# *Real-time measurement of cardiac output and other cardiac flow parameters (without concurrent cardiac imaging) using continuous wave Doppler techniques*

**June 2009**

MSAC application 1117

**Assessment report**

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

**MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.**

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## The procedure

Continuous wave Doppler ultrasound without imaging is a non-invasive monitoring tool for real-time measurement of cardiac output and other cardiac flow parameters. This technology measures cardiac output by detecting and measuring blood flow velocity and direction. The Doppler shift is dependent on the frequency and velocity of blood movement and the angle between the sound beam and direction of moving blood. Information from reflected sound waves can be computer analysed to provide graphs or images that represent blood flow through vessels.

USCOM (manufactured by USCOM Limited) is a non-invasive device that uses continuous wave Doppler ultrasound technology. It is designed and intended for use in a number of settings for patients who may require cardiac output measurement for haemodynamic monitoring.

## Medical Services Advisory Committee—role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the 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.

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. A team from IMS Health was engaged to conduct a systematic review of literature on non-invasive continuous wave Doppler ultrasound for real-time measurement of cardiac output. An advisory panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

## MSAC's assessment of non-invasive continuous wave Doppler ultrasound for real-time measurement of cardiac output

### Clinical need

Continuous wave Doppler ultrasound technology without imaging enables non-invasive measurement of cardiac output in a variety of settings and patient populations. Settings include adult and paediatric intensive care units, coronary care units, emergency departments, anaesthetics and intra-operative setting. It may also be used for patients with biventricular pacemakers who require device optimisation.

Cardiac output provides an indication of oxygen consumption and delivery to body tissues. Low or inadequate cardiac output can result in cellular hypoxia and creates potential for adverse effects in tissues and organs. Determining adequate cardiac function is regarded as an important component of haemodynamic monitoring and one that can

directly influence patient outcomes among post-operative both cardiac surgery and critically ill patients in intensive care units (Arora et al 2007, Chand et al 2006, Knobloch et al 2005).

## Research questions

The research questions addressed were:

### Non-invasive continuous wave Doppler ultrasound for patients in emergency care settings who require haemodynamic monitoring

To what extent is non-invasive continuous wave Doppler ultrasound safe, effective and cost-effective in the monitoring of patients in emergency care who require haemodynamic monitoring in addition to standard clinical care?

### Non-invasive continuous wave Doppler ultrasound for adult patients in intensive care who require haemodynamic monitoring

To what extent is non-invasive continuous wave Doppler ultrasound safe, effective and cost-effective in the monitoring of adult patients in intensive care who require haemodynamic monitoring relative to thermodilution for measuring haemodynamics in this setting?

### Non-invasive continuous wave Doppler ultrasound for paediatric patients in intensive care who require haemodynamic monitoring

To what extent is non-invasive continuous wave Doppler ultrasound safe, effective and cost-effective in the monitoring of paediatric patients in intensive care who require haemodynamic monitoring relative to PiCCO (continuous cardiac output) or thermodilution for measuring haemodynamics in this setting?

### Non-invasive continuous wave Doppler ultrasound for in coronary care who require haemodynamic monitoring

To what extent is non-invasive continuous wave Doppler ultrasound safe, effective and cost-effective in the monitoring of patients in coronary care who require haemodynamic monitoring relative to thermodilution for measuring haemodynamics in this setting?

### Non-invasive continuous wave Doppler ultrasound for intra-operative patients who require haemodynamic monitoring

To what extent is non-invasive continuous wave Doppler ultrasound safe, effective and cost-effective in the monitoring of intra-operative patients who require haemodynamic monitoring relative to thermodilution for measuring haemodynamics in this setting?

### Non-invasive continuous wave Doppler ultrasound for patients with biventricular pacemakers who require device optimisation

To what extent is non-invasive continuous wave Doppler ultrasound safe, effective and cost-effective in the optimisation of biventricular pacemakers relative to optimisation using echocardiography in this setting?

## Safety

Continuous wave Doppler ultrasound is a non-invasive test. This procedure is not considered to present safety issues for patients. The non-invasive nature of continuous wave Doppler ultrasound means that it is considered to be safer than the thermodilution technique (PAC) which is known to be associated with several safety issues.

## Effectiveness

Comparative evidence was sought to investigate the effectiveness of continuous wave Doppler ultrasound technology for measuring cardiac output in comparison with the chosen comparator (the thermodilution technique was determined to be both the reference standard and comparator test in most situations). Evidence was identified in relation to adult intensive care and intra-operative patient settings.

For tests to be considered comparable, a mean bias of less than 0.5 L/minute and limits of agreement within ± 1.0 L/minute between continuous wave Doppler ultrasound and thermodilution cardiac output measurements were required. This is equivalent to a percentage error of ± 30 per cent (Critchley et al 1999, Van Den Oever et al 2007).

Studies by Arora et al (2007) and Chand et al (2006) conducted in adult intensive care units fulfilled predefined comparability criteria. Both Arora et al (2007) and Chand et al (2006) reported mean bias of less than 0.5 L/minute (–0.13 L/min; 0.14 and 0.03 L/min, respectively), and reported limits of agreement within ± 1.0 L/minute. Therefore, outcomes reported by Arora et al (2007) and Chand et al (2006) provide evidence to suggest that there was equivalence of cardiac output estimations by USCOM continuous wave Doppler ultrasound and thermodilution techniques.

Outcomes reported by Chan et al (2006) and Tan et al (2005) in adult intensive care units did not fulfil comparability criteria. Although mean bias was less than 0.5 L/minute (0.22 and 0.18 L/min, respectively), limits of agreement in both studies exceeded ± 1.0 L/minute. Chan et al (2006) reported a percentage error of ± 52 per cent which substantially exceeds the acceptable error of ± 30 per cent. Evidence presented by Chan et al (2006) and Tan et al (2005) suggest that equivalence with cardiac output estimations by USCOM continuous wave Doppler ultrasound and thermodilution techniques was not demonstrated in the adult intensive care setting.

Knobloch et al (2005) reported a mean bias of less than 0.5 L/minute (–0.23 L/min), but did not report limits of agreement. Knobloch et al (2005) concluded that USCOM continuous wave Doppler cardiac output measurement had agreement with thermodilution measurements in adult intensive care units. However, the absence of limits of agreement and inadequate data reporting meant that a valid assessment of the predefined comparability criteria could not be established.

Knobloch et al (2005) reported no significant differences in cardiac output measurements between USCOM continuous wave Doppler ultrasound and thermodilution in the intra-operative setting. Limits of agreement were not reported. Inadequate data reporting limited the potential to demonstrate that the methods were comparable according to predefined criteria.

Results reported by Van Den Oever et al (2007) indicate a lack of agreement between cardiac output measurements from continuous wave Doppler and thermodilution for intra-operative patients. This study did not fulfil predefined comparability criteria. Although mean bias was less than 0.5 L/minute at the aortic and pulmonary valve (–0.79 and –0.17 L/min, respectively), limits of agreement at both valves exceeded ± 1.0 L/minute of the other test. Evidence presented Van Den Oever et al (2007) suggest that the tests were not considered equivalent in the intra-operative setting.

There were inconsistencies between studies regarding the optimal time required to take USCOM measurements (Tan et al 2005, Van Den Oever et al 2007). Tan et al (2005) required up to 45 minutes for data acquisition in the adult intensive care setting; Van Den Oever et al (2007) allowed no more than 10 minutes for intra-operative patients.

The presented evidence comparing USCOM continuous wave Doppler ultrasound without imaging with the thermodilution technique in the adult intensive care unit setting is inconsistent, and therefore, the equivalence of these tests can not be concluded. At this time, evidence is inconclusive that USCOM continuous wave Doppler ultrasound is comparable with thermodilution measurement. There is doubt concerning clinical utility in the intra-operative setting.

No comparative evidence was identified to enable assessment of continuous wave Doppler ultrasound technology effectiveness to measure cardiac output in haemodynamic monitoring among patients in paediatric intensive care, coronary care, and emergency settings, or for patients with biventricular pacemakers who require device optimisation.

## Cost-effectiveness

The paucity of available clinical evidence meant that it was not possible to conduct a full economic evaluation in the assessment of continuous wave Doppler ultrasound. Cost-effectiveness cannot be properly determined without establishing clinical effectiveness, and therefore, remains speculative.

# Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of non-invasive continuous wave Doppler ultrasound, a monitoring device used for real-time measurement of cardiac output. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for non-invasive continuous wave Doppler ultrasound techniques for real-time measurement of cardiac output.

# Background

## The procedure

Continuous wave Doppler ultrasound without imaging is a non-invasive monitoring tool for real-time measurement of cardiac output and other cardiac flow parameters. This technology measures cardiac output by detecting and measuring blood flow velocity and direction by reflecting sound waves from blood in a vessel. A handheld transducer applied to the skin transmits sound wave signals which are reflected off blood cells. Blood cell movement causes changes in pitch and frequency of reflected sound waves, which is known as the Doppler Effect. Doppler shift is dependent on the frequency and velocity of blood movement and the angle between the sound beam and direction of moving blood. Information from the reflected sound waves is computer analysed to produce graphical images that represent blood flow through vessels.

The USCOM device (designed and manufactured by USCOM Limited) is the only contemporary technology that uses continuous wave Doppler ultrasound without imaging that was appropriate for inclusion in this assessment[1]. It is designed and intended for use in a number of settings where cardiac output measurement for haemodynamic monitoring is required. Settings include adult and paediatric intensive care units, coronary care units, emergency facilities, anaesthetics and intra-operative care units. USCOM may also be used for patients with biventricular pacemakers who require device optimisation.


**Figure 1 Continuous wave Doppler ultrasound device without imaging by USCOM Pty Ltd**

[1] No other comparative technologies that used continuous wave Doppler ultrasound without imaging were identified from the literature search

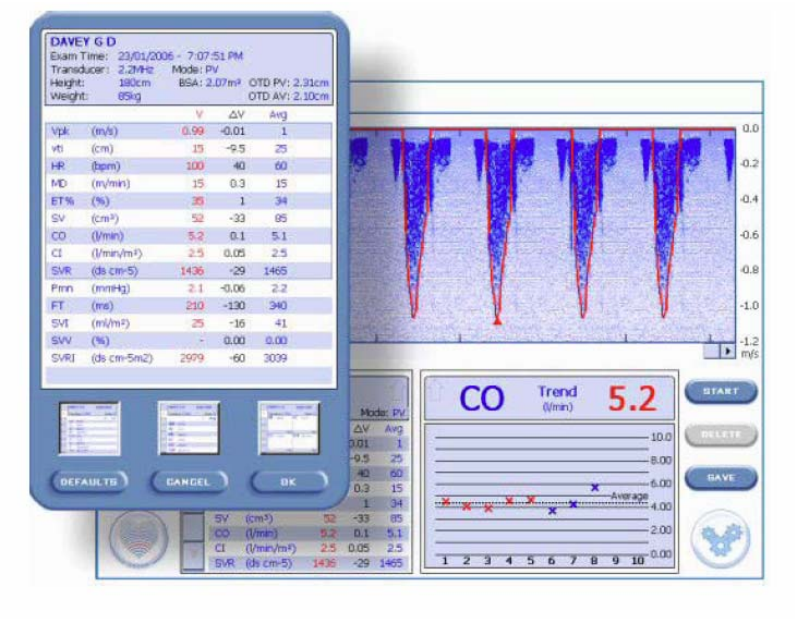


**Figure 2** **Cardiac output reading from monitor of the USCOM device, USCOM Pty Ltd**

Continuous wave Doppler ultrasound technology enables calculation of cardiac output (CO) by applying the formula:

CO = (velocity time integral × cross-sectional area of valve [CSA]) × heart rate

Heart rate and velocity time integral are determined from the Doppler trace which is captured and presented graphically. The cross-sectional area is estimated by applying formulae, derived by Nidorf (Van Den Oever et al 2007), that are integrated in the device's software.

**Cardiac output (CO) at aortic valve—suprasternal position**

d (cm) = 0.010 × height (cm) + 0.25

Aortic valve area (A) = 0.785 × $d^2$ (cm)

CO (1/min) = VTI (cm) × A × HR/1000

**Cardiac output (CO) at pulmonary valve—left parasternal position**

d (cm) = 0.011 × height (cm) + 0.274

Pulmonary valve area (A) = 0.785 × $d^2$ (cm)

CO = VTI (cm) × A × HR/1000

This approach measures left and right sided cardiac output non-invasively. Placing the transducer in the suprasternal position ensures that the ultrasound signal is parallel to blood flow in the ascending aorta. The transducer is placed in the left supraclavicular position to measure cardiac output from the pulmonary valve.

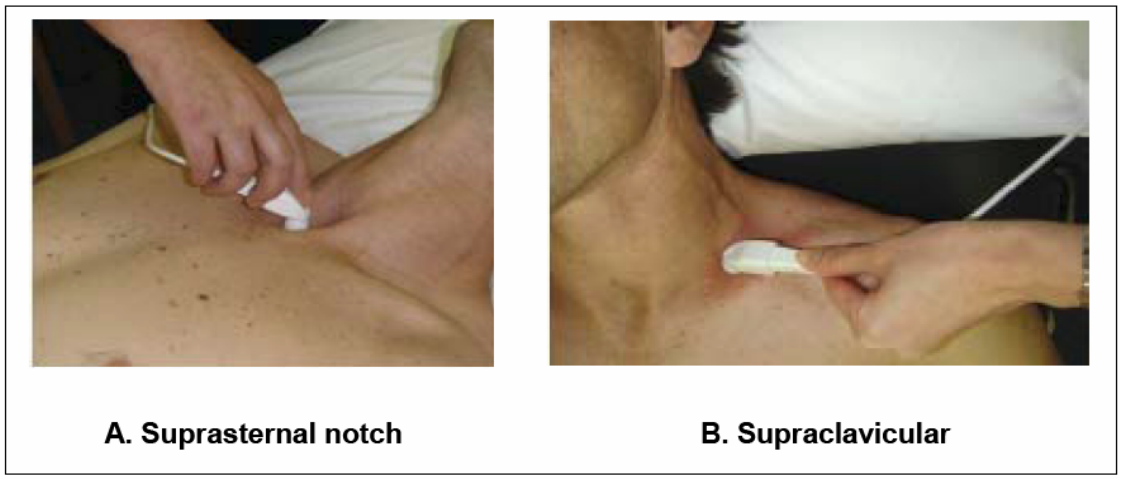


**Figure 3 Probe placements for the USCOM device**

Continuous wave Doppler ultrasound technology enables non-invasive measurement of cardiac output. Cardiac output is defined as the total volume of blood ejected and pumped by the left ventricle per minute (Allsager and Swanevelder 2003, Tibby and Murdoch 2003). Cardiac output is calculated as the product of the heart's stroke volume (the volume of blood ejected by the ventricle in one beat) and the heart rate (the number of beats per minute), expressed as litres per minute. The normal cardiac output range for adults and children (aged 2.5 to 16 years) is 5.0–7.0 L/minute and 3.5–7.0 L/minute, respectively (USCOM Limited 2006). Cardiac index also expresses cardiac output and is derived by dividing the patient's cardiac output by their body surface area. The normal cardiac index range for adults and children (aged 2.5 to 16 years) is 2.4–3.6 L/minute/$m^2$ and 3.4–5.0 L/minute/$m^2$, respectively (USCOM Limited 2006).

Cardiac output provides an indication of oxygen consumption and delivery. Low or inadequate cardiac output can result in cellular hypoxia, which can adversely affect tissues and organs, and increase risk of complications. Determination of adequate cardiac function among post-operative cardiac surgery and critically ill patients in intensive care units is regarded as an important part of haemodynamic monitoring and positive patient outcomes (Arora et al 2007, Chand et al 2006, Knobloch et al 2005). However, advice from key opinion leaders (advisory panel) suggests that the role of cardiac output measurement in the management of patient outcomes or progression of patient management is unclear. Cardiac output measurement alone may not contribute to change in patient management and outcomes.

There is currently some disagreement about the optimal method of measuring cardiac output in the clinical setting (Allsager and Swanevelder 2003). Several invasive and non-invasive methods are currently used to measure cardiac output. Invasive determination of cardiac output by thermodilution using a Swan-Ganz pulmonary artery catheter (PAC) is considered to be the clinical standard, despite uncertainty about its safety and utility, in informing clinical management and improving patient outcomes (Roizen et al 2003).

There has been an increasing interest and preference for use of non-invasive techniques to measure cardiac output. Non-invasive techniques, such as continuous wave Doppler ultrasound technology, have been trialled as an alternative. Several studies comparing use

of non-invasive techniques with thermodilution have been published (Arora et al 2007, Chan et al 2006, Chand et al 2006, Knobloch et al 2005, Tan et al 2005, Van den Oever 2007).

### Intended purpose

The intended purpose of continuous wave Doppler ultrasound without imaging is to enable non-invasive real-time measurement of cardiac output and other cardiac flow parameters in specific settings: adult and paediatric intensive care units, coronary care units, emergency departments, anaesthetics, intra-operative setting and patients with biventricular pacemakers who require device optimisation.

## Clinical need/burden of disease

Continuous wave Doppler ultrasound without imaging is designed for use with patients who may require cardiac output measurement for haemodynamic monitoring. The target populations and settings include adult and paediatric patients in intensive care units, patients in coronary care units, patients requiring emergency medical assistance, patients undergoing anaesthesia and intra-operative patients. It may also be used for patients with biventricular pacemakers who require device optimisation.

Continuous wave Doppler ultrasound without imaging is assessed for use in several clinical settings which handle many different indications. It is challenging to specify the clinical need, incidence and mortality given the diversity of potential settings and indications. In addition the proportion of patients within each condition or disease state where this technology would be useful is undetermined.

The most common conditions that occur in the nominated settings and eligible patient numbers and hospital admissions data were estimated. There were approximately 124,255 admissions to intensive care units throughout Australia and New Zealand during 2003 (Australian and New Zealand Intensive Care Adult Patient Database). The Australian and New Zealand Intensive Care Paediatric database recorded that there were 7329 paediatric admissions to intensive care units in Australia and New Zealand during 2004.

There were 595,761 procedures conducted in hospitals that related to cardiovascular health during 2006–2007 (AIHW National Hospital Morbidity Database).
The percentage of patients in the target populations who could benefit from use of continuous wave Doppler ultrasound technology to measure cardiac output is unclear Roizen et al 2003).

## Existing procedures

### Thermodilution

Thermodilution by pulmonary artery catheterisation (PAC) uses a thermistor-tipped Swan-Ganz catheter inserted from a peripheral vein into the pulmonary artery to measure right atrial and right ventricular filling pressures, pulmonary artery pressure and

pulmonary wedged pressure as a marker of left atrial filling pressure (AHFMR 2006). This technique is generally considered to be suitable for patients over 8 years of age.

