Australian Government

Medical Services Advisory Committee

Public Summary Document

Application 1139 – Measurement and Determination of Procalcitonin

Applicant: **BRAHMS Aktiengesellschaft, Germany**

Date of MSAC consideration: **54th MSAC meeting, 29 November 2011**

1. Purpose of application

In April 2009 an application was received from BRAHMS Aktiengesellschaft, Germany requesting Medicare Benefits Schedule (MBS) listing of a commercial immunoluminometric assay (ILMA) used to determine the concentration of procalcitonin (PCT) in human serum and plasma for diagnosing life threatening infections and sepsis in patients, and monitoring the course and control of antibiotic therapy.

Although the application was received from a single proprietary manufacturer, MSAC's usual approach is to consider assessments across a 'generic' group of related products because an MBS item is usually described as a professional service, not a particular brand of technology. Therefore, on advice from the Advisory Panel, the objective of the assessment to be conducted was broadened. The intervention of interest was defined as 'measurement of procalcitonin' – that is, the assessment was not limited to consideration of the BRAHMS commercial products.

2. Background

A commercial ILMA is used to determine the concentration of procalcitonin (PCT) in human serum and plasma for diagnosing life threatening infections and sepsis in patients and monitoring the course and control of antibiotic therapy. Currently there are five different commercial immunoassays available for quantitative determination of PCT concentrations, with the choice of assay dependent on the intended clinical use. In all assays, serum or plasma samples may be used. Sample size depends on the assay choice.

PCT, a glycoprotein, is a peptide precursor of the hormone calcitonin. However the exact origin and mechanisms of PCT remain largely unknown. In microbial infections and severe systemic inflammatory responses, the serum level of PCT markedly increases approximately three hours after a pro-inflammatory stimulus or bacterial induction, reaching maximum values after 6-8 hours. Serum levels have been shown to reach levels >0.1 ng/mL in localised infection (e.g., lower respiratory tract infections (LRTIs)) and between 10 and 100 ng/mL or greater in severe sepsis. The increase in serum PCT levels in response to bacterial infection has been shown to correlate with the severity of the infection and with mortality.

Measured serum and plasma PCT levels are interpreted based on the clinical setting, the site and extent of infection, and co-morbidities. Increased levels of PCT may not always be related to systemic bacterial infection; the level of PCT has also been shown to markedly increase in:

- neonates <48 hours of age (physiological elevation);
- patients undergoing treatment with OKT3 antibodies and other drugs stimulating the release of pro-inflammatory cytokines;

- patients with invasive fungal infections, acute attacks of plasmodium falciparum malaria;
- patients with prolonged or severe cardiogenic shock, prolonged severe organ perfusion anomalies, small cell lung cancer, medullary C-cell carcinoma of the thyroid; and
- patients with severe systemic inflammatory conditions such as inhalational injury, pulmonary aspiration, severe burns , pancreatitis, heat stroke, mesenteric infarction), multi-trauma, extensive surgery, and infections such as pneumonitis.

The requested listing is for measurement of PCT to be included alongside clinical assessment, other indirect biomarkers of infection (e.g. C-reactive protein) and other tests, and not as a stand-alone diagnostic test for bacterial infection. The Assessment Report stressed that PCT testing should always be interpreted in the clinical context of the patient and the PCT results used in conjunction with other laboratory findings.

Sepsis refers to a bacterial infection in the bloodstream or body tissues. Sepsis and related conditions are significant causes of morbidity and mortality, particularly in the elderly, immunocompromised and critically ill patients, and therefore utilise considerable healthcare resources.

The measurement of PCT is a two-site immunoassay used to determine the concentration of PCT in human serum and plasma. All assays are based on the formation of a "sandwich" antigen-antibody complex. The intended purpose of the measurement of PCT is to determine the concentration of PCT in human serum and plasma in patients suspected of bacterial infection and to guide microbial therapy.

3. Prerequisites to implementation of any funding advice

The test for the measurement of PCT is listed, but not registered, with the Australian Therapeutics Goods Administration (TGA) as 'BRAHMS Dynotest or BRAHMS Lumitest kits' Australian Register of Therapeutic Goods (ARTG) 26781. At the time of application, in-vitro diagnostic medical devices (IVDs) were exempt from pre-market regulatory scrutiny under the *Therapeutic Goods Act 1989*.

The new Medical Devices Amendment Regulations that commenced on 1 July 2010 implemented a new regulatory framework that incorporates IVDs under Chapter 4 of *Therapeutic Goods Act 1989*. A four-year transition period from the current regulatory framework for IVDs to the new regulatory framework has been provided. IVDs that are currently listed, registered, or exempt, will be required to be included prior to the end of the transition period.

