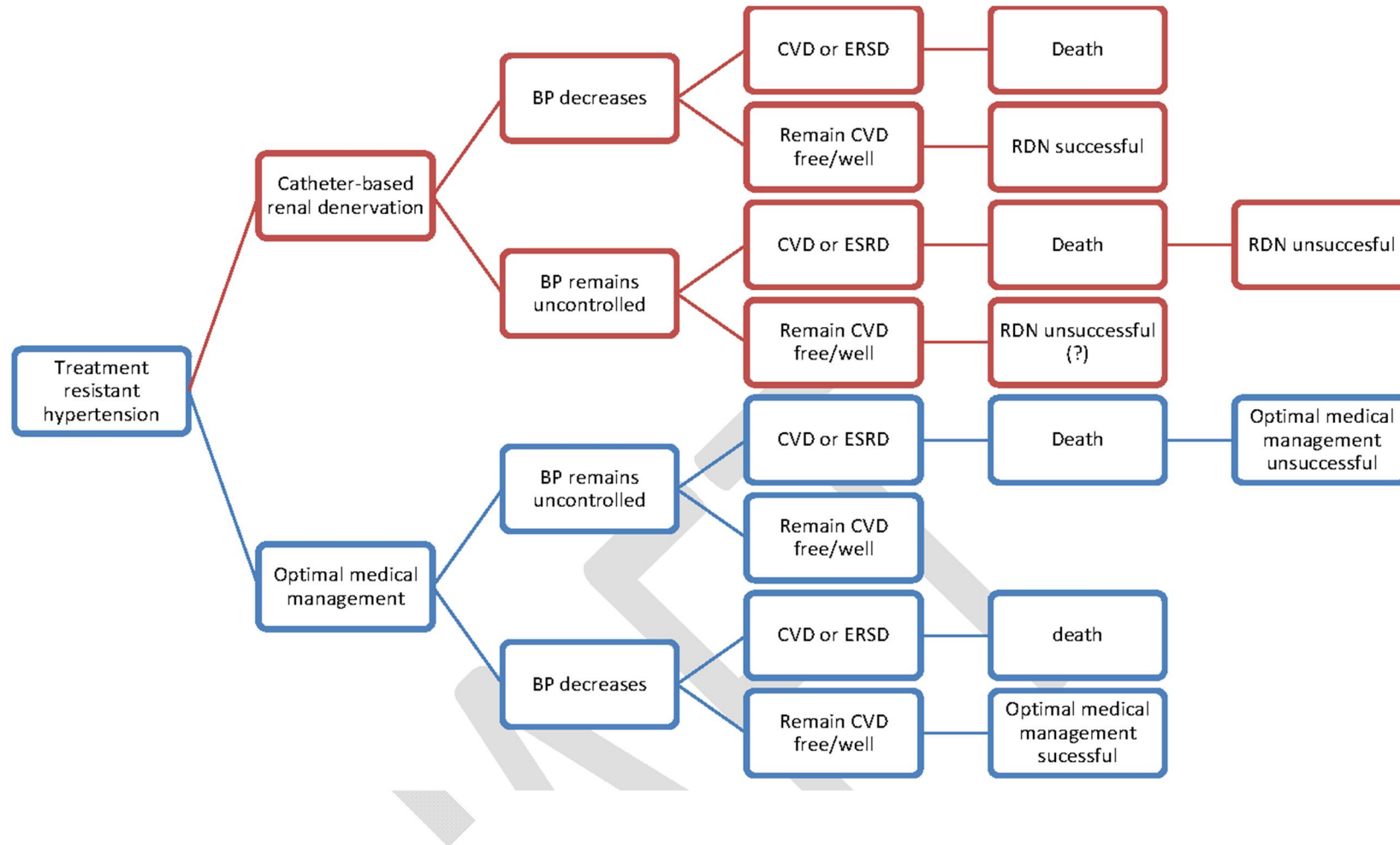
Primary questions for public funding

- From local data, what proportion of people in Australia fit the definition of treatment-resistant hypertension, and of this population how many would be eligible for the proposed service?
- What is the safety of catheter-based renal denervation in addition to optimal medical management in patients with treatment-resistant hypertension compared to optimal medical management alone? This information should be provided for each group of devices (e.g. RFA devices, ultrasound devices, any other ablative device designed specifically for use in the renal arteries).
 - Secondary question for safety of catheter-based renal denervation: PASC recognises that each manufactured device (e.g. for RFA) is unique and may have a different clinical and technical profile to other devices and brands in the same group. What is the evidence-base for each device, and are all devices equivalent in terms of safety?
- What is the effectiveness of catheter-based renal denervation in addition to optimal medical management in patients with treatment-resistant hypertension compared to optimal medical management alone? This information should be provided for each group of devices (e.g. RFA devices, ultrasound devices, any other ablative device designed specifically for use in the renal arteries).
 - Secondary question for effectiveness of catheter-based renal denervation: PASC recognises that each manufactured device (e.g. for RFA) is unique and may have a different clinical and technical profile to other devices and brands in the same group. What is the evidence-base for each device, and are all devices equivalent in terms of effectiveness?
- For which devices are evidence available regarding safety and effectiveness?
- What is the cost-effectiveness of catheter-based renal denervation in addition to optimal medical management in patients with treatment-resistant hypertension compared to optimal medical management alone? This information should be provided for each group of devices (e.g. RFA devices, ultrasound devices, any other ablative device designed specifically for use in the renal arteries).

- Sensitivity analyses should account for any identified clinically relevant differences between devices or brands (e.g. number of angiography runs, procedural time etc.).

FEMNAL

Decision analytic



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