### PiCCO

PiCCO (continuous cardiac output) uses a femoral or axillary artery catheter and a central venous catheter to monitor continuous haemodynamic measurements including cardiac output. This technology uses real-time continuous monitoring through arterial pulse contour analysis with intermittent thermodilution measurement via the transpulmonary method. PiCCO is suitable for both adult and paediatric patients (Dr M Crawford, personal communication, 2 May 2008).

### Echocardiography

Echocardiography provides a two- or three-dimensional image of the heart and can be used to determine cardiac output using both pulse wave (PW) and continuous wave (CW) Doppler ultrasound technology. Echocardiography is a more complex technology, providing a combination of structural and functional data and has diagnostic capability. This meant that echocardiography was not appropriate to use as a comparator for continuous wave Doppler ultrasound technology for this assessment.

An exception occurs in the use of echocardiography for the optimisation of implanted biventricular devices. Results depend substantially on the training and expertise of the investigator and the quality of the image produced (AHFMR 2006).

Echocardiography was not considered to be the appropriate main comparator in this assessment because it is seldom used in monitoring applications.

### Standard clinical practice

Standard clinical practice was considered to be the relevant existing procedure for the emergency patient population where there is no current standard procedure for measuring cardiac output in emergency departments.

## Comparator

Thermodilution uses a specialised thermistor-tipped catheter (Swan-Ganz pulmonary artery catheter [PAC]) that is inserted via a peripheral vein into the pulmonary artery (AHFMR 2006). This invasive technique is currently the gold standard in cardiac output measurement. The PAC technique also provides right atrial and right ventricular filling pressures, pulmonary artery pressure, and pulmonary wedge pressure as a marker of left atrial filling pressure (AHFMR 2006).

There are indications of lack of improvement in patient outcomes. Serious PAC-related complications have been reported to occur in 0.1 to 0.5 per cent of surgical patients (Smartt 2005, Roizen et al 2003).

Evidence indicating increased benefits on patient outcomes from monitoring cardiac output using any method, including the gold standard (thermodilution), is currently inconclusive. Similarly, evidence demonstrating how monitoring cardiac output can change patient management is also limited and inconclusive.

## Marketing status of the device

The technology that was considered to be appropriate for inclusion in this assessment was the USCOM device. This device is designed, manufactured and distributed by USCOM Limited. The device was approved and registered by the Australian Therapeutic Goods Administration (TGA) in November 2001 (ARTG number 81047), and in February 2005 by the Food and Drug Administration (FDA) in the United States. USCOM received CE Mark certification in December 2003 enabling distribution in Europe.

## Current reimbursement arrangement

Medicare Benefits Schedule (MBS) items 22015, 35200, 38203 and 38206 refer to left or right cardiac catheterisation but are usually assigned for diagnostic purposes; and therefore, not applicable to this assessment of a monitoring technology. During the period from July 2007 to June 2008 there were 6897 services associated with these MBS items in Australia (Australian Medicare Statistics www.medicareaustralia.gov.au/statistics/mbs_item.shtml). There were also 446 services associated with MBS item 13818, which represents right cardiac catheterisation used for cardiac output measurement in intensive care settings. However, 446 services is likely to be a gross underestimate of the use of this procedure because it represents billing in the private sector only and does not include use in public facilities.

MBS item 13876 is also associated with the use of the comparator technology, thermodilution with a pulmonary artery catheter, which permits up to four pressures to be billed. A limitation in data reporting is that pressures being charged are not classified, although most intensive care units use suffixes to denote that 01 is arterial pressure, 02 is venous, 03 is pulmonary artery and 04 is usually intracranial pressure. The suffixes are not reported by Medicare. The closest estimate to derive the number of PACs in use, per year, is application of Medicare item 13876 three times per day, implying that the PAC is still in place. During the period between July 2007 and June 2008, MBS item 13876 was charged 197,725 times. It is not possible to estimate what proportion of the use of this procedure could be replaced by non-invasive cardiac Doppler ultrasound without imaging.

The volume of procedures that may use continuous wave Doppler ultrasound technology, such as USCOM, to replace PAC use is difficult to estimate given the lack of clarity on public use and the proportion of clinicians who may choose the technology in favour of PAC thermodilution.

# Approach to assessment

## Research questions and clinical pathways

### Non-invasive continuous wave Doppler ultrasound for patients in emergency settings who require haemodynamic monitoring

PPICO criteria (target population, prior tests, index test, comparator, outcomes) for use of non-invasive continuous wave Doppler ultrasound for patients in emergency settings who require haemodynamic monitoring are indicated in Table 1.

**Table 1 PPICO criteria for use of non-invasive continuous wave Doppler ultrasound for patients in emergency settings who require haemodynamic monitoring**

| Population | Prior tests | Intervention/test | Comparator | Reference standard | Outcomes |
|---|---|---|---|---|---|
| Patients in emergency settings who require haemodynamic monitoring | Standard clinical assessment<br>No prior test | Non-invasive continuous wave Doppler ultrasound | Standard clinical care | Standard clinical care | Change in clinical outcomes[a]<br>Change in clinical management[b]<br>Technical accuracy[c]<br>Safety outcomes[d] |

[a] Length of hospital stay; morbidity and mortality; time to correct diagnosis
[b] Changes to treatment (such as admission for further hospital care; further haemodynamic monitoring; change of medication)
[c] Technical accuracy (correlation); reproducibility
[d] Adverse events known to be associated with non-invasive continuous wave Doppler ultrasound are patient discomfort/tolerance to the procedure

The research question for this indication, based on these criteria, was as follows.

To what extent is non-invasive continuous wave Doppler ultrasound:

- safe
- effective (including diagnostic performance and the impact of diagnosis on changes in clinical management and changes in clinical outcomes), and
- cost-effective

in the monitoring of patients in emergency settings who require haemodynamic monitoring in addition to standard clinical care?

The clinical pathway for the use of non-invasive continuous wave Doppler ultrasound for patients in emergency settings who require haemodynamic monitoring is shown in Figure 4.

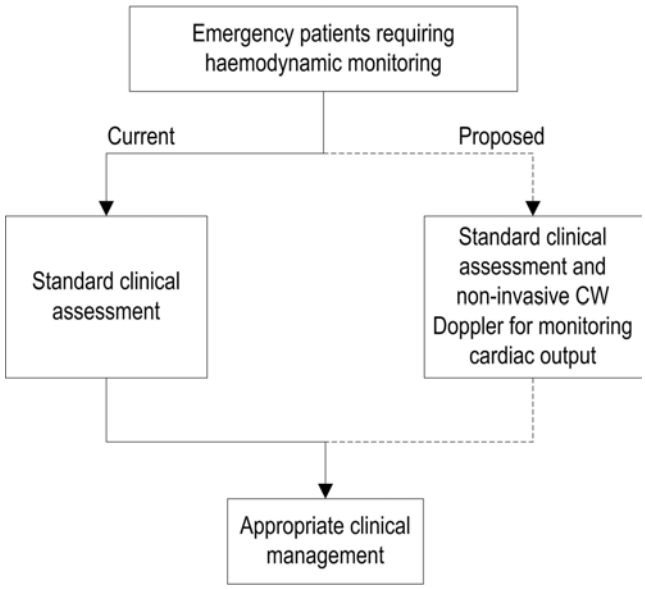


**Figure 4** **Clinical pathway for use of non-invasive continuous wave Doppler ultrasound for patients in emergency settings who require haemodynamic monitoring**

Abbreviation: CW, continuous wave

## Non-invasive continuous wave Doppler ultrasound for adult patients in intensive care settings who require haemodynamic monitoring

The PPICO criteria (target population, prior tests, index test, comparator, outcomes) for use of non-invasive continuous wave Doppler ultrasound for adult patients in intensive care settings who require haemodynamic monitoring are indicated in Table 2.

**Table 2** **PPICO criteria for use of non-invasive continuous wave Doppler ultrasound for adult patients in intensive care settings who require haemodynamic monitoring**

| Population | Prior tests | Intervention/test | Comparator | Reference standard | Outcomes |
|---|---|---|---|---|---|
| Adult patients in intensive care settings who require haemodynamic monitoring | Standard clinical assessment<br>No prior tests | Non-invasive continuous wave Doppler ultrasound | Thermodilution | Thermodilution | Change in clinical outcomes[a]<br>Change in clinical management[b]<br>Technical accuracy[c]<br>Safety outcomes[d] |

[a] Length of hospital stay; length of stay in intensive care unit; morbidity and mortality; time to correct diagnosis; readmission rates
[b] Alterations in treatment plan (such as admission for further hospital care; further haemodynamic monitoring; changes to medication)
[c] Technical accuracy (correlation); reproducibility
[d] Adverse events known to be associated with non-invasive continuous wave Doppler ultrasound or its comparators (such as death, pulmonary artery rupture, bleeding, pneumothorax, infection, stroke, arrhythmias, respiratory obstruction and jugular vein thrombosis); patient discomfort/tolerance to the procedure

The research question for this indication, based on these criteria, was as follows.

To what extent is non-invasive continuous wave Doppler ultrasound:

- safe
- effective (including diagnostic performance and the impact of diagnosis on changes in clinical management and changes in clinical outcomes), and
- cost-effective

in the monitoring of adult patients in intensive care settings who require haemodynamic monitoring in addition to standard clinical care?

The clinical pathway for the use of non-invasive continuous wave Doppler ultrasound for adult patients in intensive care settings who require haemodynamic monitoring is shown in Figure 5.

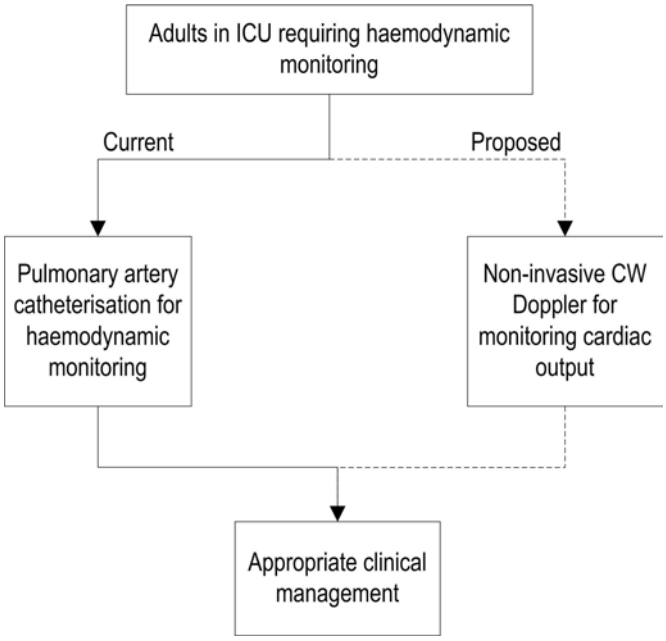


**Figure 5 Clinical pathway for the use of non-invasive continuous wave Doppler ultrasound for adult patients in intensive care requiring haemodynamic monitoring**

Abbreviations: ICU, intensive care unit; CW, continuous wave

## Non-invasive continuous wave Doppler ultrasound for paediatric patients in intensive care settings who require haemodynamic monitoring

The PPICO criteria (target population, prior tests, index test, comparator, outcomes) for use of non-invasive continuous wave Doppler ultrasound for paediatric patients in intensive care settings who require haemodynamic monitoring are indicated in Table 3.

**Table 3 PPICO criteria for use of non-invasive continuous wave Doppler ultrasound for paediatric patients in intensive care settings who require haemodynamic monitoring**

| Population | Prior tests | Intervention/test | Comparator | Reference standard | Outcomes |
|---|---|---|---|---|---|
| Paediatric patients in intensive care settings who require haemodynamic monitoring | Standard clinical assessment<br>No prior tests | Non-invasive continuous wave Doppler ultrasound | PiCCO[a]<br>Thermodilution[b] | Thermodilution | Change in clinical outcomes[c]<br>Change in clinical management[d]<br>Technical accuracy[e]<br>Safety outcomes[f] |

Abbreviation: PiCCO, continuous cardiac output

[a] For use in patients < 8 years of age

[b] For use in patients ≥ 8 years of age

[c] Length of hospital stay; length of stay in intensive care unit; morbidity and mortality; time to correct diagnosis; readmission rates

[d] Alterations in treatment plan (such as admission for further hospital care; further haemodynamic monitoring; change to medication)

[e] Technical accuracy (correlation); reproducibility

[f] Adverse events known to be associated with non-invasive continuous wave Doppler ultrasound or its comparators (such as death, pulmonary artery rupture, bleeding, pneumothorax, infection, stroke, arrhythmias, respiratory obstruction and jugular vein thrombosis); patient discomfort/tolerance to the procedure

The research question for this indication, based on these criteria, was as follows.

To what extent is non-invasive continuous wave Doppler ultrasound:

- safe
- effective (including diagnostic performance and the impact of diagnosis on changes in clinical management and changes in clinical outcomes), and
- cost-effective

in the monitoring of paediatric patients in intensive care settings who require haemodynamic monitoring in addition to standard clinical care?

The clinical pathway for the use of non-invasive continuous wave Doppler ultrasound for paediatric patients in intensive care settings who require haemodynamic monitoring is shown in Figure 6.

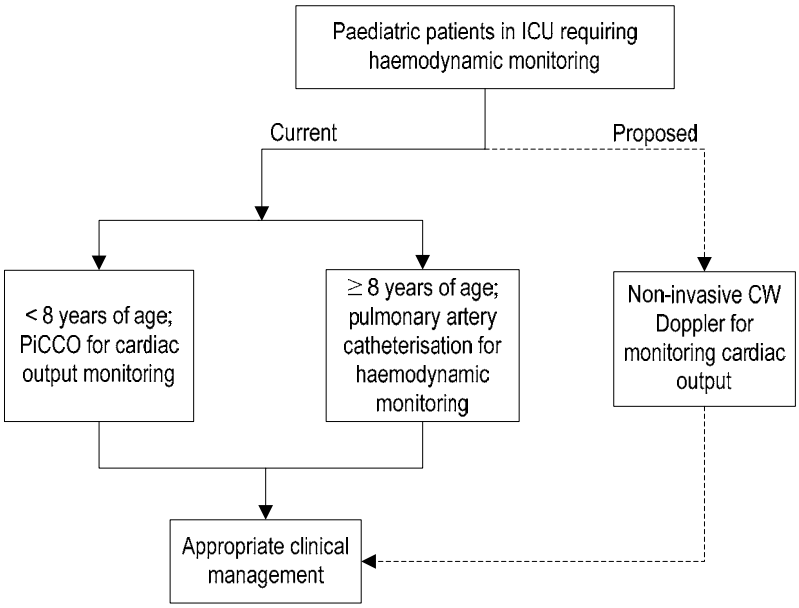


**Figure 6** **Clinical pathway for the use of non-invasive continuous wave Doppler ultrasound for paediatric patients in intensive care requiring haemodynamic monitoring**

Abbreviations: ICU, intensive care unit; PiCCO, continuous cardiac output; CW, continuous wave

## Non-invasive continuous wave Doppler ultrasound for patients in coronary care unit settings who require haemodynamic monitoring

The PPICO criteria (target population, prior tests, index test, comparator, outcomes) for use of non-invasive continuous wave Doppler ultrasound for patients in coronary care unit settings who require haemodynamic monitoring are indicated in Table 4.

**Table 4** **PPICO criteria for use of non-invasive continuous wave Doppler ultrasound for patients in coronary care unit settings who require haemodynamic monitoring**

| Population | Prior tests | Intervention/test | Comparator | Reference standard | Outcomes |
|---|---|---|---|---|---|
| Patients in coronary care unit settings who require haemodynamic monitoring | Standard clinical assessment<br>No prior tests | Non-invasive continuous wave Doppler ultrasound | Thermodilution | Thermodilution | Change in clinical outcomes[a]<br>Change in clinical management[b]<br>Technical accuracy[c]<br>Safety outcomes[d] |

[a] Length of hospital stay; length of stay in coronary care unit; morbidity and mortality; time to correct diagnosis; readmission rates
[b] Alterations in treatment plan (such as admission for further hospital care; further haemodynamic monitoring; changes to medication)
[c] Technical accuracy (correlation); reproducibility
[d] Adverse events known to be associated with non-invasive continuous wave Doppler ultrasound or its comparators (such as death, pulmonary artery rupture, bleeding, pneumothorax, infection, stroke, arrhythmias, respiratory obstruction and jugular vein thrombosis); patient discomfort/tolerance to the procedure

The research question for this indication, based on these criteria, was as follows.

To what extent is non-invasive continuous wave Doppler ultrasound:

- safe
- effective (including diagnostic performance and the impact of diagnosis on changes in clinical management and changes in clinical outcomes), and
- cost-effective

in the monitoring of patients in coronary care unit settings who require haemodynamic monitoring in addition to standard clinical care?

The clinical pathway for the use of non-invasive continuous wave Doppler ultrasound for patients in coronary care unit settings who require haemodynamic monitoring is shown in Figure 7.

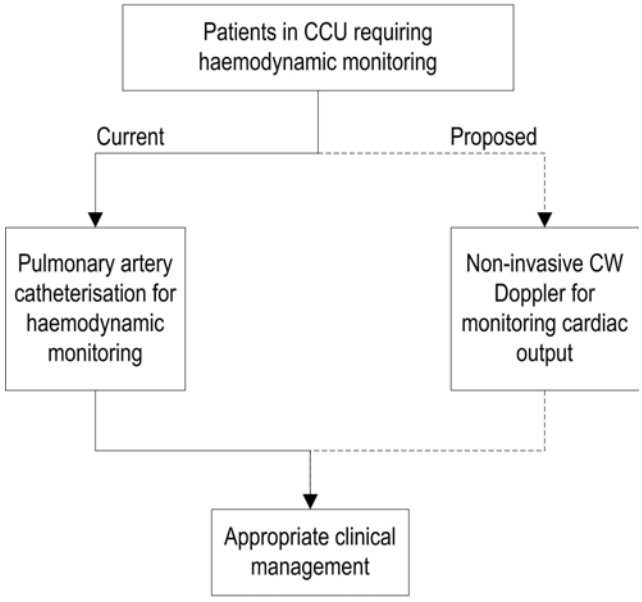


**Figure 7 Clinical pathway for the use of non-invasive continuous wave Doppler ultrasound for patients in coronary care unit requiring haemodynamic monitoring**

Abbreviations: CCU, coronary care unit; CW, continuous wave

## Non-invasive continuous wave Doppler ultrasound for intra-operative patients who require haemodynamic monitoring

The PPICO criteria (target population, prior tests, index test, comparator, outcomes) for use of non-invasive continuous wave Doppler ultrasound for intra-operative patients who require haemodynamic monitoring are indicated in Table 5.