All pathology tests require a quality assurance program such as those administered through the National Association of Testing Authorities, (NATA), Australia and the Royal College of Pathologists of Australia (RCPA).

4. Proposal for public funding

Although not directly specified in the application, the MBS listing implied by the application could be summarised as presented in the following table:

Proposed MBS item descriptor

Category 6 – PATHOLOGY SERVICES
Quantitation in human serum or plasma by any method except reagent tablet or reagent strip (with or without reflectance meter) of procalcitonin-1 test
Fee: $60.00

Currently, there are no MBS items listed for measurement of procalcitonin. However, other relevant items are listed that directly or indirectly indicate the presence of sepsis. These include blood cultures for pathogenic micro-organisms - identification of cultured pathogens and if necessary antibiotic sensitivity; microscopy and culture to detect pathogenic micro-organisms from

specimens of sputum - pathogen identification and antibiotic sensitivity testing and leucocyte count and C-reactive protein quantitation.

Sepsis is a major cause of morbidity and mortality and the diagnosis of infection is essential to the success of antibiotic therapy and should be made before commencement of therapy. Early diagnosis and assessment of the systemic inflammatory response to infection is crucial. However, there are certain limitations to the microbiological culture technique, concerning low sensitivity and the time until reliable culture results are available. There is a need for a timely laboratory marker to discriminate systemic inflammatory response syndrome (SIRS) from a non-infectious cause and sepsis.

The Advisory Panel advised that the populations who have the greatest capacity to benefit from the measurement of PCT include:

1. patients in an intensive care unit who have the signs and symptoms of sepsis; and
2. patients who present to a general practitioner (GP) or the emergency department (ED) with the signs and symptoms of lower respiratory tract infections (LRTI).

The applicant suggested that the request for measurement of PCT will be made by physicians to diagnose, differentiate or manage patients with severe or systemic bacterial infections, and that the service will only be provided by Approved Pathology Providers as determined by the Commonwealth.

The majority of PCT measurements will be performed by a clinical laboratory (either in a public hospital or by a private pathology organisation) as a response to requests from clinicians (specialist or general practitioners). No additional staff are required to perform the diagnostic assay PCT as these scientists/technicians/nurses will already be employed by the laboratory/hospital.

5. Consumer Impact Statement

It appears that a procalcitonin test would be of most value if it could be a stand-alone or highly indicative test that clinical treatment could be guided by – rather than one of a number of tests. The present evidence does not support this in the areas where the most work has been done, that is: in intensive care, or for patients who present to a general practitioner or the emergency department with the signs and symptoms of pneumonia/lower respiratory tract infection.

Meningitis in children is an area of concern for parents as the signs and symptoms are often not clearly differentiated from influenza (for parents and the medical profession), and the consequences of not detecting bacterial meningitis quickly enough can be dire. However, good quality evidence of the efficacy of a PCT test in diagnosing bacterial meningitis was lacking but it is acknowledged that this is an area that would be very hard to study with randomised controlled trials.

6. Proposed intervention's place in clinical management

PCT is simple to measure by different immunoassay methods. The measurement of PCT will be used in addition to current clinical practice (which does not include routine PCT testing).

The population in an intensive care unit who are at risk of sepsis is distinguished from patients who present to a GP or the ED with the signs and symptoms of LRTI because the clinical management of the former group of patients differs from that of the latter.

Typical management algorithms for both populations are presented in Figure 1 and Figure 2. For each population, the clinical decision is a scenario where the measurement of PCT is not available (the current scenario) and the clinical decision is a scenario where the measurement of PCT is available (the proposed scenario) is presented.

Figure 1: Clinical decision tree for patients suspected of, or with, sepsis in ICU

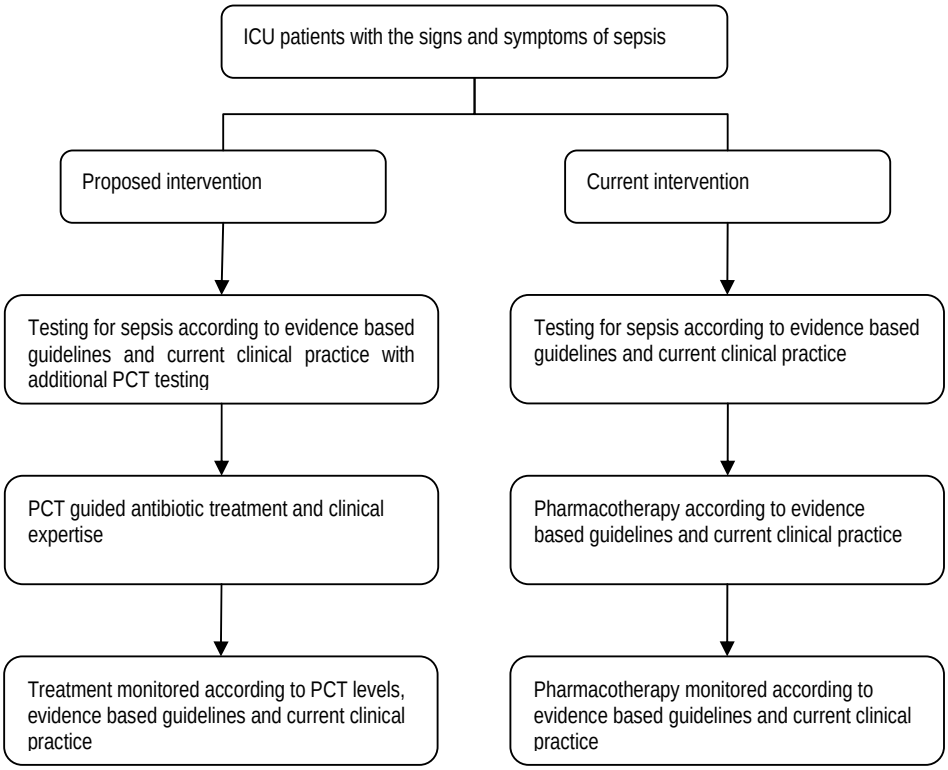
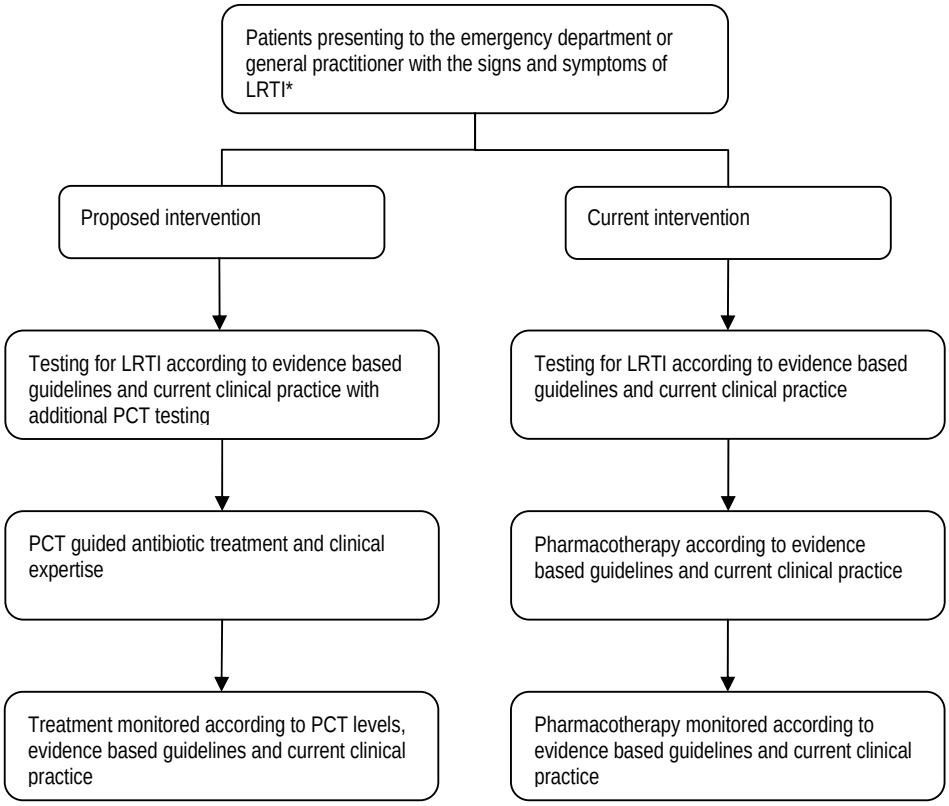


Figure 2: Clinical decision tree for diagnosis of LRTI in a patient presenting to a general practitioner or emergency department



The MSAC assessment addressed the research question of whether management that involves the use of measurement of PCT to determine the presence of a bacterial infection and to guide antibiotic therapy compared with current management excluding this test, results in an improvement in quality-adjusted survival for patients who have the signs and symptoms of sepsis in an intensive care unit; and patients who present to their GP or ED with a suspected LRTI.