**Table 5 PPICO criteria for use of non-invasive continuous wave Doppler ultrasound for intra-operative patients who require haemodynamic monitoring**

| Population | Prior tests | Intervention/test | Comparator | Reference standard | Outcomes |
|---|---|---|---|---|---|
| Intra-operative patients who require haemodynamic monitoring | Standard clinical assessment<br>No prior tests | Non-invasive continuous wave Doppler ultrasound | Thermodilution | Thermodilution | Change in clinical outcomes[a]<br>Change in clinical management[b]<br>Technical accuracy[c]<br>Safety outcomes[d] |

[a] Length of hospital stay; morbidity and mortality; readmission rates
[b] Alterations in treatment plan (such as admission for further hospital care; further haemodynamic monitoring; changes to medication; changes to anaesthesia)
[c] Technical accuracy (correlation); reproducibility
[d] Adverse events known to be associated with non-invasive continuous wave Doppler ultrasound or its comparators (such as death, pulmonary artery rupture, bleeding, pneumothorax, infection, stroke, arrhythmias, respiratory obstruction and jugular vein thrombosis); patient discomfort/tolerance to the procedure

The research question for this indication, based on these criteria, was as follows.

To what extent is non-invasive continuous wave Doppler ultrasound:

- safe
- effective (including diagnostic performance and the impact of diagnosis on changes in clinical management and changes in clinical outcomes), and
- cost-effective

in the monitoring of intra-operative patients who require haemodynamic monitoring in addition to standard clinical care?

The clinical pathway for the use of non-invasive continuous wave Doppler ultrasound for intra-operative patients who require haemodynamic monitoring is shown in Figure 8.

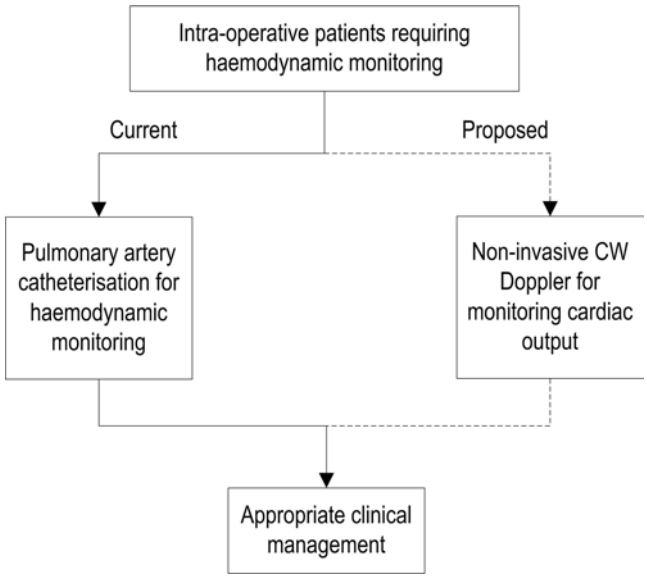


**Figure 8 Clinical pathway for use of non-invasive continuous wave Doppler ultrasound for intra-operative patients who require haemodynamic monitoring**

Abbreviation: CW, continuous wave

## Non-invasive continuous wave Doppler ultrasound for patients with biventricular pacemakers who require device optimisation

The PPICO criteria (target population, prior tests, index test, comparator, outcomes) for use of non-invasive continuous wave Doppler ultrasound for patients with biventricular pacemakers who require device optimisation are indicated in Table 6.

**Table 6 PPICO criteria for use of non-invasive continuous wave Doppler ultrasound for patients with biventricular pacemakers who require device optimisation**

| Population | Prior tests | Intervention/test | Comparator | Reference standard | Outcomes |
|---|---|---|---|---|---|
| Patients with biventricular pacemakers who require device optimisation | No prior tests | Non-invasive continuous wave Doppler ultrasound to optimise AV and/or VV intervals | Echocardiography to optimise AV and/or VV intervals | Echocardiography | Change in clinical outcomes[a]<br>Change in clinical management[b]<br>Technical accuracy[c]<br>Safety outcomes[d] |

Abbreviations: AV, atrioventricular VV interventricular

[a] Morbidity and mortality; NYHA functional class, quality of life

[b] Alterations in treatment plan (such as admission for further hospital care; further haemodynamic monitoring; change of medication)

[c] Technical accuracy (correlation); reproducibility

[d] Adverse events known to be associated with non-invasive continuous wave Doppler ultrasound or its comparators; patient discomfort/tolerance to the procedure

The research question for this indication, based on these criteria, was as follows.

To what extent is non-invasive continuous wave Doppler ultrasound:

- safe
- effective (including diagnostic performance and the impact of diagnosis on changes in clinical management and changes in clinical outcomes), and
- cost-effective

in the monitoring of patients with biventricular pacemakers who require device optimisation?

The clinical pathway for the use of non-invasive continuous wave Doppler ultrasound for patients with biventricular pacemakers who require device optimisation is shown in Figure 9.

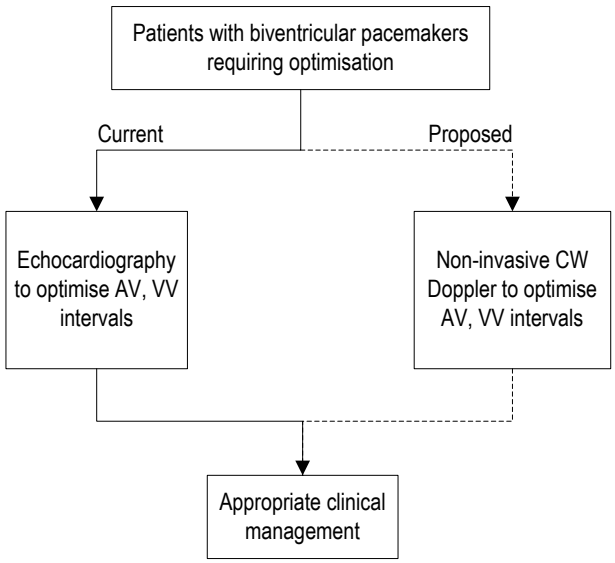


**Figure 9 Clinical pathway for use of non-invasive continuous wave Doppler ultrasound for patients with biventricular pacemakers who require device optimisation**

Abbreviations: AV, atrioventricular; VV, interventricular; CW, continuous wave

# Assessment framework

## Types of evidence

A systematic review of the literature was undertaken to identify relevant studies that investigated the use of non-invasive continuous wave Doppler ultrasound technology in the measurement of cardiac output. Comparative evidence was sought to assess the level of agreement in cardiac output measurements between continuous wave Doppler ultrasound and other techniques.

# Review of literature

## Search strategy

The literature was searched to identify all relevant studies and reviews published before July 2008. The primary databases that were searched are indicated in Table 7.

**Table 7 Primary databases searched for the review of non-invasive continuous wave Doppler ultrasound technology in the measurement of cardiac output**

| Database | Date searched |
|---|---|
| EMBASE.com | 26 July 2008 |
| Cochrane Library | 28 August 2008 |
| PreMedline | 28 August 2008 |

Separate searches were conducted in each of the primary databases for:

- Doppler ultrasound
- thermodilution
- PiCCO
- echocardiography and pacemakers.

Details of the literature searches are presented in Appendix E.

A review of databases maintained by health technology assessment (HTA) agencies was undertaken to identify existing assessments of continuous wave Doppler ultrasound. Details of secondary databases that were searched are also presented in Appendix E.

## Selection criteria

Selection criteria (Table 8, Table 9, Table 10, Table 11, Table 12, and Table 13) were applied to the citations identified in the literature search results. Studies that did not meet specified inclusion criteria were excluded from further analysis.

**Table 8 Inclusion criteria for identification of relevant studies evaluating non-invasive continuous wave Doppler ultrasound for patients in emergency care settings who require haemodynamic monitoring**

| Characteristic | Criteria |
|---|---|
| Publication type | Clinical studies included. Non-systematic reviews, letters, editorials, animal, *in vitro* and laboratory studies excluded |
| Patient | Patients in emergency care settings who require haemodynamic monitoring |
| Prior tests | Standard clinical assessment |
| Intervention/test | Non-invasive continuous wave Doppler ultrasound |
| Comparators | Standard clinical care |
| Reference standard | Standard clinical care |
| Outcome | Change in clinical management<br>Change in clinical outcomes<br>Technical accuracy |
| Language | Non-English language articles excluded unless they appear to provide a higher level of evidence than English language articles |

**Table 9 Inclusion criteria for identification of relevant studies evaluating non-invasive continuous wave Doppler ultrasound for adult patients in intensive care settings who require haemodynamic monitoring**

| Characteristic | Criteria |
|---|---|
| Publication type | Clinical studies included. Non-systematic reviews, letters, editorials, animal, *in vitro* and laboratory studies excluded |
| Patient | Adult patients in intensive care settings who require haemodynamic monitoring |
| Prior tests | Standard clinical assessment |
| Intervention/test | Non-invasive continuous wave Doppler ultrasound |
| Comparators | Thermodilution |
| Reference standard | Thermodilution |
| Outcome | Change in clinical management<br>Change in clinical outcomes<br>Technical accuracy |
| Language | Non-English language articles excluded unless they appear to provide a higher level of evidence than English language articles |

**Table 10 Inclusion criteria for identification of relevant studies evaluating non-invasive continuous wave Doppler ultrasound for paediatric patients in intensive care settings who require haemodynamic monitoring**

| Characteristic | Criteria |
|---|---|
| Publication type | Clinical studies included. Non-systematic reviews, letters, editorials, animal, *in vitro* and laboratory studies excluded |
| Patient | Paediatric patients in intensive care settings who require haemodynamic monitoring |
| Prior tests | Standard clinical assessment |
| Intervention/test | Non-invasive continuous wave Doppler ultrasound |
| Comparators | PiCCO (patients < 8 years of age); thermodilution (patients $\geq$ 8 years of age) |
| Reference standard | Thermodilution |
| Outcome | Change in clinical management<br>Change in clinical outcomes<br>Technical accuracy |
| Language | Non-English language articles will be excluded unless they appear to provide a higher level of evidence than English language articles |

**Table 11 Inclusion criteria for identification of relevant studies evaluating non-invasive continuous wave Doppler ultrasound for patients in coronary care settings who require haemodynamic monitoring**

| Characteristic | Criteria |
|---|---|
| Publication type | Clinical studies included. Non-systematic reviews, letters, editorials, animal, *in vitro* and laboratory studies excluded |
| Patient | Patients in coronary care settings who require haemodynamic monitoring |
| Prior tests | Standard clinical assessment |
| Intervention/test | Non-invasive continuous wave Doppler ultrasound |
| Comparators | Thermodilution |
| Reference standard | Thermodilution |
| Outcome | Change in clinical management<br>Change in clinical outcomes<br>Technical accuracy |
| Language | Non-English language articles excluded unless they appear to provide a higher level of evidence than English language articles |

**Table 12 Inclusion criteria for identification of relevant studies evaluating non-invasive continuous wave Doppler ultrasound for intra-operative patients who require haemodynamic monitoring**

| Characteristic | Criteria |
|---|---|
| Publication type | Clinical studies included. Non-systematic reviews, letters, editorials, animal, *in vitro* and laboratory studies excluded |
| Patient | Intra-operative patients who require haemodynamic monitoring |
| Prior tests | Standard clinical assessment |
| Intervention/test | Non-invasive continuous wave Doppler ultrasound |
| Comparators | Thermodilution |
| Reference standard | Thermodilution |
| Outcome | Change in clinical management<br>Change in clinical outcomes<br>Technical accuracy |
| Language | Non-English language articles will be excluded unless they appear to provide a higher level of evidence than English language articles |

**Table 13 Inclusion criteria for identification of relevant studies evaluating non-invasive continuous wave Doppler ultrasound for patients with biventricular pacemakers who require device optimisation**

| Characteristic | Criteria |
|---|---|
| Publication type | Clinical studies included. Non-systematic reviews, letters, editorials, animal, *in vitro* and laboratory studies excluded |
| Patient | Patients with biventricular pacemakers who require device optimisation |
| Prior tests | Standard clinical assessment |
| Intervention/test | Non-invasive continuous wave Doppler ultrasound |
| Comparators | Echocardiography |
| Reference standard | Echocardiography |
| Outcome | Change in clinical management<br>Change in clinical outcomes<br>Technical accuracy |
| Language | Non-English language articles will be excluded unless they appear to provide a higher level of evidence than English language articles |

## Search results

The QUOROM (quality of reporting of meta-analyses) flowchart summarises reasons for exclusion of studies. A total of 2842 non-duplicate references were identified in the searches. Of these, six studies were reviewed for evidence of clinical effectiveness of continuous wave Doppler ultrasound.

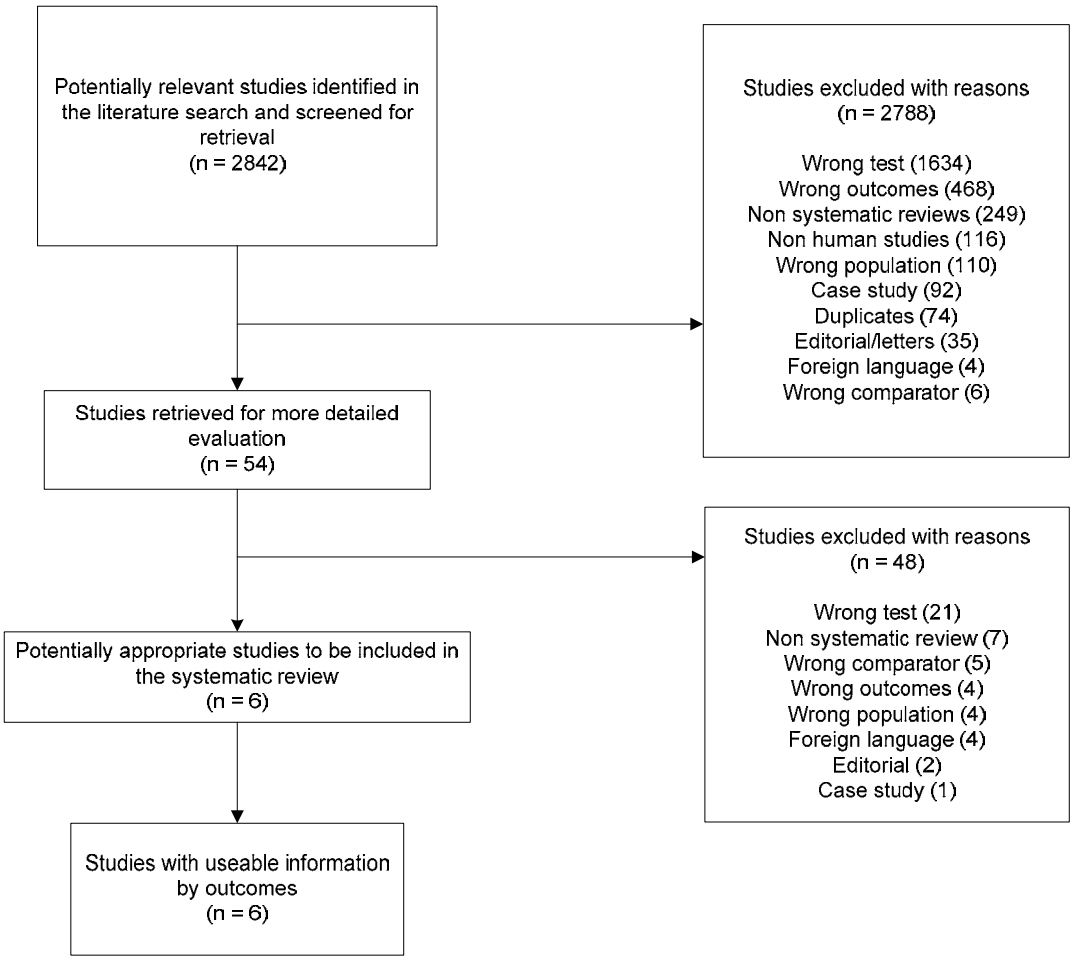


**Figure 10** **QUOROM flowchart used to identify and select studies for the literature review of real-time measurement of cardiac output and other cardiac flow parameters (without concurrent cardiac imaging) using continuous wave Doppler techniques**

## Study appraisal

Evidence retrieved from the literature searches was assessed according to the NHMRC dimensions of evidence (Table 14). The dimensions include three main domains: strength of the evidence, size of the effect, and relevance of the evidence. Strength of evidence is derived directly from the literature relating to a particular intervention. Determination of the size of effect and relevance of the evidence require expert clinical input as part of the evaluation process. An aspect of the strength of the evidence domain is the level of evidence of the study. Levels of evidence were assigned using the NHMRC levels of evidence (Table 15).

**Table 14 Dimensions of evidence**

| Type of evidence | Definition |
|---|---|
| Strength of the evidence | |
| Level | The study design used, as an indicator of the degree to which bias has been eliminated by design[a] |
| Quality | The methods used by investigators to minimise bias within a study design |
| Statistical precision | The *p* value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect |
| Size of effect | The distance of the study estimate from the null value and the inclusion of only clinically important effects in the confidence interval |
| Relevance of evidence | The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used |

Source NHMRC (2008). NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Stage 2 consultation: early 2008–end June 2009. National Health and Medical Research Council, Canberra ACT. Available at: http://www.nhmrc.gov.au/consult/add_levels_grades_dev_guidelines2.htm
[a] See Table 15

**Table 15 Designations of levels of evidence according to type of research question**

| Level | Intervention[b] | Diagnosis[e] |
|---|---|---|
| I [a] | A systematic review of level II studies | A systematic review of level II studies |
| II | A randomised controlled trial | A study of test accuracy with: an independent, blinded comparison with a valid reference standard[f] among consecutive patients with a defined clinical presentation[g] |
| III-1 | A pseudo-randomised controlled trial (ie alternate allocation or some other method) | A study of test accuracy with: an independent, blinded comparison with a valid reference standard[f] among non-consecutive patients with a defined clinical presentation[g] |
| III-2 | A comparative study with concurrent controls:\| Non-randomised, experimental trial[c] Cohort study Case-control study Interrupted time series with a control group | A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence |
| III-3 | A comparative study without concurrent controls: Historical control study Two or more single arm study[d] Interrupted time series without a parallel control group | Diagnostic case-control study[g] |
| IV | Case series with either post-test or pre-test/post-test outcomes | Study of diagnostic yield (no reference standard)[h] |

NHMRC (2008). NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Stage 2 consultation: early 2008—end June 2009. National Health and Medical Research Council, Canberra ACT. Available at: http://www.nhmrc.gov.au/consult/add_levels_grades_dev_guidelines2.htm

[a] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence

[b] Definitions of these study designs are provided on pages 7–8 How to use the evidence: assessment and application of scientific evidence (NHMRC 2000b)

[c] This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (ie, utilise A vs. B and B vs. C, to determine A vs. C)

[d] Comparing single arm studies ie, case series from two studies

[e] The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes. See *MSAC (2004) Guidelines for the assessment of diagnostic technologies*. Available at: www.msac.gov.au

[f] The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study. See Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology* 2003 3: 25

[g] Well-designed population based case-control studies (eg. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice

[h] Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard

**Note 1**: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results

**Note 2**: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence

The quality of studies of technical accuracy will be ranked using the composite grading system described in the assessment of studies of diagnostic accuracy guidelines[2] (Table 16). In accordance with MSAC guidelines, studies of technical accuracy are described according to the extent that they achieved the component factors of study validity.

[2] Medical Services Advisory Committee (2005) *Guidelines for the assessment of diagnostic technologies*. Canberra, Commonwealth of Australia.

**Table 16 Grading system for the appraisal of studies evaluating diagnostic tests**

| Validity criteria | Description | Grading system |
|---|---|---|
| **Appropriate comparison** | Did the study evaluate a direct comparison of the index test strategy versus the comparator test strategy? | C1 direct comparison<br>CX other comparison |
| **Applicable population** | Did the study evaluate the index test in a population that is representative of the subject characteristics (age and sex) and clinical setting (disease prevalence, disease severity, referral filter and sequence of tests) for the clinical indication of interest? | P1 applicable<br>P2 limited<br>P3 different population |
| **Quality of study** | Was the study designed to avoid bias? | Study design: NHMRC level of evidence |
| | High quality = no potential for bias based on pre-defined key quality criteria | Q1: high quality |
| | Fair quality = some potential for bias in areas other than those pre-specified as key criteria | Q2: fair quality |
| | Poor quality = poor reference standard and/or potential for bias based on key pre-specified criteria | Q3: poor reference standard, poor quality |

Source: Medical Services Advisory Committee (MSAC) (2005). *Guidelines for the assessment of diagnostic technologies*. Canberra, Commonwealth of Australia

# Data analysis

## Data extraction

A single reviewer extracted relevant information using a standardised data extraction form designed specifically for this assessment. Any uncertainties were resolved by discussion with another reviewer.

## Measurement of test agreement

Continuous wave Doppler ultrasound is designed as a non-invasive *monitoring* tool. Therefore, evaluating the accuracy of this technology as a diagnostic test and comparing it with its comparators and a reference standard was not considered to be a valid approach. The Bland Altman plot method was applied in the studies identified in this assessment to assess agreement between thermodilution and continuous wave Doppler ultrasound measurements of cardiac output. This method was deemed to be more appropriate and less misleading than correlation coefficients that measure the strength of the association only, and not the level of agreement between the methods (Bland and Altman 1986). Data in poor agreement can produce high correlations.

The extent of agreement in a Bland Altman analysis is examined by plotting the differences between pairs of measurements on the vertical axis and the mean of each pair on the horizontal axis to derive a mean difference. If one method is known to be accurate, then the mean difference indicates whether there is a systematic bias (higher or lower than the true value) in the other measurement. In most cases, a true value or quantity is unknown. Therefore, comparison with an established technique or reference

standard is required to assess agreement between novel and mature methods. Analytic comparison also reveals the mean difference between methods which indicates whether a change in approach would alter patient management decisions and outcomes. Assigning 95 per cent limits of agreement will show that 95 per cent of differences will lie within this range. It is recommended that that the following variables be presented in studies that apply Bland Altman analyses to assess agreement between techniques: mean cardiac output (μ), the mean difference or bias (d) and the standard deviation (SD) of the differences, the limits of agreement (d ± 2 SD) and percentage error (± 2 SD/μ) (Critchley et al 1999).

A level should be set to assess if the mean difference and 95 per cent limits of agreement are sufficiently harmonious to warrant a method being replaced, or to enable methods to be used interchangeably, especially where there are cost or access advantages. To confirm clinically acceptable agreement between methods, a systematic error or bias of less than 0.5 L/minute, and 95 per cent of observations by one method (limits of agreement, or precision), should fall within ± 1.0 L/minute of the other (Van Den Oever et al 2007). This approach is consistent with Critchley meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques (Critchley 1999). Analysis showed that limits of agreement of up to ± 30 per cent were acceptable.

## Expert advice

An advisory panel with expertise in measurement of cardiac output was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for advisory panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. The advisory panel is chaired by a member of MSAC. Membership of the advisory panel is provided at Appendix B.

## Assessment of the body of evidence

The overall body of evidence has been assessed as well as individual studies. An evidence level from A (excellent) to D (poor) was assigned by considering each of the components outlined in the body of evidence matrix outlined in Table 17.

**Table 17 Body of evidence assessment matrix**

| Component | A | B | C | D |
|---|---|---|---|---|
| | **Excellent** | **Good** | **Satisfactory** | **Poor** |
| Volume of evidence | Several level I or II studies with low risk of bias | One or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias | Level III studies with low risk of bias, or level I or II studies with moderate risk of bias | Level IV studies, or level I to III studies with high risk of bias |
| Consistency | All studies consistent | Most studies consistent and inconsistency may be explained | Some inconsistency reflecting genuine uncertainty around clinical question | Evidence is inconsistent |
| Clinical impact | Very large | Substantial | Moderate | Slight or restricted |
| Generalisability | Population/s studied in body of evidence are the same as the target population for the guideline | Population/s studied in the body of evidence are similar to the target population for the guideline | Population/s studied in body of evidence different to target population but it is clinically sensible to apply this evidence to target population | Population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population |
| Applicability | Directly applicable to Australian healthcare context | Applicable to Australian healthcare context with few caveats | Probably applicable to Australian healthcare context with some caveats | Not applicable to Australian healthcare context |

Abbreviation: SR, systematic review

NHMRC (2008). NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Stage 2 consultation: early 2008–end June 2009. National Health and Medical Research Council, Canberra ACT. Available at: http://www.nhmrc.gov.au/consult/add_levels_grades_dev_guidelines2.htm

# Results of assessment

## Summary

Comparative evidence was sought to investigate the effectiveness of continuous wave Doppler ultrasound technology in measuring cardiac output compared with thermodilution, which was both the reference standard and comparator. Evidence relating to adult intensive care and intra-operative patient settings was identified.

Tests required a mean bias of less than 0.5 L/minute and limits of agreement within ± 1.0 L/minute for continuous wave Doppler ultrasound and thermodilution cardiac output measurements to be considered comparable. This is equivalent to a percentage error of ± 30 per cent (Critchley et al 1999, Van Den Oever et al 2007).

Arora et al (2007) and Chand et al (2006) conducted studies in adult intensive care unit settings that fulfilled quality criteria established by Critchley et al (1999). Both reported a mean bias of less than 0.5 L/minute (–0.13 L/min; 0.14 and 0.03 L/min, respectively) and had mutual limits of agreement within ± 1.0 L/minute.

Outcomes reported by Chan et al (2006) and Tan et al (2005) in the adult intensive care setting did not fulfil the requirements to enable analysis according to Critchley (1999) criteria. Although mean bias was less than 0.5 L/minute (0.22 and 0.18/L min respectively), limits of agreement mutually exceeded ± 1.0 L/minute. Chan et al (2006) reported a percentage error of ± 52 per cent which substantially exceeded the acceptable error rate of ± 30 per cent.

Knobloch et al (2005) reported a mean bias of less than 0.5 L/minute (—0.23 L/min) in the adult intensive care setting and did not report limits of agreement. Knobloch et al (2005) reported no significant difference between cardiac output measurements in continuous wave Doppler ultrasound USCOM and thermodilution among intra-operative patients. Limits of agreement were not reported.

Results from Van Den Oever et al (2007) indicated a lack of agreement between cardiac output measurements from continuous wave Doppler and thermodilution among intra-operative patients. Reporting in this study did not fulfil the comparative criteria proposed by Critchley et al (1999). Although mean bias was less than 0.5 L/minute at the aortic and pulmonary valves (–0.79 and –0.17 L/min, respectively), limits of agreement at both exceeded ± 1.0 L/minute of the other test.

The presented evidence suggests that continuous wave Doppler ultrasound without imaging is not comparable with thermodilution measurement and has limited clinical utility in the adult intensive care and intra-operative setting.

No evidence was identified to assess the effectiveness of continuous wave Doppler ultrasound technology to measure cardiac output in haemodynamic monitoring among patients in paediatric intensive care, coronary care, emergency settings or patients with biventricular pacemakers who require device optimisation.

## Is it safe?

Continuous wave Doppler ultrasound is a non-invasive test. This procedure is not considered to present safety issues for patients. Comparative studies assessing safety were not identified. Because it is not invasive, continuous wave Doppler ultrasound is considered to be safer than the thermodilution technique (pulmonary artery catheterisation [PAC]) which has been associated with several safety issues.

Serious PAC-related complications have been reported to occur in 0.1 to 0.5 per cent of surgical patients (Smartt 2005).

## Is it effective?

Comparative evidence was sought to investigate the effectiveness of continuous wave Doppler ultrasound technology without imaging to measure cardiac output in the following populations requiring haemodynamic monitoring:

- patients in emergency settings
- adult patients in intensive care settings
- paediatric patients in intensive care settings
- patients in coronary care settings
- intra-operative patients, and
- patients with biventricular pacemakers who require device optimisation.

From the body of literature, six studies were identified that enabled comparison to be made between non-invasive continuous wave Doppler technology and thermodilution via PAC. Of these, five were considered to provide evidence regarding agreement between the tests in focus for adult patients in intensive care settings (Arora et al 2007, Chan et al 2006, Chand et al 2006, Knobloch et al 2005, Tan et al 2005). The studies by Knobloch et al (2005) and Van Den Oever et al (2007) were deemed to be appropriate to inform a comparative assessment of both methods among intra-operative patients who require haemodynamic monitoring. No evidence was identified to assess the effectiveness of continuous wave Doppler ultrasound technology to measure cardiac output among patients in emergency settings, paediatric patients in intensive care, patients in coronary care units who require haemodynamic monitoring, or patients with biventricular pacemakers who require device optimisation. The characteristics of the six included trials are presented in Table 18.

**Table 18 Characteristics of included studies**

| Author (year) Country | Study design | Patient characteristics (n) | Test characteristics | Quality and applicability |
|---|---|---|---|---|
| Arora (2007) India | Comparative study<br>Prospective<br>Blinded[a] | Post-operative patients who underwent elective off-pump coronary artery bypass surgery<br>Male: n = 26<br>Female: n = 4<br>Mean age: 59.20 ± 10.14 years | Technology: ultrasonic cardiac output monitor (USCOM) non-invasive continuous wave Doppler<br>Performed at the pulmonary artery from 3–5 intercostal space in the left parasternal area<br>Comparator: thermodilution PAC<br>10 mL 0.9% normal saline at room temperature in the right atrial lumen | NHMRC III-3<br>C1, P1, Q2<br>**Quality:** Fair<br>**Applicability:** Applicable |
| Chan (2006) Australia | Comparative study<br>Prospective<br>Blinded[a] | Post cardiac surgery patients in intensive care<br>Male: n = 21<br>Female: n = 9<br>Mean age: 60.6 ± 16.1 years | Technology: ultrasonic cardiac output monitor (USCOM) non-invasive continuous wave Doppler<br>Performed on the left anterior surface of patient's chest in parasternal intercostal space 3–4<br>Comparator: thermodilution PAC<br>Procedure NR | NHMRC III-3<br>C1, P1, Q2<br>**Quality:** Fair<br>**Applicability:** Applicable |
| Chand (2006) India | Comparative study<br>Prospective<br>Blinded[a] | Post-operative patients who underwent elective off-pump coronary artery bypass surgery<br>Male: n = 43<br>Female: n = 7<br>Mean age: 59.20 ± 10.14 years | Technology: ultrasonic cardiac output monitor (USCOM) non-invasive continuous wave Doppler<br>Performed at both ascending aorta, from the suprasternal notch and pulmonary artery, intercostal space 3–5 in the left parasternal area<br>Comparator: thermodilution PAC<br>10 mL of 0.9% normal saline solution | NHMRC III-3<br>C1, P1, Q2<br>**Quality:** Fair<br>**Applicability:** Applicable |
| Knobloch (2005) Australia | Comparative study<br>Prospective<br>Blinding NR | Patients undergoing cardiac surgery and post surgical patients in intensive care<br>Male: n = 26<br>Female: n = 10<br>Mean age: 67.2 ± 10 years | Technology: ultrasonic cardiac output monitor (USCOM) non-invasive continuous wave Doppler<br>Performed on left parasternal intercostal space 3–4<br>Comparator: thermodilution PAC<br>Procedure NR | NHMRC III-3<br>C1, P1, Q3<br>**Quality:** Poor<br>Inadequate data reporting<br>**Applicability:** Applicable |
| Tan (2005) Australia | Comparative study<br>Prospective<br>Blinded[a] | Intensive care patients who recently underwent cardiac surgery<br>Male: n = 16<br>Female: n = 6<br>Mean age: 63.5 years (range 43–78 years) | Technology: ultrasonic cardiac output monitor (USCOM) non-invasive continuous wave Doppler<br>Performed to measure trans-aortic blood flow, from the suprasternal position and transpulmonary blood flow, from the left parasternal position<br>Comparator: thermodilution PAC<br>10 mL bolus injection 5% dextrose-water at 4°C | NHMRC III-3<br>C1, P1, Q2<br>**Quality:** Fair<br>**Applicability:** Applicable |

| Author (year) Country | Study design | Patient characteristics (n) | Test characteristics | Quality and applicability |
|---|---|---|---|---|
| Van Den Oever (2007) Australia | Comparative study<br>Prospective<br>Blinded[a] | Patients undergoing cardiac surgery<br>Male: n = 13<br>Female: n = 9<br>Mean age: range 24–85 years | Technology: ultrasonic cardiac output monitor (USCOM) non-invasive continuous wave Doppler<br>Performed at both aortic valves, from the suprasternal notch or above the clavicle and pulmonary valve, from intercostal space2, 3 or 4 in the parasternal area<br>Comparator: thermodilution PAC<br>10 mL iced 5% dextrose injected into the right atrium | NHMRC III-3<br>C1, P1, Q2<br>**Quality:** Fair<br>**Applicability:** Applicable |

Abbreviations: NR, not reported; PAC, pulmonary artery catheter
[a] USCOM and thermodilution operators were unaware of the findings obtained by the other during their estimation of cardiac output

## Non-invasive continuous wave Doppler ultrasound for patients in emergency settings who require haemodynamic monitoring

No comparative evidence was identified to assess the effectiveness of continuous wave Doppler ultrasound technology in measuring cardiac output among patients in emergency settings who require haemodynamic monitoring.

## Non-invasive continuous wave Doppler ultrasound among adult patients in intensive care settings who require haemodynamic monitoring

There were five studies identified that compared cardiac output measurement agreement of continuous wave Doppler ultrasound (USCOM) with the reference standard, thermodilution, among adult intensive care patients (Arora et al 2007, Chan et al 2006, Chand et al 2006, Knobloch et al 2005, Tan et al 2005). The results of these studies are summarised in Table 19.

Arora et al (2007) compared cardiac output measurements estimated by the non-invasive continuous wave Doppler device, USCOM, with thermodilution techniques among patients who underwent elective off-pump coronary bypass surgery during the post-operative period. This prospective, comparative study measured cardiac output on the first post-operative day in 30 patients; a total of 120 pairs of data were collected. Patients on a ventilator, with an intra-aortic balloon pump, moderate or severe mitral regurgitation, and those undergoing combined procedures, or who experienced atrial fibrillation, surgical emphysema or pneumothorax, were excluded. USCOM cardiac output measurements were estimated from an average of three systolic outflow cycles; thermodilution cardiac output measurements were taken as the average of three measurements, all within 10 per cent range. Non-invasive and thermodilution measurements were made almost simultaneously. The same clinician performed all USCOM estimates and a nurse made thermodilution estimations. Both observers were blinded to findings from the other test. The results showed a mean bias of –0.13 L/minute; measurements made using USCOM had a tendency to be higher than thermodilution by an average of 0.13 L/minute; (95% CI: [–0.86, 0.59 L/minute]). According to criteria established by Critchley et al (1999), this level of agreement is acceptable. When classified according to NHMRC levels of evidence (NHMRC 2005), this study was considered to provide level III-3 evidence.

Chan et al (2006) sought to determine the clinical utility of USCOM to measure cardiac output compared with the invasive thermodilution technique among post-cardiothoracic surgical patients who had pulmonary catheters in place and who were admitted to intensive care units. There were 34 paired measurements obtained prospectively from 26 patients. Inadequate Doppler readings from four patients were excluded from the analysis. Between one and three sets of paired measurements was taken from each patient. USCOM and thermodilution cardiac index estimations were made within 15 minute timeframes and measurements were made between 24 and 48 hours post-surgery. USCOM measurements were performed by a single observer and thermodilution measurements were made by intensive care staff. Both observers were blinded to findings from the other test. The results showed the mean bias of 0.22 L/minute/$m^2$. USCOM results tended to be lower than thermodilution measurements by an average of 0.22 L/minute/$m^2$. Limits of agreement for the two techniques were –1.17 and 1.62 L/minute/$m^2$ for USCOM and thermodilution, respectively. According to Chan et al (2006), the USCOM device had limited clinical utility in this group of intensive care patients. A percentage error of ± 52 per cent was reported. According to criteria established by Critchley et al (1999), results reported by Chan et al (2006) suggest that the level of agreement is not acceptable. When classified according to NHMRC levels of evidence (NHMRC 2005), this study was considered to provide level III-3 evidence.

Chand et al (2006) compared cardiac output measured by USCOM and thermodilution post-operatively among patients following elective off-pump coronary bypass surgery. There were 50 participant patients enrolled in the study. Poor quality Doppler signals occurred in 15 patients whose results were excluded from the analysis. USCOM cardiac output measurements were estimated from an average of three systolic outflow cycles and thermodilution cardiac output measurements were taken as the average of three measurements, all within the 10 per cent range. Continuous wave Doppler ultrasound and thermodilution measurements were made almost simultaneously. The same clinician performed all USCOM estimations and a member of the nursing team made the thermodilution estimations. Both observers were blinded to findings from the other test. Limits of agreement were calculated; at the ascending aorta, a mean bias of 0.14 L/minute and limits of agreement at –0.39 and 0.11 L/minute were reported; at the pulmonary artery, a mean bias of 0.03 L/minute and limits of agreement at –0.19 and 0.13 L/minute were observed. On average, USCOM measurements tended to be lower than thermodilution. According to criteria proposed by Critchley et al (1999), the level of agreement in the study by Chand et al (2006) is acceptable. When classified according to NHMRC levels of evidence (NHMRC 2005), this study was considered to provide level III-3 evidence.