7. Comparator to the proposed intervention

For patients in an intensive care unit (ICU) who have the signs and symptoms of sepsis and patients who present to a GP or ED with the signs and symptoms of LRTI, the measurement of PCT is not likely to be used in isolation for decision making. It is recommended that PCT should always be interpreted in the clinical context of the patient and the PCT results used in conjunction with other laboratory findings.

It was considered that the use of the measurement of PCT is unlikely to replace any of the currently used biological markers of infection to any substantial degree and would not be used in isolation for decision making.

The comparator assumed to be relevant to the assessment of the measurement of PCT is therefore current practice, or "no use of the measurement of PCT".

Routine diagnostic investigations currently utilised for diagnosing severe bacterial infection and/or sepsis, directly and indirectly are summarise below:

Direct tests

- Blood culture; and
- Microscopy and culture (e.g urine, sputum, Cerebrospinal fluid (CSF)).

Indirect tests

- C-reactive protein (CRP);
- Erythrocyte sedimentation rate (ESR);
- White cell count (WCC) and differential; and
- Chest X-ray.

Relevant existing tests that are included on the MBS include blood cultures, and C-reactive protein. The following table provides a list of relevant MBS items of relevant diagnostic investigations:

MBS items of relevant diagnostic investigations

Item	Item description	Schedule fee	75% benefit	85% benefit
Blood tests				
66500	Quantitation in serum, plasma, urine or other body fluid (except amniotic fluid), by any method except reagent tablet or reagent strip (with or without reflectance meter) of: acid phosphatase, alanine aminotransferase, albumin, alkaline phosphatase, ammonia, amylase, aspartate aminotransferase, bicarbonate, bilirubin (total), bilirubin (any fractions), C-reactive protein, calcium (total or corrected for albumin), chloride, creatine kinase, creatinine, gamma glutamyl transferase, globulin, glucose, lactate dehydrogenase, lipase, magnesium, phosphate, potassium, sodium, total protein, total cholesterol, triglycerides, urate or urea - 1 test	$9.75	$7.35	$8.30
65060	Haemoglobin, erythrocyte sedimentation rate, blood viscosity - 1 or more tests	$7.90	$5.95	$6.75
73802	Leucocyte count, erythrocyte sedimentation rate, examination of blood film (including differential leucocyte count), haemoglobin, haematocrit or erythrocyte count - 1 test	$4.60	$3.45	$3.95
Microscopy and culture				
69354	Blood culture for pathogenic micro-organisms (other than viruses), including sub-cultures and (if performed): (a) identification of any cultured pathogen; and (b) necessary antibiotic susceptibility testing; to a maximum of 3 sets of cultures - 1 set of cultures	$30.95	$23.25	$26.35
69357	2 sets of cultures described in 69354	$61.85	$46.40	$52.60
69360	3 sets of cultures described in 69354	$92.80	$69.60	$78.90
69318	Microscopy and culture to detect pathogenic micro-organisms from specimens of sputum (except when part of items 69324, 69327 and 69330), including (if performed): (a) pathogen identification and antibiotic susceptibility testing; or (b) a service described in items 69300, 69303, 69306 and 69312; 1 or more tests on 1 or more specimens	$34.00	$25.50	$28.90
69333	Urine examination (including serial examination) by any means other than simple culture by dip slide, including: (a) cell count; and (b) culture; and (c) colony count; and (d) (if performed) stained preparations; and (e) (if performed) identification of cultured pathogens; and (f) (if performed) antibiotic susceptibility testing; and (g) (if performed) examination for pH, specific gravity, blood, albumin, urobilinogen, sugar, acetone or bile salts	$20.70	$15.55	$17.60
69321	Microscopy and culture of post-operative wounds, aspirates of body cavities, synovial fluid, CSF or operative or biopsy specimens, for the presence of pathogenic micro-organisms involving aerobic and anaerobic cultures and the use of different culture media, and including (if performed): (a) pathogen identification and antibiotic susceptibility testing; or (b) a service described in item 69300, 69303, 69306, 69312 or 69318; specimens from 1 or more sites	$48.45	$36.35	$41.20
Chest X-ray				
58500	Chest (lung fields) by direct radiography (NR) Bulk bill incentive	$35.35	$26.55	$30.05
58503	Chest (lung fields) by direct radiography (R) Bulk bill incentive	$47.15	$35.40	$40.10

Source: January 2011 Medicare Benefits Schedule

8. Comparative safety

A literature search located studies that directly addressed the question of whether the use of measurement of PCT was used to guide antibiotic use and the consequence of using PCT-guided antibiotic therapy.

The literature search found no reports that related to studies that specifically investigated the safety of measurement of serum PCT.