Knobloch et al (2005) assessed the reliability of non-invasive continuous wave Doppler cardiac output measurements compared with the invasive thermodilution technique among patients with pulmonary artery catheters (PAC) during and after cardiac surgery. Knobloch et al (2005) prospectively examined 36 post-operative patients in the intensive care unit setting to yield 180 paired measurements. Blinding procedures were not reported nor who performed the measurements. Details about how cardiac output measurements from both USCOM and thermodilution were calculated or estimated were not reported. The mean bias was reported as –0.23 L/minute. Limits of agreement were not reported. This study was considered poor quality evidence due to a lack of data reporting. When classified according to NHMRC levels of evidence (NHMRC 2005), this study was considered to provide level III-3 evidence.

Tan et al (2005) evaluated the accuracy of the USCOM device compared with thermodilution among intensive care patients who had recently undergone cardiac surgery. The reported methodology indicated that one to three sets of paired measurements were obtained from each patient to give a total of 40 pairs from 22 patients. Measures were taken to minimise time differences between the paired sets of measurements. USCOM measurements were performed by a single observer who was blinded to the pulmonary artery catheter results. There were three to five thermodilution readings performed and the mean value was recorded. Results show a mean bias of 0.18 L/minute. On average, USCOM measurements tended to be lower than thermodilution results by 0.18 L/minute (95% CI: [–1.43, 1.78 L/minute]). According to criteria proposed by Critchley et al (1999), this level of agreement was not acceptable. When classified according to NHMRC levels of evidence (NHMRC 2005), this study was considered to provide level III-3 evidence.

**Table 19 Cardiac output measurement agreement between USCOM and thermodilution in adult patients in intensive care settings**

| Author (year) Country | USCOM mean cardiac output measurement | Thermodilution mean cardiac output measurement | Mean bias (SD) | Limits of agreement | Quality and applicability |
|---|---|---|---|---|---|
| Arora (2007) India | 4.76 L/min | 4.63 L/min | – 0.13 L/mL | –0.86 and 0.59 L/min | NHMRC III-3 C1, P1, Q2 **Quality:** Fair **Applicability:** Applicable |
| Chan (2006)[a] Australia | 2.56±0.63 L/min/$m^2$ | 2.78±0.73 L/min/$m^2$ | 0.22 (0.71) L/min/$m^2$ | –1.17 and 1.62 L/min/$m^2$ | NHMRC III-3 C1, P1, Q2 **Quality:** Fair **Applicability:** Applicable |
| Chand (2006) India | NR | NR | Ascending aorta: 0.14 (0.79) L/min Pulmonary artery: 0.03 (0.55) L/min | Ascending aorta: –0.39 and 0.11 L/min Pulmonary artery: – 0.19 and 0.13 L/min | NHMRC III-3 C1, P1, Q2 **Quality:** Fair **Applicability:** Applicable |
| Knobloch (2005) Australia | 5.15±1.98 L/min | 4.92±2.0 L/min | –0.23 (1.01) L/min | NR | NHMRC III-3 C1, P1, Q3 **Quality:** Poor Inadequate data reporting **Applicability:** Applicable |
| Tan (2005) Australia | NR | NR | 0.18 (0.82) L/min | –1.43 and 1.78 L/min | NHMRC III-3 C1, P1, Q2 **Quality:** Fair **Applicability:** Applicable |

Abbreviations: NR, not reported; SD, standard deviation
[a] Cardiac index

### Non-invasive continuous wave Doppler ultrasound among paediatric patients in intensive care units who require haemodynamic monitoring

No comparative evidence was identified to inform assessment of the effectiveness of continuous wave Doppler ultrasound technology in measuring cardiac output among paediatric patients in intensive care unit settings who require haemodynamic monitoring.

### Non-invasive continuous wave Doppler ultrasound among patients in coronary care unit settings who require haemodynamic monitoring

No comparative evidence was identified to inform assessment of the effectiveness of continuous wave Doppler ultrasound technology in measuring cardiac output among patients in coronary care unit settings who require haemodynamic monitoring.

### Non-invasive continuous wave Doppler ultrasound among intra-operative patients who require haemodynamic monitoring

There were two studies identified that assessed cardiac output measurement agreement between USCOM and thermodilution among intra-operative patients who required haemodynamic monitoring (Knobloch et al 2005, Van Den Oever et al 2007). The results of these studies are summarised in Table 20.

Knobloch et al (2005) investigated cardiac surgery patients post-operatively, and six patients intra-operatively, obtaining 18 paired measurements. The results established that there was no difference between direct and invasive measurements in these six patients. This study was considered to possess poor quality evidence due a lack of data reporting. When classified by NHMRC levels for evidence (NHMRC 2005), this study is considered to provide level III-3 evidence.

Van Den Oever et al (2007) compared USCOM-derived cardiac output measurements from patients' aortic and pulmonary valves with thermodilution during surgery. Cardiac output measurements were determined simultaneously during surgery using both PAC access and USCOM. USCOM measurements were conducted in triplicate and thermodilution was measured five times and averaged. The USCOM operator was blinded to thermodilution measurements. At the aortic window, the results showed a mean bias of –0.79 L/minute (n = 20 observations). Aortic trace measurements by the USCOM device tended to be greater than thermodilution measurements by an average of 0.79 L/minute (95% CI: [–3.66 and 2.08 L/minute]). USCOM measurements at the pulmonary window showed a mean bias of –0.17 L/minute (n = 36 observations). USCOM measurements at the pulmonary window are greater than results using thermodilution by an average of 0.17 L/minute (95% CI: [–3.30 and 2.97 L/minute]). According to criteria established by Critchley et al (1999), this level of agreement is not acceptable. When classified according to NHMRC levels of evidence (NHMRC 2005), this study was considered to provide level III-3 evidence.

**Table 20 Cardiac output measurement agreement between USCOM and thermodilution in intra-operative patients**

| Author (year) Country | USCOM mean cardiac output measurement | Thermodilution mean cardiac output measurement | Mean bias | Agreement | Quality and applicability |
|---|---|---|---|---|---|
| Knobloch (2005)<br>Australia | 4.95±1.02 L/min | 4.97±0.98 L/min | No difference | No difference | NHMRC III-3<br>C1, P1, Q3<br>**Quality:** Poor<br>Inadequate data reporting<br>**Applicability:** Applicable |
| Van Den Oever (2007)<br>Australia | NR | NR | At the aortic valve:<br>–0.79 (1.43) L/min<br>At the pulmonary valve:<br>–0.17 (1.57) L/min | At the aortic valve:<br>-3.66 and 2.08 L/min<br>At the pulmonary valve:<br>–3.30 and 2.97 L/min | NHMRC III-3<br>C1, P1, Q2<br>**Quality:** Fair<br>**Applicability:** Applicable |

Abbreviation: NR, not reported

## Non-invasive continuous wave Doppler ultrasound for patients with biventricular pacemakers who require device optimisation

No comparative evidence was identified to inform assessment of the effectiveness of continuous wave Doppler ultrasound technology for measuring cardiac output among patients with biventricular pacemakers.

## Variability among included studies

Variations between mean bias measurements and limits of agreement were identified among the included studies. Several assumptions were made about monitoring cardiac output using continuous wave Doppler ultrasound technology:

- Measurement using the USCOM device depends on an accurate estimation of the cross-sectional area at the aortic valve and pulmonary valve levels. (Chan et al 2006). In this assessment it was assumed that the cross-sectional area remained constant during measurement (Arora et al 2007). Error in measuring the cross-sectional area can lead to significant error in determining the cardiac output.

- The manufacturer, USCOM Ltd, recommends a 45 degree angle between the handle of the ultrasound beam and the direction of blood flow. To achieve optimal readings, the operator can manipulate the angle of the probe to obtain the best signal. Chan et al (2006) reported that operators changed angles until a good reading was obtained. Patients were excluded from the study when adequate readings could not be obtained (Chand et al 2006).

- Tan et al (2005) indicated that measurements are operator dependent and that USCOM operators experience learning and experience phases. This study inferred that operator errors occur during the learning phase and that

measurement quality could be enhanced by deriving an average from several measurements taken at short intervals (Tan et al 2005).

- There were inconsistencies between studies about the optimal time required to take USCOM measurements (Tan et al 2005, Van Den Oever et al 2007). Tan et al (2005) indicated a required time of up to 45 minutes for data acquisition in the adult intensive care setting but Van Den Oever et al (2007) allowed no more than 10 minutes for intra-operative patients.

- Expert opinion from the advisory panel suggested there may be some concern about the efficacy of continuous wave Doppler ultrasound at extreme measurements. There is currently no evidence available evaluating the accuracy of this technology at extreme measurements that could be vital to the performance of devices such as USCOM in the relevant populations.

## Body of evidence

Individual rankings for components of the body of evidence are shown in Table 21. Evidence was limited to studies ranked as level III that provided some applicability but lacked consistency in presented findings. The clinical impact of results could not be assessed because of inconsistencies in the presented evidence. The studies represented the patient population in this assessment.

**Table 21 Body of evidence**

| Component | Rank | Reason |
|---|---|---|
| Volume of evidence | C | Level III studies by Arora et al (2007), Chan et al (2006), Chand et al (2006), Knobloch et al (2005), Tan et al (2005), Van Den Oever et al (2007) provided comparative evidence between continuous wave Doppler ultrasound and thermodilution techniques in the measurement of cardiac output |
| | | Studies by Arora et al (2007), Chan et al (2006), Chand et al (2006), Knobloch et al (2005), and Tan et al (2005) provided evidence for the adult intensive care population; Knobloch et al (2005) and Van Den Oever et al (2007) addressed the intra-operative population |
| | | Studies by Arora et al (2007), Chan et al (2006), Chand et al (2006), Tan et al (2005), Van Den Oever et al (2007) were assessed as providing fair quality evidence. The study by Knobloch et al (2005) was considered to present poor quality evidence and data reporting was inadequate |
| Consistency | D | In the adult intensive care population, studies by Arora et al (2007), Chand et al (2006) and Knobloch et al (2005) found acceptable agreement between continuous wave Doppler and thermodilution cardiac output measurements. The study by Knobloch et al (2005) was considered to provide poor quality evidence. Studies by Chan et al (2006) and Tan et al (2005) reported unacceptable levels of agreement |
| | | In the intra-operative population, the poor quality study by Knobloch et al (2005) reported acceptable agreement between continuous wave Doppler and thermodilution cardiac output measurements; Van Den Oever et al (2007), which provided fair quality evidence, reported unacceptable levels of agreement |
| Clinical impact | NA | The clinical impact of the results could not be assessed because of inconsistent evidence presented |
| Generalisability | B | Populations in the studies by Arora et al (2007), Chan et al (2006), Chand et al (2006), Knobloch et al (2005) and Tan et al (2005) corresponded with the research question relating to adult patients in intensive care settings. Populations considered by Knobloch et al (2005) and Van Den Oever et al (2007) corresponded with the research question relating to intra-operative patients |
| Applicability | B | All studies considered the USCOM device for continuous wave Doppler ultrasound technology. Evidence was therefore considered applicable to the Australian healthcare system. Issues concerning intra-observer training and reliability should be considered |

Abbreviations: NA, Not applicable

## Patient management

No pre-test/post-test studies were identified that assessed the impact of continuous wave Doppler ultrasound without imaging for real-time measurement of cardiac output on patient management.

As with all techniques used to measure cardiac output, there is a possibility that inappropriate clinical interventions may result from incorrect measurement or interpretation of the results. However, deficits in the available evidence meant that this could not be assessed.

## Treatment effectiveness

No treatment effectiveness evidence was identified for the use of continuous wave Doppler ultrasound without imaging for real-time measurement of cardiac output.

# What are the economic considerations?

# Summary

Owing to the paucity of clinical evidence available it was not possible to conduct a full economic evaluation in the assessment of continuous wave Doppler ultrasound. Cost-effectiveness cannot be properly determined without establishing clinical effectiveness and therefore remains speculative.

## Background

An economic evaluation of continuous wave Doppler ultrasound in patients requiring haemodynamic monitoring is not feasible for this evaluation. This is due to inconclusive findings from the available published effectiveness data comparing continuous wave Doppler ultrasound with thermodilution. Comparative effectiveness data were identified for two out of six relevant patient populations. In assessing the available data, it is not possible to conclude that continuous Doppler ultrasound is equivalent to the thermodilution technique by pulmonary artery catheterisation.

## Existing literature

No published economic evaluations were identified in the literature that compared USCOM or similar continuous wave Doppler equipment with thermodilution by pulmonary artery catheterisation (PAC).

## Methods

### Evidence about effectiveness of the intervention from this review

A systematic review of the literature identified six published studies of continuous wave Doppler ultrasound compared with thermodilution; data were available for two of the six patient groups of interest to this evaluation. The six included studies included considered patients in adult intensive care and intra-operative population groups. No applicable studies were identified for patients in emergency care, paediatric intensive care, or coronary care settings, or concerning patients with biventricular pacemakers who require device optimisation.

Comparative effectiveness between continuous wave Doppler ultrasound and the main comparator, thermodilution, was assessed in terms of cardiac output measurement agreement, where thermodilution was the reference standard. Of the five studies that included an adult intensive care patient population, two met comparability criteria demonstrating acceptable equivalence between continuous wave Doppler ultrasound and thermodilution. Of the two studies that included intra-operative patient populations, one reported agreement in cardiac output measurement; however, this conclusion could not be confirmed using criteria that were applied to assess all studies. In summary, comparative effectiveness data of continuous wave Doppler ultrasound are inconclusive. It is therefore not possible to demonstrate equivalence between the strategies.

### Proposed economic evaluation

It is not feasible to conduct an economic evaluation where comparative effectiveness cannot be established. A cost-effectiveness analysis can be conducted where either superior effectiveness and/or safety can be demonstrated compared with the comparator. A cost minimisation analysis can be conducted where equivalence of effectiveness and safety, in addition to fewer associated costs, can be demonstrated compared with the comparator. Neither of these scenarios fit the current evaluation. An economic evaluation was therefore not proposed for this evaluation.

### Financial implications

Financial implications for the Australian healthcare system can be estimated by applying the cost per service to the expected uptake of the service. The net cost to the Australian healthcare system can be estimated by subtracting the cost of thermodilution services that are anticipated to be substituted by continuous wave Doppler ultrasound. However, it is unclear what proportion of tests currently performed using thermodilution would be replaced by continuous wave Doppler ultrasound should it be listed on the MBS.

# Other considerations

## The patient journey

Continuous wave Doppler ultrasound without imaging is a non-invasive test that enables real-time measurement of cardiac output that can be used in a variety of settings for patients who require cardiac output measurement for haemodynamic monitoring. Potential settings include adult and paediatric intensive care units, coronary care units, emergency departments, anaesthetics and intra-operative settings and for patients with biventricular pacemakers who require device optimisation. The usual alternative technology applied for haemodynamic monitoring for most of these settings is thermodilution to measure cardiac output during pulmonary arterial catheterisation (PAC). This approach carries a recognised risk of complications and may not be widely available in a timely fashion. However, PAC provides additional information including measurement of filling pressures. Given its non-invasive nature continuous wave Doppler ultrasound without imaging is considered to be safe. Although comparative evidence assessing the diagnostic accuracy of continuous wave Doppler ultrasound without imaging was identified in intensive care and intra-operative settings, the studies were not consistent in their findings. Furthermore, the identified evidence did not demonstrate how such information would change management or improve health outcomes.

# Research recommendations

After reviewing the body of evidence addressing each research question, the evaluators developed specific research recommendations using a modified EPICOT (evidence, population, intervention, comparison, outcome, time stamp) format (Brown et al 2006). The research recommendations also address the prior test element.

**Table 22 Research recommendations for use of non-invasive continuous wave Doppler ultrasound for adult patients in intensive care settings who require haemodynamic monitoring**

| Element | Description |
|---|---|
| Evidence | Studies by Arora et al (2007), Chan et al (2006), Chand et al (2006), Knobloch et al (2005) and Tan et al (2005) assessed cardiac output measurement agreement between continuous wave Doppler and thermodilution in adult patients in intensive care settings who require haemodynamic monitoring. |
| | Studies by Arora et al (2007) and Chand et al (2006) demonstrated continuous wave Doppler ultrasound to be in acceptable agreement with thermodilution cardiac output measurement according to criteria proposed by Critchley et al (1999) in this setting. |
| | Arora et al (2007) reported that continuous wave Doppler ultrasound cardiac output measurements had a tendency to be higher than results from thermodilution. Chand et al (2006) reported that continuous wave Doppler cardiac output measurements tended to be lower than thermodilution measurements. |
| | Chan et al (2006) and Tan et al (2005) demonstrated that continuous wave Doppler ultrasound did not achieve acceptable levels of agreement with thermodilution cardiac output measurement according to criteria proposed by Critchley et al (1999) in this setting. |
| | Chan et al (2006) and Tan et al (2005) reported that continuous wave Doppler ultrasound measurements tended to be lower than thermodilution cardiac output measurements. |
| | The study by Knobloch et al (2005) was subject to bias and had inadequate data reporting |
| Population | Adult patients in intensive care settings who require haemodynamic monitoring |
| Prior tests | Standard clinical assessment/ no prior tests |
| Intervention/test | Non-invasive continuous wave Doppler ultrasound |
| Comparator | Thermodilution |
| Outcome | Change in clinical outcomes[a] |
| | Change in clinical management[b] |
| | Technical accuracy[c] |
| | Safety outcomes[d] |
| Time stamp | |

[a] Length of hospital stay; length of ICU stay; morbidity and mortality; time to correct diagnosis; readmission rates
[b] Alterations in treatment plan (such as admission for further hospital care; further haemodynamic monitoring; changes to medication)
[c] Technical accuracy (correlation); reproducibility
[d] Adverse events known to be associated with non-invasive continuous wave Doppler ultrasound or its comparators (such as death, pulmonary artery rupture, bleeding, pneumothorax, infection, stroke, arrhythmias, respiratory obstruction and jugular vein thrombosis); patient discomfort/tolerance to the procedure

**Table 23 Research recommendations for the use of non-invasive continuous wave Doppler ultrasound for intra-operative patients who require haemodynamic monitoring**

| Element | |
|---|---|
| Evidence | Knobloch et al (2005) and Van Den Oever et al (2007) assessed cardiac output measurement agreement between continuous wave Doppler ultrasound and thermodilution in intra-operative patients requiring haemodynamic monitoring. |
| | Van Den Oever et al (2007) reported that continuous wave Doppler ultrasound was not in acceptable agreement with thermodilution cardiac output measurements according to criteria proposed by Critchley et al (1999) in this setting. Continuous wave Doppler ultrasound cardiac output measurements had a tendency to be higher than results from thermodilution. |
| | Knobloch et al (2005) demonstrated no difference between continuous wave Doppler ultrasound and thermodilution cardiac output measurements in this setting. This study was subject to bias and data reporting was inadequate |
| Population | Intra-operative patients who require haemodynamic monitoring |
| Prior tests | Standard clinical assessment/ no prior tests |
| Intervention/test | Non-invasive continuous wave Doppler ultrasound |
| Comparator | Thermodilution |
| Outcome | Change in clinical outcomes[a] |
| | Change in clinical management[b] |
| | Technical accuracy[c] |
| | Safety outcomes[d] |
| Time stamp | |

[a] Length of hospital stay; length of ICU stay; morbidity and mortality; time to correct diagnosis; readmission rates
[b] Alterations in treatment plan (such as admission for further hospital care; further haemodynamic monitoring; changes to medication)
[c] Technical accuracy (correlation); reproducibility
[d] Adverse events known to be associated with non-invasive continuous wave Doppler ultrasound or its comparators (such as death, pulmonary artery rupture, bleeding, pneumothorax, infection, stroke, arrhythmias, respiratory obstruction and jugular vein thrombosis); patient discomfort/tolerance to the procedure

# Conclusions

## Safety

Continuous wave Doppler ultrasound is a non-invasive test. This procedure is not considered to present safety issues for patients. Although comparative studies assessing safety were not identified, it is likely that continuous wave ultrasound is safer than the invasive thermodilution technique performed during pulmonary artery catheterisation (PAC).

## Effectiveness

A systematic review of the literature sought evidence which would compare the effectiveness of Doppler ultrasound technology (without imaging) to thermodilution, the reference standard. Predefined criteria were used in the comparison of technologies to determine whether or not there was clinically acceptable agreement: mean bias of less than 0.5 L/minute and limits of agreement within ± 1.0 L/minute between continuous wave Doppler ultrasound and thermodilution cardiac output measurements, which is equivalent to a percentage error of ± 30 per cent (Critchley et al 1999, Van Den Oever et al 2007).

In the adult intensive care setting, studies by Arora et al (2007) and Chand et al (2006) fulfilled criteria outlined by Critchley et al (1999). The trials reported mean bias of less than 0.5 L/minute (–0.13 L/min; 0.14 and 0.03 L/min, respectively) and limits of agreement within ± 1.0 L/minute. This evidence suggests equivalence between cardiac output estimations measured by USCOM continuous wave Doppler ultrasound and thermodilution. The studies by Chan et al (2006) and Tan et al (2005) did not fulfil criteria to enable appropriate comparison. These studies demonstrated lack of agreement between USCOM continuous wave Doppler ultrasound and thermodilution. Mean biases were less than 0.5 L/minute (0.22 and 0.18 L/min, respectively), but limits of agreement in both studies exceeded ± 1.0 L/minute of the other test. Additionally, a percentage error of ± 52 per cent was reported by Chan et al (2006), which exceeds the acceptable error of ± 30 per cent.

Knobloch et al (2005) provided results from intensive care and intra-operative settings. The study reported a mean bias of less than 0.5 L/minute (–0.23 L/min) but did not describe limits of agreement. The absence of reported limits of agreement coupled with inadequate data reporting meant that a valid assessment of the predefined comparability criteria could not be conducted.

A trial of the USCOM device by Van Den Oever et al (2007) in an intra-operative patient population showed a lack of agreement between cardiac output measurements performed by continuous wave Doppler ultrasound and thermodilution. Mean bias was less than 0.5 L/minute at the aortic and pulmonary valve (–0.79 and –0.17 L/min, respectively). However, limits of agreement at both valves exceeded ± 1.0 L/minute. These results suggest that the tests were not equivalent in the intra-operative setting.

In summary, evidence comparing USCOM continuous wave Doppler ultrasound without imaging with the thermodilution technique in the adult intensive care setting is not consistent. Determination of equivalence between the tests cannot be concluded.

No comparative evidence was identified to inform assessment of the effectiveness of continuous wave Doppler ultrasound technology in measuring cardiac output as a component of haemodynamic monitoring for patients in paediatric intensive care, coronary care, or emergency settings, or patients with biventricular pacemakers who require device optimisation.

## Cost-effectiveness

The lack of data regarding the clinical effectiveness of continuous wave Doppler ultrasound meant that a full economic evaluation could not be conducted. Cost-effectiveness cannot be properly determined without establishing clinical effectiveness, and therefore, results remain speculative.

Further, it is unclear what proportion of the comparative procedure would be replaced by the new technology, nor the impact on MBS utilisation. Therefore, further financial implications cannot be established until the potential rate of use is clear.

# Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

| **Member** | **Expertise or affiliation** |
|---|---|
| Professor Robyn Ward (Chair) | medical oncology |
| Dr William Glasson (Deputy Chair) | ophthalmology |
| Associate Professor Frederick Khafagi (Deputy Chair) | nuclear medicine |
| Associate Professor John Atherton | cardiology |
| Professor Justin Beilby | health research |
| Professor Jim Butler | health economics |
| Professor Peter Cameron | trauma and emergency medicine |
| Associate Professor Kirsty Douglas | health research |
| Dr Kwun Fong | thoracic medicine |
| Professor Richard Fox | medical oncology |
| Professor Jim Bishop OA | Chief Medical Officer, Department of Health and Ageing |
| Professor Helen Lapsley | health economics |
| Mr Russell McGowan | consumer health issues |
| Dr Ian Prosser | haematology |
| Dr Judy Soper | radiology |
| Dr Graeme Suthers | genetics/medical oncology |
| Dr Shiong Tan | general practice |
| Professor Ken Thomson | radiology |
| Professor Andrew Wilson | public health physician |
| Dr Caroline Wright | colorectal surgery |

# Appendix B Advisory panel and Evaluators

## Advisory panel for MSAC application 1117

## Real-time measurement of cardiac output and other cardiac flow parameters (without concurrent cardiac imaging) using continuous wave Doppler techniques

| | |
|---|---|
| **Associate Professor John Atherton (Chair)**<br>Cardiology | Member of MSAC |
| **Professor Geoff Farrell (Deputy Chair)**<br>until 2 October 2008 | Member of MSAC |
| **Dr Stephen Blamey (Deputy Chair)**<br>from 3 October 2008 | Member of MSAC |
| **Dr Walter Abhayarantna** | Cardiac Society of Australia and New Zealand nominee |
| **Dr John Philip O'Shea** | Cardiac Society of Australia and New Zealand nominee |
| **Dr Matthew Crawford**<br>Intensivist | Co-opted member |
| **Associate Professor Robert J Dunn**<br>Emergency physician | Co-opted member |
| **Ms Jill Frock**<br>Consumer health | Consumers' Health Forum nominee |

## Evaluators

| | |
|---|---|
| **Alasdair Godfrey** | IMS Health Australia P/L |
| **Carmel Guarnieri** | IMS Health Australia P/L |
| **Dan Jackson** | IMS Health Australia P/L |
| **Ann Jones** | IMS Health Australia P/L |
| **Laurence Fong** | IMS Health Australia P/L |
| **John Gillespie** | IMS Health Australia P/L |

**Jane Adams** IMS Health Australia P/L

**Adam Gordois** IMS Health Australia P/L

# Appendix C Studies included in the review

| Author (year)<br>Country<br>Study design | Patient characteristics (n) | Test characteristics | Study outcomes | Quality and applicability |
|---|---|---|---|---|
| Arora (2007)<br>India<br>Comparative study<br>Prospective<br>Blinded[a] | Post-operative patients who underwent elective off-pump coronary artery bypass surgery<br>Male: n = 26<br>Female: n = 4<br>Mean age: 59.20±10.14 years | Technology: ultra sonic cardiac output monitor (USCOM) non-invasive continuous wave Doppler<br>Performed at the pulmonary artery from 3—5 intercostal space in the left parasternal area<br>Comparator: thermodilution (PAC)<br>10 mL 0.9% normal saline at room temperature in the right atrial lumen | **Adult intensive care**<br>**Mean bias:**<br>–0.13 L/mL<br>**Limits of agreement:**<br>–0.86 and 0.59 L/min | NHMRC III-3<br>C1, P1, Q2<br>**Quality:** Fair<br>**Applicability:** Applicable |
| Chan (2006)<br>Australia Comparative study<br>Prospective<br>Blinded[a] | Post cardiac surgery patients in the intensive care<br>Male: n = 21<br>Female: n = 9<br>Mean age: 60.6±16.1 years | Technology: ultra sonic cardiac output monitor (USCOM) non-invasive continuous wave Doppler<br>Performed on the left anterior surface of the patients chest in the parasternal intercostal space 3—4<br>Comparator: thermodilution PAC<br>Procedure NR | **Adult intensive care**<br>**Mean bias**:<br>0.22 (0.71) L/min/$m^2$<br>**Limits of agreement:**<br>—1.17 and 1.62 L/min/$m^2$ | NHMRC III-3<br>C1, P1, Q2<br>**Quality:** Fair<br>**Applicability:** Applicable |
| Chand (2006)<br>India Comparative study<br>Prospective<br>Blinded[a] | Post-operative period in patients who underwent elective off-pump coronary artery bypass surgery<br>Male: n = 43<br>Female: n = 7<br>Mean age: 59.20±10.14 years | Technology: ultra sonic cardiac output monitor (USCOM) non-invasive continuous wave Doppler<br>Performed at both ascending aorta, from the suprasternal notch and pulmonary artery, intercostal space 3—5 in the left parasternal area<br>Comparator: thermodilution (PAC)<br>10 mL 0.9% normal saline solution | **Adult intensive care**<br>**Mean bias:**<br>Ascending aorta: 0.14 (0.79) L/min<br>Pulmonary artery: 0.03 (0.55) L/min<br>**Limits of agreement:**<br>Ascending aorta:<br>— 0.39 and 0.11L/min<br>Pulmonary artery:<br>— 0.19 and 0.13 L/min | NHMRC III-3<br>C1, P1, Q2<br>**Quality:** Fair<br>**Applicability:** Applicable |
| Knobloch (2005)<br>Australia Comparative study<br>Prospective<br>Blinding NR | Patients undergoing cardiac surgery and post surgical patients in intensive care<br>Males: n = 26<br>Female: n = 10<br>Mean age: 67.2±10 years | Technology: ultra sonic cardiac output monitor (USCOM) non-invasive continuous wave Doppler<br>Performed on left parasternal intercostal space 3—4<br>Comparator: thermodilution (PAC)<br>Procedure NR | **Adult intensive care**<br>**Mean bias:**<br>— 0.23 (1.01) L/min<br>**Limits of agreement:**<br>NR<br>**Intra-operative**<br>No difference | NHMRC III-3<br>C1, P1, Q3<br>**Quality:** Poor<br>Inadequate data reporting<br>**Applicability:** Applicable |

| Author (year)<br>Country<br>Study design | Patient characteristics (n) | Test characteristics | Study outcomes | Quality and applicability |
|---|---|---|---|---|
| Tan (2005)<br>Australia<br>Comparative study<br>Prospective<br>Blinded[a] | Intensive care patients who recently underwent cardiac surgery<br>Males: n = 16<br>Female: n = 6<br>Mean age: 63.5 (range 43–78 years) | Technology: ultra sonic cardiac output monitor (USCOM) non-invasive continuous wave Doppler<br>Performed to measure trans-aortic blood flow, from the suprasternal position and transpulmonary blood flow, from the left parasternal position<br>Comparator: thermodilution (PAC)<br>10 mL bolus injection of 5% dextrose-water at 4 degrees | **Mean bias:**<br>0.18 (0.82) L/min<br>**Limits of agreement**<br>−1.43 and 1.78 L/min | NHMRC III-3<br>C1, P1, Q2<br>**Quality:** Fair<br>**Applicability:** Applicable |
| Van Den Oever (2007)<br>Australia<br>Comparative study<br>Prospective<br>Blinded[a] | Patients undergoing cardiac surgery<br>Males: n = 13<br>Female: n = 9<br>Mean age: range 24–85 years | Technology: ultra sonic cardiac output monitor (USCOM) non-invasive continuous wave Doppler<br>Performed at both aortic valve, from the suprasternal notch or above the clavicle and pulmonary valve, from the intercostal space 2, 3 or 4 in the parasternal area<br>Comparator: thermodilution (PAC)<br>10 mL iced 5% dextrose into the right atrium | **Intra-operative**<br>**Mean bias:**<br>At the aortic valve:<br>−0.79 (1.43) l/min<br>At the pulmonary valve:<br>−0.17 (1.57) l/min<br>**Limits of agreement:**<br>At the aortic valve:<br>-3.66 and 2.08L/min<br>At the pulmonary valve:<br>−3.30 and 2.97L/min | NHMRC III-3<br>C1, P1, Q2<br>**Quality:** Fair<br>**Applicability:** Applicable |

Abbreviations: NR, not reported; PAC, pulmonary artery catheter

[a] USCOM and thermodilution operators were unaware of the findings obtained by the other during their estimation of cardiac output

# Appendix D Excluded studies


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# Appendix E Literature search

**Table 24 EMBASE.com search for Doppler (25 July 2008)**

| | Keywords/search history | Results |
|---|---|---|
| 1 | 'doppler flowmetry'/exp | 17,898 |
| 2 | 'doppler flowmeter'/exp | 4666 |
| 3 | 'doppler echocardiography'/exp | 15,880 |
| 4 | 'doppler echography'/exp | 17,912 |
| 5 | 'color ultrasound flowmetry'/exp | 14,679 |
| 6 | #1 OR #2 OR #3 OR #4 OR #5 | 68,001 |
| 7 | 'echography'/de | 159,765 |
| 8 | 'echocardiography'/de | 67,917 |
| 9 | #7 OR #8 | 222,098 |
| 10 | doppler:ab,ti | 67,836 |
| 11 | #9 AND #10 | 15,656 |
| 12 | 'doppler ultrasound':ab,ti OR 'doppler effect':ab,ti OR 'doppler *1 shift':ab,ti | 9111 |
| 13 | 'doppler method':ab,ti OR 'doppler system':ab,ti OR 'doppler technique':ab,ti | 2570 |
| 14 | 'doppler ultrasonic':ab,ti OR 'doppler imaging':ab,ti | 4233 |
| 15 | 'doppler *1 flow detector':ab,ti OR 'doppler *1 flow meter':ab,ti | 238 |
| 16 | 'doppler *1 flowmeter':ab,ti OR 'doppler *1 meter':ab,ti | 1460 |
| 17 | 'ultrasonic flow meter':ab,ti OR 'ultrasonic flowmeter':ab,ti OR 'ultrasonic flow detector':ab,ti | 221 |
| 18 | 'ultrasound flow detector':ab,ti OR 'ultrasound flow meter':ab,ti OR 'ultrasound flowmeter ':ab,ti | 87 |
| 19 | 'doppler *1 echocardiography':ab,ti OR 'doppler *1 ultrasonography':ab,ti | 13,247 |
| 20 | 'doppler echo':ab,ti OR 'doppler echography':ab,ti | 488 |
| 21 | 'transcranial doppler':ab,ti OR 'transcranial ultrasonography':ab,ti | 4878 |
| 22 | 'color doppler':ab,ti OR 'doppler color *1 flowmetry':ab,ti | 8644 |
| 23 | 'color ultrasound flowmetry':ab,ti OR 'ultrasound color flowmetry':ab,ti | 2 |
| 24 | 'doppler *1 sonography':ab,ti OR 'color flow echocardiography':ab,ti | 5601 |
| 25 | #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #23 OR #24 | 36,385 |
| 26 | #6 OR #11 OR #25 | 80,774 |
| 27 | 'continuous wave':ab,ti | 3345 |
| 28 | #26 AND #27 | 1651 |
| 29 | 'non invasive procedure'/exp | 2236 |
| 30 | 'non invasive measurement'/exp | 8764 |
| 31 | noninvasive*:ab,ti OR 'non invasive':ab,ti OR invasive*:ab,ti | 193,151 |
| 32 | #29 OR #30 OR #31 | 196,011 |
| 33 | #28 AND #32 | 463 |
| 34 | 'ultrasonic cardiac output monitor':de | 1 |
| 35 | uscom:ab,ti,df,dn OR 'ultrasonic cardiac output monitor':ab,ti,df,dn OR 'ultrasonic cardiac output monitors':ab,ti,df,dn | 18 |
| 36 | 'ultrasonic cardiac output monitoring *1 device':ab,ti | 2 |
| 37 | 'ultrasonic *3 cardiac output monitoring':ab,ti | 3 |
| 38 | #34 OR #35 OR #36 OR #37 | 18 |

| | Keywords/search history | Results |
|---|---|---|
| 39 | 'hemodynamic monitoring'/exp | 22,607 |
| 40 | 'hemodynamics'/exp | 495,258 |
| 41 | 'hemodynamic parameters'/exp | 430,110 |
| 42 | hemodynamic*:ab,ti OR haemodynamic*:ab,ti | 121,175 |
| 43 | #39 OR #40 OR #41 OR #42 | 556,837 |
| 44 | #28 AND #43 | 809 |
| 45 | 'emergency'/exp | 20,958 |
| 46 | 'emergency treatment'/exp | 95,455 |
| 47 | 'emergency health service'/exp | 43,096 |
| 48 | 'emergency medicine'/exp | 14,667 |
| 49 | 'emergency physician'/exp | 659 |
| 50 | 'emergency nursing'/exp | 710 |
| 51 | 'emergency nurse practitioner'/exp | 68 |
| 52 | 'emergency patient'/exp | 178 |
| 53 | 'emergency ward'/exp | 20,983 |
| 54 | 'ambulance'/exp | 5946 |
| 55 | emergency:ab,ti OR emergencies:ab,ti | 124,063 |
| 56 | 'accident *1 service':ab,ti OR triage:ab,ti | 5708 |
| 57 | 'trauma center':ab,ti OR 'trauma centers':ab,ti | 4895 |
| 58 | 'trauma centre':ab,ti OR 'trauma centres':ab,ti | 542 |
| 59 | ambulance*:ab,ti OR ambulatory:ab,ti | 56,071 |
| 60 | #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 | 296,132 |
| 61 | #28 AND #60 | 39 |
| 62 | 'intensive care'/exp | 273,022 |
| 63 | 'intensive care unit'/exp | 37,215 |
| 64 | 'intensive care':ab,ti OR 'critical care':ab,ti OR 'subacute care':ab,ti | 75,734 |
| 65 | 'intensive therapy':ab,ti OR 'close attention unit':ab,ti | 3968 |
| 66 | 'respiratory care unit':ab,ti OR 'respiratory care units':ab,ti | 88 |
| 67 | 'special care unit':ab,ti OR 'special care unit':ab,ti | 307 |
| 68 | #62 OR #63 OR #64 OR #65 OR #66 OR #67 | 322,384 |
| 69 | #28 AND #68 | 64 |
| 70 | 'thermodilution'/exp | 2446 |
| 71 | 'thermal dilution':ab,ti OR thermodilution:ab,ti | 3178 |
| 72 | #70 OR #71 | 4036 |
| 73 | #28 AND #72 | 40 |
| 74 | 'pulse countour cardiac output system':de | 1 |
| 75 | 'pulse contour cardiac output':de | 8 |
| 76 | 'pulse contour analysis':de | 24 |
| 77 | 'arterial pulse contour analysis':de | 2 |
| 78 | picco:ab,ti,df,dn OR 'pulse induced contour cardiac output':ab,ti,df,dn OR pulsion:ab,ti,df,dn | 430 |
| 79 | pcco:ab,ti,df,dn OR 'pulse contour cardiac output':ab,ti,df,dn | 69 |
| 80 | 'pulse contour':ab,ti | 342 |

| | Keywords/search history | Results |
|---|---|---|
| 81 | 'pulsion medical systems':ab,ti | 32 |
| 82 | #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 | 740 |
| 83 | #28 AND #82 | 1 |
| 84 | 'coronary artery disease'/exp | 135,634 |
| 85 | 'coronary care unit'/exp | 5455 |
| 86 | 'cardiovascular nursing'/exp | 23 |
| 87 | 'coronary *1 disease':ab,ti OR 'coronary *1 diseases':ab,ti | 88,362 |
| 88 | 'coronary *1 unit':ab,ti OR 'coronary *1 units':ab,ti | 4109 |
| 89 | 'cardiac care facilities':ab,ti OR 'cardiologic unit':ab,ti | 6 |
| 90 | 'hospital cardiology service':ab,ti OR 'heart center ':ab,ti | 189 |
| 91 | 'heart center':ab,ti OR 'heart centre':ab,ti OR 'coronary care':ab,ti | 4761 |
| 92 | #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 | 188,016 |
| 93 | #28 AND #92 | 40 |
| 94 | 'intraoperative period'/exp | 50,163 |
| 95 | 'peroperative echography'/exp | 1650 |
| 96 | 'patient monitoring'/de | 41,604 |
| 97 | intraoperative:ab,ti OR peroperative:ab,ti | 58,104 |
| 98 | 'intra operative':ab,ti OR 'per operative':ab,ti | 5545 |
| 99 | intraoperation:ab,ti OR peroperation:ab,ti | 63 |
| 100 | 'intra operation':ab,ti OR 'per operation':ab,ti | 133 |
| 101 | #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 | 131,102 |
| 102 | #28 AND #101 | 47 |
| 103 | 'pacemaker'/exp | 27,690 |
| 104 | pacemaker*:ab,ti | 25,688 |
| 105 | #103 OR #104 | 37,688 |
| 106 | biventricular:ab,ti OR 'bi ventricular':ab,ti | 3852 |
| 107 | #105 AND #106 | 708 |
| 108 | 'biventricular pacemaker':de | 4 |
| 109 | 'cardiac resynchronization therapy'/exp | 2018 |
| 110 | 'biventricular pacing':ab,ti OR 'bi ventricular pacing':ab,ti | 893 |
| 111 | 'biventricular resynchronisation':ab,ti OR 'bi ventricular resynchronisation':ab,ti | 9 |
| 112 | 'biventricular resynchronization':ab,ti OR 'bi ventricular resynchronization':ab,ti | 28 |
| 113 | 'cardiac resynchronisation':ab,ti OR 'cardiac resynchronization':ab,ti | 1776 |
| 114 | 'ventricular resynchronisation':ab,ti OR 'ventricular resynchronization':ab,ti | 86 |
| 115 | #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 | 3295 |
| 116 | #28 AND #115 | 4 |
| 117 | #33 OR #38 OR #44 OR #61 OR #69 OR #73 OR #83 OR #93 OR #102 OR #116 | 1086 |

**Table 25 EMBASE.com search for thermodilution (25 July 2008)**

| | Keywords/search history | Results |
|---|---|---|
| 1 | 'thermodilution'/exp | 2446 |
| 2 | 'thermal dilution':ab,ti OR thermodilution:ab,ti | 3178 |
| 3 | #1 OR #2 | 4036 |
| 4 | 'hemodynamic monitoring'/exp | 22,607 |
| 5 | 'hemodynamics'/exp | 495,258 |
| 6 | 'hemodynamic parameters'/exp | 430,110 |
| 7 | hemodynamic*:ab,ti OR haemodynamic*:ab,ti | 121,175 |
| 8 | #4 OR #5 OR #6 OR #7 | 556,837 |
| 9 | #3 AND #8 | 2611 |
| 10 | 'intensive care'/exp | 273,022 |
| 11 | 'intensive care unit'/exp | 37,215 |
| 12 | 'intensive care':ab,ti OR 'critical care':ab,ti OR 'subacute care':ab,ti | 75,734 |
| 13 | 'intensive therapy':ab,ti OR 'close attention unit':ab,ti | 3968 |
| 14 | 'respiratory care unit':ab,ti OR 'respiratory care units':ab,ti | 88 |
| 15 | 'special care unit':ab,ti OR 'special care unit':ab,ti | 307 |
| 16 | #10 OR #11 OR #12 OR #13 OR #14 OR #15 | 322,384 |
| 17 | #3 AND #16 | 950 |
| 18 | 'coronary artery disease'/exp | 135,634 |
| 19 | 'coronary care unit'/exp | 5455 |
| 20 | 'cardiovascular nursing'/exp | 23 |
| 21 | 'coronary *1 disease':ab,ti OR 'coronary *1 diseases':ab,ti | 88,362 |
| 22 | 'coronary *1 unit':ab,ti OR 'coronary *1 units':ab,ti | 4109 |
| 23 | 'cardiac care facilities':ab,ti OR 'cardiologic unit':ab,ti | 6 |
| 24 | 'hospital cardiology service':ab,ti OR 'heart center ':ab,ti | 189 |
| 25 | 'heart center':ab,ti OR 'heart centre':ab,ti OR 'coronary care':ab,ti | 4761 |
| 26 | #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 | 188,016 |
| 27 | #3 AND #26 | 296 |
| 28 | 'intraoperative period'/exp | 50,163 |
| 29 | 'peroperative echography'/exp | 1650 |
| 30 | 'patient monitoring'/de | 41,604 |
| 31 | intraoperative:ab,ti OR peroperative:ab,ti | 58,104 |
| 32 | 'intra operative':ab,ti OR 'per operative':ab,ti | 5545 |
| 33 | intraoperation:ab,ti OR peroperation:ab,ti | 63 |
| 34 | 'intra operation':ab,ti OR 'per operation':ab,ti | 133 |
| 35 | #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 | 131,102 |
| 36 | #3 AND #35 | 342 |
| 37 | #9 OR #17 OR #27 OR #36 | 3,010 |
| 38 | #9 AND #17 | 623 |
| 39 | #9 AND #27 | 251 |
| 40 | #9 AND #36 | 241 |
| 41 | 'adult'/exp | 3,554,380 |
| 42 | 'aged'/exp | 1,594,066 |

| | Keywords/search history | Results |
|---|---|---|
| 43 | 'adulthood'/exp | 58,912 |
| 44 | 'senescence'/exp | 9141 |
| 45 | #41 OR #42 OR #43 OR #44 | 3,956,542 |
| 46 | #37 AND #45 | 1281 |
| 47 | 'child'/exp | 1,319,497 |
| 48 | 'childhood'/exp | 17,355 |
| 49 | 'pediatrics'/exp | 51,524 |
| 50 | 'pediatric hospital'/exp | 3587 |
| 51 | 'pediatric cardiology'/exp | 128 |
| 52 | 'pediatric nursing'/exp | 1104 |
| 53 | 'pediatric ward'/exp | 403 |
| 54 | 'child health care'/exp | 40,395 |
| 55 | 'pediatric nurse practitioner'/exp | 14 |
| 56 | 'pediatric surgery'/exp | 8991 |
| 57 | pediatric*:ab,ti OR paediatric*:ab,ti | 162,560 |
| 58 | #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 | 1,418,833 |
| 59 | #37 AND #58 | 97 |
| 60 | #38 OR #39 OR #40 OR #46 OR #59 | 1769 |
| 61 | 'doppler flowmetry'/exp | 17,898 |
| 62 | 'doppler flowmeter'/exp | 4666 |
| 63 | 'doppler echocardiography'/exp | 15,880 |
| 64 | 'doppler echography'/exp | 17,912 |
| 65 | 'color ultrasound flowmetry'/exp | 14,679 |
| 66 | doppler:ab,ti | 67,836 |
| 67 | #61 OR #62 OR #63 OR #64 OR #65 OR #66 | 92,021 |
| 68 | #60 NOT #67 | 1502 |
| 69 | #1 AND #68 | 956 |
| 70 | #4 OR #5 OR #6 | 520,723 |
| 71 | #69 AND #70 | 767 |
| 72 | #10 OR #11 | 297,898 |
| 73 | #69 AND #72 | 501 |
| 74 | #18 OR #19 OR #20 | 140,437 |
| 75 | #69 AND #74 | 71 |
| 76 | #28 OR #29 OR #30 | 89,795 |
| 77 | #69 AND #76 | 170 |
| 78 | #71 OR #73 OR #75 OR #77 | 911 |

**Table 26 EMBASE.com search for echocardiography and pacemaker (26 July 2008)**

| | Keywords/search history | Results |
|---|---|---|
| 1 | 'echography'/exp | 310,268 |
| 2 | 'echocardiography'/exp | 109,061 |
| 3 | echography:ab,ti OR echocardiography:ab,ti OR ultrasonogram:ab,ti | 66,237 |
| 4 | doptone:ab,ti OR echogram:ab,ti OR echoscopy:ab,ti OR echosound:ab,ti | 584 |
| 5 | sonogram:ab,ti OR sonography:ab,ti OR ultrasonography:ab,ti | 77,375 |
| 6 | 'ultrasonic diagnosis':ab,ti OR 'ultrasonic echo':ab,ti | 1942 |
| 7 | 'ultrasonic examination':ab,ti OR 'ultrasonic scanning':ab,ti | 1920 |
| 8 | 'ultrasonic detection':ab,ti OR 'ultrasonic scintillation':ab,ti | 221 |
| 9 | 'ultrasound diagnosis':ab,ti OR 'ultrasound scanning ':ab,ti | 3900 |
| 10 | 'cardiac scanning':ab,ti OR cardioechography:ab,ti | 63 |
| 11 | 'echo cardiography':ab,ti OR echocardiogram:ab,ti | 6568 |
| 12 | 'heart echo sounding':ab,ti OR 'heart echography':ab,ti | 2 |
| 13 | 'heart scanning':ab,ti OR 'myocardium scanning':ab,ti | 32 |
| 14 | ultrasound:ab,ti AND cardiography:ab,ti OR 'echo cardiogram':ab,ti | 138 |
| 15 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 | 345, 252 |
| 16 | 'pacemaker'/exp | 27,704 |
| 17 | pacemaker*:ab,ti | 25,703 |
| 18 | #16 OR #17 | 37,705 |
| 19 | biventricular:ab,ti OR 'bi ventricular':ab,ti | 3855 |
| 20 | #18 AND #19 | 710 |
| 21 | 'biventricular pacemaker':de | 4 |
| 22 | 'cardiac resynchronization therapy'/exp | 2022 |
| 23 | 'biventricular pacing':ab,ti OR 'bi ventricular pacing':ab,ti | 894 |
| 24 | 'biventricular resynchronisation':ab,ti OR 'bi ventricular resynchronisation':ab,ti | 9 |
| 25 | 'biventricular resynchronization':ab,ti OR 'bi ventricular resynchronization':ab,ti | 28 |
| 26 | 'cardiac resynchronisation':ab,ti OR 'cardiac resynchronization':ab,ti | 1780 |
| 27 | 'ventricular resynchronisation':ab,ti OR 'ventricular resynchronization':ab,ti | 86 |
| 28 | #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 | 3301 |
| 29 | #15 AND #28 | 1040 |
| 30 | 'doppler flowmetry'/exp | 17,900 |
| 31 | 'doppler flowmeter'/exp | 4666 |
| 32 | 'doppler echocardiography'/exp | 15,889 |
| 33 | 'doppler echography'/exp | 17,927 |
| 34 | 'color ultrasound flowmetry'/exp | 14,684 |
| 35 | doppler:ab,ti | 67,854 |
| 36 | #30 OR #31 OR #32 OR #33 OR #34 OR #35 | 92,056 |
| 37 | #29 NOT #36 | 568 |

**Table 27 EMBASE.com search for PiCCO (26 July 2008)**

| | Keywords/search history | Results |
|---|---|---|
| 1 | 'pulse countour cardiac output system':de | 1 |
| 2 | 'pulse contour cardiac output':de | 8 |
| 3 | 'pulse contour analysis':de | 24 |
| 4 | 'arterial pulse contour analysis':de | 2 |
| 5 | picco:ab,ti,df,dn OR 'pulse induced contour cardiac output':ab,ti,df,dn OR pulsion:ab,ti,df,dn | 430 |
| 6 | pcco:ab,ti,dn,df OR 'pulse contour cardiac output':ab,ti,dn,df | 69 |
| 7 | 'pulse contour':ab,ti | 342 |
| 8 | 'pulsion medical systems':ab,ti | 32 |
| 9 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 | 740 |
| 10 | 'hemodynamic monitoring'/exp | 22,614 |
| 11 | 'hemodynamics'/exp | 495,382 |
| 12 | 'hemodynamic parameters'/exp | 430,216 |
| 13 | hemodynamic*:ab,ti OR haemodynamic*:ab,ti | 121,208 |
| 14 | #10 OR #11 OR #12 OR #13 | 556,971 |
| 15 | #9 AND #14 | 374 |
| 16 | 'intensive care'/exp | 273,109 |
| 17 | 'intensive care unit'/exp | 37,233 |
| 18 | 'intensive care':ab,ti OR 'critical care':ab,ti OR 'subacute care':ab,ti | 75,769 |
| 19 | 'intensive therapy':ab,ti OR 'close attention unit':ab,ti | 3968 |
| 20 | 'respiratory care unit':ab,ti OR 'respiratory care units':ab,ti | 88 |
| 21 | 'special care unit':ab,ti OR 'special care unit':ab,ti | 307 |
| 22 | #16 OR #17 OR #18 OR #19 OR #20 OR #21 | 322,486 |
| 23 | #9 AND #22 | 210 |
| 24 | #15 OR #23 | 437 |
| 25 | #15 AND #23 | 147 |
| 26 | 'adult'/exp | 3,555,163 |
| 27 | 'aged'/exp | 1,594,427 |
| 28 | 'adulthood'/exp | 58,939 |
| 29 | 'senescence'/exp | 9145 |
| 30 | #26 OR #27 OR #28 OR #29 | 3,987,421 |
| 31 | #24 AND #30 | 217 |
| 32 | 'child'/exp | 1,319,648 |
| 33 | 'childhood'/exp | 17,360 |
| 34 | 'pediatrics'/exp | 51,552 |
| 35 | 'pediatric hospital'/exp | 3595 |
| 36 | 'pediatric cardiology'/exp | 128 |
| 37 | 'pediatric nursing'/exp | 1,104 |
| 38 | 'pediatric ward'/exp | 404 |
| 39 | 'child health care'/exp | 40,406 |
| 40 | 'pediatric nurse practitioner'/exp | 18 |
| 41 | 'pediatric surgery'/exp | 8995 |
| 42 | pediatric*:ab,ti OR paediatric*:ab,ti | 162,628 |

| | Keywords/search history | Results |
|---|---|---|
| 43 | #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 | 1,419,032 |
| 44 | #24 AND #43 | 27 |
| 45 | #25 OR #31 OR #44 | 300 |
| 46 | 'doppler flowmetry'/exp | 17,900 |
| 47 | 'doppler flowmeter'/exp | 4666 |
| 48 | 'doppler echocardiography'/exp | 15,889 |
| 49 | 'doppler echography'/exp | 17,927 |
| 50 | 'color ultrasound flowmetry'/exp | 14,684 |
| 51 | doppler:ab,ti | 67,854 |
| 52 | #46 OR #47 OR #48 OR #49 OR #50 OR #51 | 92,056 |
| 53 | #45 NOT #52 | 277 |

**Table 28 Cochrane search for Doppler (28 August 2008)**

| | Keywords/search history | Results |
|---|---|---|
| 1 | MeSH descriptor Echocardiography, Doppler explode all trees | 670 |
| 2 | MeSH descriptor Ultrasonography, Doppler explode all trees | 1785 |
| 3 | MeSH descriptor Laser-Doppler Flowmetry, this term only | 437 |
| 4 | (#1 OR #2 OR #3) | 2209 |
| 5 | MeSH descriptor Ultrasonics, this term only | 170 |
| 6 | MeSH descriptor Ultrasonography, this term only | 684 |
| 7 | MeSH descriptor Echocardiography, this term only | 1654 |
| 8 | (#5 OR #6 OR #7) | 2490 |
| 9 | (doppler) | 4895 |
| 10 | (#8 AND #9) | 309 |
| 11 | "Doppler ultrasound" or "doppler effect" or (doppler near shift) | 556 |
| 12 | "doppler method" or "doppler system" or "doppler technique" | 154 |
| 13 | "doppler ultrasonic" or "Doppler imaging" | 232 |
| 14 | (doppler near ("flow detector", "flow meter")) | 0 |
| 15 | (doppler near (flowmeter, meter)) | 113 |
| 16 | "ultrasonic flow meter" or "ultrasonic flowmeter" or "ultrasonic flow detector" | 6 |
| 17 | "ultrasound flow detector" or "ultrasound flow meter" or "ultrasound flowmeter " | 5 |
| 18 | (Doppler near (echocardiography, ultrasonography)) | 2255 |
| 19 | "doppler echo" or "doppler echography" | 121 |
| 20 | "transcranial doppler" or "transcranial ultrasonography" | 489 |
| 21 | "color doppler" or ("doppler color" near flowmetry) | 286 |
| 22 | "color ultrasound flowmetry" or "ultrasound color flowmetry" | 31 |
| 23 | (Doppler near Sonography) or "Color Flow Echocardiography" | 274 |
| 24 | (#11 OR #12 OR #13 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23) | 3270 |
| 25 | (#4 OR #10 OR #24) | 3699 |
| 26 | "continuous wave" | 133 |
| 27 | (#25 AND #26) | 54 |
| 28 | (noninvasive* or "non invasive" or invasive*) | 8638 |
| 29 | (#27 AND #28) | 13 |

| | Keywords/search history | Results |
|---|---|---|
| 30 | "ultrasonic cardiac output monitor" | 0 |
| 31 | (uscom or "ultrasonic cardiac output monitors") | 4 |
| 32 | "ultrasonic cardiac output monitoring" near device | 0 |
| 33 | ultrasonic near "cardiac output monitoring" | 0 |
| 34 | (#30 or #31 or #32 or #33) | 4 |
| 35 | MeSH descriptor Hemodynamics explode all trees | 34,430 |
| 36 | (Hemodynamic* or Haemodynamic*) | 15,974 |
| 37 | (#35 OR #36) | 40117 |
| 38 | (#27 AND #37) | 31 |
| 39 | MeSH descriptor Emergency Treatment explode all trees | 2800 |
| 40 | MeSH descriptor Emergency Medical Services explode all trees | 1999 |
| 41 | MeSH descriptor Emergencies, this term only | 569 |
| 42 | MeSH descriptor Emergency Medicine, this term only | 130 |
| 43 | MeSH descriptor Emergency Nursing, this term only | 45 |
| 44 | (emergency or emergencies) | 8296 |
| 45 | (accident near service) or triage | 472 |
| 46 | "trauma center" or "trauma centers" | 389 |
| 47 | "trauma centre" or "trauma centres" | 77 |
| 48 | (ambulance* or ambulatory) | 11,498 |
| 49 | (#39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48) | 21,855 |
| 50 | (#27 AND #49) | 4 |
| 51 | MeSH descriptor Intensive Care explode all trees | 873 |
| 52 | MeSH descriptor Intensive Care Units explode all trees | 1858 |
| 53 | "intensive care" or "critical care" or "subacute care" | 14,350 |
| 54 | "intensive therapy" or "close attention unit" | 428 |
| 55 | "respiratory care unit" or "respiratory care units" | 20 |
| 56 | "special care unit" or "special care unit" | 41 |
| 57 | (#51 OR #52 OR #53 OR #54 OR #55 OR #56) | 14,939 |
| 58 | (#27 AND #57) | 4 |
| 59 | MeSH descriptor Thermodilution, this term only | 103 |
| 60 | "thermal dilution" or thermodilution | 349 |
| 61 | (#59 OR #60) | 349 |
| 62 | (#27 AND #61) | 1 |
| 63 | (picco or "Pulse induced contour cardiac output" or pulsion) | 26 |
| 64 | (pcco or "Pulse contour cardiac output") | 5 |
| 65 | "pulse contour" OR "pulse contour analysis" | 26 |
| 66 | "pulsion medical systems" | 2 |
| 67 | (#63 OR #64 OR #65 OR #66) | 52 |
| 68 | (#27 AND #67) | 0 |
| 69 | MeSH descriptor Coronary Artery Disease, this term only | 1240 |
| 70 | MeSH descriptor Coronary Care Units, this term only | 150 |
| 71 | (coronary near disease*) | 11,871 |
| 72 | (coronary near unit*) | 557 |

| | Keywords/search history | Results |
|---|---|---|
| 73 | "cardiac care facilities" or "cardiologic unit" | 22 |
| 74 | "hospital cardiology service" or "heart center " | 286 |
| 75 | "heart center" or "heart centre" or "coronary care" | 887 |
| 76 | (#69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75) | 12,641 |
| 77 | (#27 AND #76) | 2 |
| 78 | MeSH descriptor Intraoperative Period, this term only | 902 |
| 79 | MeSH descriptor Intraoperative Care, this term only | 913 |
| 80 | MeSH descriptor Monitoring, Intraoperative, this term only | 906 |
| 81 | MeSH descriptor Monitoring, Physiologic, this term only | 1421 |
| 82 | (intraoperative or peroperative) | 7507 |
| 83 | "intra operative" or "per operative" | 752 |
| 84 | (intraoperation or peroperation) | 1 |
| 85 | "intra operation" or "per operation" | 27 |
| 86 | (#78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85) | 9323 |
| 87 | (#27 AND #86) | 3 |
| 88 | MeSH descriptor Pacemaker, Artificial, this term only | 464 |
| 89 | (pacemaker*) | 985 |
| 90 | (#88 OR #89) | 985 |
| 91 | (biventricular or "bi ventricular") | 152 |
| 92 | (#90 AND #91) | 54 |
| 93 | MeSH descriptor Cardiac Pacing, Artificial, this term only | 746 |
| 94 | "biventricular pacing" or "bi ventricular pacing" | 83 |
| 95 | "biventricular resynchronisation" or "bi ventricular resynchronisation" | 2 |
| 96 | "biventricular resynchronization" or "bi ventricular resynchronization" | 0 |
| 97 | "cardiac resynchronisation" or "cardiac resynchronization" | 133 |
| 98 | "ventricular resynchronisation" or "ventricular resynchronization" | 8 |
| 99 | (#92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98) | 795 |
| 100 | (#27 AND #99) | 1 |
| 101 | (#29 OR #34 OR #38 OR #50 OR #58 OR #62 OR #68 OR #77 OR #87 OR #100) | 47 |

**Table 29 Cochrane search for thermodilution (28 August 2008)**

| | Keywords/search history | Results |
|---|---|---|
| 1 | MeSH descriptor Thermodilution, this term only | 103 |
| 2 | "thermal dilution" or thermodilution | 349 |
| 3 | (#1 OR #2) | 349 |
| 4 | MeSH descriptor Hemodynamics explode all trees | 34,430 |
| 5 | (Hemodynamic* or Haemodynamic*) | 15,974 |
| 6 | "hemodynamic parameters" | 841 |
| 7 | (#4 OR #5 OR #6) | 40,117 |
| 8 | (#3 AND #7) | 301 |
| 9 | MeSH descriptor Intensive Care explode all trees | 873 |
| 10 | MeSH descriptor Intensive Care Units explode all trees | 1858 |
| 11 | "intensive care" or "critical care" or "subacute care" | 14,350 |

| | Keywords/search history | Results |
|---|---|---|
| 12 | "intensive therapy" or "close attention unit" | 428 |
| 13 | "respiratory care unit" or "respiratory care units" | 20 |
| 14 | "special care unit" or "special care unit" | 41 |
| 15 | (#9 OR #10 OR #11 OR #12 OR #13 OR #14) | 14,939 |
| 16 | (#3 AND #15) | 107 |
| 17 | MeSH descriptor Coronary Artery Disease, this term only | 1240 |
| 18 | MeSH descriptor Coronary Care Units, this term only | 150 |
| 19 | (coronary near disease*) | 11,871 |
| 20 | (coronary near unit*) | 557 |
| 21 | "cardiac care facilities" or "cardiologic unit" | 22 |
| 22 | "hospital cardiology service" or "heart center " | 286 |
| 23 | "heart center" or "heart centre" or "coronary care" | 887 |
| 24 | "heart center" or "heart centre" or "coronary care" | 887 |
| 25 | (#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24) | 12,641 |
| 26 | (#3 AND #25) | 55 |
| 27 | MeSH descriptor Intraoperative Period, this term only | 902 |
| 28 | MeSH descriptor Intraoperative Care, this term only | 913 |
| 29 | MeSH descriptor Monitoring, Intraoperative, this term only | 906 |
| 30 | MeSH descriptor Monitoring, Physiologic, this term only | 1421 |
| 31 | (intraoperative or peroperative) | 7507 |
| 32 | "intra operative" or "per operative" | 752 |
| 33 | (intraoperation or peroperation) | 1 |
| 34 | "intra operation" or "per operation" | 27 |
| 35 | (#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34) | 9323 |
| 36 | (#3 AND #35) | 54 |
| 37 | (#8 OR #16 OR #26 OR #36) | 321 |
| 38 | (#8 AND #16) | 95 |
| 39 | (#8 AND #26) | 51 |
| 40 | (#8 AND #36) | 49 |
| 41 | MeSH descriptor Adult explode all trees | 365 |
| 42 | (adult* OR "middle age") | 239,522 |
| 43 | (aged OR elder* OR senescence) | 252,227 |
| 44 | (Octogenarian* OR Centenarian* OR Nonagenarian*) | 42 |
| 45 | (#41 OR #42 OR #43 OR #44) | 333,430 |
| 46 | (#37 AND #45) | 270 |
| 47 | MeSH descriptor Child explode all trees | 0 |
| 48 | MeSH descriptor Pediatrics explode all trees | 386 |
| 49 | MeSH descriptor Hospitals, Pediatric, this term only | 160 |
| 50 | MeSH descriptor Pediatric Nursing, this term only | 91 |
| 51 | MeSH descriptor Pediatric Assistants, this term only | 0 |
| 52 | (child OR children OR childhood) | 63,635 |
| 53 | (pediatric* or paediatric*) | 24,636 |
| 54 | (#47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53) | 68,221 |

| | Keywords/search history | Results |
|---|---|---|
| 55 | (#37 AND #54) | 13 |
| 56 | (#38 OR #39 OR #40 OR #46 OR #55) | 293 |
| 57 | MeSH descriptor Echocardiography, Doppler explode all trees | 670 |
| 58 | MeSH descriptor Ultrasonography, Doppler explode all trees | 1785 |
| 59 | MeSH descriptor Laser-Doppler Flowmetry, this term only | 437 |
| 60 | (doppler) | 4895 |
| 61 | (#57 OR #58 OR #59 OR #60) | 4895 |
| 62 | (#56 AND NOT #61) | 259 |

**Table 30 Cochrane search for echocardiography and pacemakers (28 August 2008)**

| | Keywords/search history | Results |
|---|---|---|
| 1 | MeSH descriptor Echocardiography explode all trees | 2566 |
| 2 | MeSH descriptor Ultrasonography, this term only | 684 |
| 3 | (echography or echocardiography or ultrasonogram) | 4316 |
| 4 | (doptone or echogram or echoscopy or echosound) | 4 |
| 5 | (sonogram or sonography or ultrasonography) | 7691 |
| 6 | "ultrasonic diagnosis" or "ultrasonic echo" | 7 |
| 7 | "ultrasonic examination" or "ultrasonic scanning" | 39 |
| 8 | "ultrasonic detection" or "ultrasonic scintillation" | 1 |
| 9 | "ultrasound diagnosis" or "ultrasound scanning " | 177 |
| 10 | "cardiac scanning" or cardioechography | 1 |
| 11 | "echo cardiography" or echocardiogram | 305 |
| 12 | "heart echo sounding" or "heart echography" | 0 |
| 13 | "heart scanning" or "myocardium scanning" | 0 |
| 14 | (ultrasound cardiography or "echo cardiogram") | 8 |
| 15 | (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) | 10,636 |
| 16 | MeSH descriptor Pacemaker, Artificial, this term only | 464 |
| 17 | (pacemaker*) | 985 |
| 18 | (#16 OR #17) | 985 |
| 19 | (biventricular or "bi ventricular") | 152 |
| 20 | (#18 AND #19) | 54 |
| 21 | MeSH descriptor Cardiac Pacing, Artificial, this term only | 746 |
| 22 | "biventricular pacing" or "bi ventricular pacing" | 83 |
| 23 | "biventricular resynchronisation" or "bi ventricular resynchronisation" | 2 |
| 24 | "biventricular resynchronization" or "bi ventricular resynchronization" | 0 |
| 25 | "cardiac resynchronisation" or "cardiac resynchronization" | 133 |
| 26 | "ventricular resynchronisation" or "ventricular resynchronization" | 8 |
| 27 | (#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26) | 795 |
| 28 | (#15 AND #27) | 123 |
| 29 | MeSH descriptor Echocardiography, Doppler explode all trees | 670 |
| 30 | MeSH descriptor Ultrasonography, Doppler explode all trees | 1785 |
| 31 | MeSH descriptor Laser-Doppler Flowmetry, this term only | 437 |
| 32 | (doppler) | 4895 |

| | Keywords/search history | Results |
|---|---|---|
| 33 | (#29 OR #30 OR #31 OR #32) | 4895 |
| 34 | (#28 AND NOT #33) | 76 |

**Table 31 Cochrane search for PiCCO (28 August 2008)**

| | Keywords/search history | Results |
|---|---|---|
| 1 | (picco or "Pulse induced contour cardiac output" or pulsion) | 26 |
| 2 | (pcco or "Pulse contour cardiac output") | 5 |
| 3 | "pulse contour" OR "pulse contour analysis" | 26 |
| 4 | "pulsion medical systems" | 2 |
| 5 | (#1 OR #2 OR #3 OR #4) | 52 |
| 6 | MeSH descriptor Hemodynamics explode all trees | 34,430 |
| 7 | (Hemodynamic* or Haemodynamic*) | 15,974 |
| 8 | (#6 OR #7) | 40,117 |
| 9 | (#5 AND #8) | 30 |
| 10 | MeSH descriptor Intensive Care explode all trees | 873 |
| 11 | "intensive care" or "critical care" or "subacute care" | 14,350 |
| 12 | "intensive therapy" or "close attention unit" | 428 |
| 13 | "respiratory care unit" or "respiratory care units" | 20 |
| 14 | "special care unit" or "special care unit" | 41 |
| 15 | MeSH descriptor Intensive Care Units explode all trees | 1858 |
| 16 | (#10 OR #11 OR #12 OR #13 OR #14 OR #15) | 14,939 |
| 17 | (#5 AND #16) | 13 |
| 18 | (#9 OR #17) | 35 |
| 19 | (#9 AND #17) | 8 |
| 20 | MeSH descriptor Adult explode all trees | 365 |
| 21 | (adult* OR "middle age") | 239,522 |
| 22 | (aged OR elder* OR senescence) | 252,227 |
| 23 | (Octogenarian* OR Centenarian* OR Nonagenarian*) | 42 |
| 24 | (#20 OR #21 OR #22 OR #23) | 333,430 |
| 25 | (#18 AND #24) | 24 |
| 26 | MeSH descriptor Child explode all trees | 0 |
| 27 | MeSH descriptor Pediatrics explode all trees | 386 |
| 28 | MeSH descriptor Hospitals, Pediatric, this term only | 160 |
| 29 | MeSH descriptor Pediatric Nursing, this term only | 91 |
| 30 | MeSH descriptor Pediatric Assistants, this term only | 0 |
| 31 | (child OR children OR childhood) | 63,635 |
| 32 | (pediatric* or paediatric*) | 24,636 |
| 33 | (#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32) | 68,221 |
| 34 | (#18 AND #33) | 3 |
| 35 | (#19 OR #25 OR #34) | 28 |
| 36 | MeSH descriptor Echocardiography, Doppler explode all trees | 670 |
| 37 | MeSH descriptor Ultrasonography, Doppler explode all trees | 1785 |

| | Keywords/search history | Results |
|---|---|---|
| 38 | MeSH descriptor Laser-Doppler Flowmetry, this term only | 437 |
| 39 | (doppler) | 4895 |
| 40 | (#36 OR #37 OR #38) | 2209 |
| 41 | (#35 AND NOT #40) | 28 |

**Table 32 HTA websites searched in this review (10 December 2007)**

| | |
|---|---|
| **Australia** | Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S) http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm<br>Centre for Clinical Effectiveness, Monash University http://www.med.monash.edu.au/healthservices/cce/evidence/<br>Health Economics Unit, Monash University http://chpe.buseco.monash.edu.au |
| **Austria** | Institute of Technology Assessment / HTA unit http://www.oeaw.ac.at/ita/e1-3.htm |
| **Canada** | Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/site/index.php?home<br>Institute of Health Economics (IHE) http://www.ihe.ca/index.html<br>Canadian Coordinating Office for Health Technology Assessment (CCHOTA) http://www.ccohta.ca/entry_e.html<br>Canadian Health Economics Research Association (CHERA/ACRES)—Cabot database http://www.mycabot.ca<br>Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org<br>Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca<br>Health Utilities Index (HUI) http://www.fhs.mcmaster.ca/hug/index.htm<br>Institute for Clinical and Evaluative Studies (ICES) http://www.ices.on.ca |
| **Denmark** | Danish Institute for Health Technology Assessment (DIHTA) http://www.dihta.dk/publikationer/index_uk.asp<br>Danish Institute for Health Services Research (DSI) http://www.dsi.dk/engelsk.html |
| **Finland** | FINOHTA http://finohta.stakes.fi/EN/index.htm |
| **France** | L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES) http://www.anaes.fr/ |
| **Germany** | German Institute for Medical Documentation and Information (DIMDI) / HTA http://www.dimdi.de/dynamic/en/index.html |
| **Netherlands** | Health Council of the Netherlands Gezondheidsraad http://www.gr.nl/adviezen.php |
| **New Zealand** | New Zealand Health Technology Assessment (NZHTA) http://nzhta.chmeds.ac.nz/ |
| **Norway** | Norwegian Knowledge Centre for the Health Services http://www.kunnskapssenteret.no/index.php?show=38&expand=14,38 |
| **Spain** | Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I/Health Technology Assessment Agency (AETS) http://www.isciii.es/htdocs/en/index.jsp |
| | Catalan Agency for Health Technology Assessment (CAHTA) http://www.aatrm.net/html/en/Du8/index.html |
| **Sweden** | Swedish Council on Technology Assessment in Health Care (SBU) http://www.sbu.se/www/index.asp<br>Center for Medical Health Technology Assessment (CMT) http://www.cmt.liu.se/english?l=en |
| **Switzerland** | Swiss Network on Health Technology Assessment (SNHTA) http://www.snhta.ch/home/portal.php |
| **United Kingdom** | National Health Service Quality Improvement: Scotland (NHS QIS) http://www.nhshealthquality.org/nhsqis/43.0.140.html<br>National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA) http://www.hta.nhsweb.nhs.uk/<br>University of York NHS Centre for Reviews and Dissemination (NHS CRD) http://www.york.ac.uk/inst/crd/<br>National Institute for Clinical Excellence (NICE) http://www.nice.org.uk/ |
| **United States** | Agency for Healthcare Research and Quality (AHRQ) http://www.ahrq.gov/clinic/techix.htm<br>Harvard School of Public Health—Cost-Utility Analysis Registry http://www.tufts-nemc.org/cearegistry/<br>US Blue Cross/ Blue Shield Association Technology Evaluation Center http://www.bcbs.com/consumertec/index.html |

# Abbreviations

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|---|---|
| μ | mean cardiac output |
| AIHW | Australian Institute of Health and Welfare |
| AV | atrioventricular |
| BPM | beats per minute |
| CCU | coronary care unit |
| CI | confidence interval |
| CO | cardiac output |
| CSA | cross-sectional area |
| CW | continuous wave |
| d | mean difference or bias |
| FDA | Food and Drug Administration (USA) |
| HTA | health technology assessment |
| ICU | intensive care unit |
| MSAC | Medical Services Advisory Committee |
| NHMRC | National Health and Medical Research Council |
| PAC | pulmonary artery catheter |
| PiCCO | continuous cardiac output |
| PPICO | target population, prior tests, index tests, comparator, outcome |
| PW | pulse wave |
| QUOROM | quality reporting of meta-analyses |
| SD | standard deviation |
| VV | interventricular |

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