The medical literature was searched to identify relevant studies and reviews to inform the assessment of measurement of PCT as a means of determining bacterial infection and guiding antibiotic therapy. Table 3A in the Assessment Report (page xvi) outlines the 14 included randomised controlled studies – seven intensive care studies and seven emergency department/primary care studies.

MSAC and ESC noted that, given the nature of this intervention, it is not anticipated that it would be associated with any safety issues as the determination of PCT levels requires a blood test which poses little or no risk to patient safety.

Measurement of PCT requires patients to undergo a simple blood test, as such it is not anticipated that there would be any safety concerns with this intervention aside from harm that may arise from a false positive or false negative result.

9. Comparative effectiveness

A literature search located studies that directly addressed the question of whether the use of measurement of PCT was used to guide antibiotic use and the consequence of using PCT-guided antibiotic therapy.

A literature search identified a total of 14 randomised controlled trials (RCTs) (seven studies in the ED / GP setting and seven studies in the ICU setting). Two RCTs were conducted in the GP setting, five RCTs in the ED setting and seven RCTs in the ICU setting. The key results from these studies are discussed below.

Two systematic reviews and meta-analyses investigated the diagnostic accuracy of PCT.

Across the RCTs, seven outcome measures are reporting in the Assessment Report (mortality, antibiotics prescribed, hospitalisations, length of stay in hospital, admission to ICU, days with adverse events from antibiotics and disease-specific complications / organ support).

Mortality

Four studies with mortality as a primary endpoint were included. Analysis from the individual studies does not reveal any significant difference in mortality between the PCT-guided arm and the control arm. Pooling the mortality data from the four studies supports the conclusion that mortality was comparable between the two treatment groups. The study by Svoboda et al (2007) appears to show quite a strong trend towards fewer deaths in the PCT-guided arm, but the confidence intervals (CIs) are wide due to the small numbers in this study (information about whether the sample size was powered to detect a difference in mortality was not provided in the study report). The mortality endpoint reported by Schuetz et al. (2009) forms part of a composite primary endpoint of adverse events.

Thirteen studies included the number of patients who were deceased during the course of the trial. The exception was the study by Briel (2008), conducted in a primary care setting. Burkhardt (2010) is not included in the analysis as no patients were recorded as having died during the trial period. Pooled analysis indicated that the use of PCT-guided antibiotic therapy did not appear to have a deleterious effect on patients, or a beneficial effect.

MSAC and ESC noted that there was no statistically significant difference in mortality detected in any of these studies.

Antibiotics Prescribed

Seven RCTs reported as an outcome, the number of antibiotics prescribed. All studies, with the exception of Kristoffersen (2009), reported significant reductions in antibiotic prescribing. The use of a PCT guided algorithm resulted in a significant decrease in antibiotic prescribing, across the studies, pooled OR 0.21 (95%CI 0.08, 0.51). However, there was significant heterogeneity in the results ((χ2=107.18, I2=94%). Across the studies, the rate of antibiotic prescribing in the control arm varied markedly, from a low of 37.1% to 99% reflecting differences in the trial populations and the trial settings. Both trials conducted in the primary setting had results that were very favourable towards PCT-guided therapy. Briel (2008), in particular, was very favourable.

The rate of antibiotic prescription was 798/1100 (72%) in the PCT-guided group and 972/1115 (87%) in the control group. The use of a PCT-guided algorithm resulted in a significant decrease in antibiotic prescribing, pooled OR 0.33 (95% CI 0.15, 0.71)). However, significant heterogeneity remains across the trials ((χ2=28.27, I2=86%). The study by Kristoffersen (2009) has results that differ in direction from the other studies. This is likely because the investigators did not contact the participating departments or physicians to check whether they were actually adhering to the PCT guidelines. Additionally, in this study, the guidelines recommended a lower level of PCT (>0.5 ug/l) at which to initiate antibiotic therapy.

MSAC and ESC noted that six RCTs reported a statistically significant reduction in antibiotic prescribing in the PCT group and that the applicant commented that Kristoffersen (2009) recommended a higher level of PCT.

Hospitalisations

Five RCTs reported on hospitalisation as an outcome measure. None of the studies reported a significant difference between PCT-guided patients or control/standard therapy in patients requiring hospitalisations. MSAC and ESC noted no RCTs reported a statistically significant difference in numbers of patients requiring hospitalisation.

Length of Stay in Hospital

All studies (13 RCTs – five in GP / ED setting and eight in ICU setting) reported on length of hospital/ICU stay as a trial outcome. The studies by Hochreiter (2009) and Nobre(2008) reported a significant decrease in ICU stay for patients in the PCT-guided group, of 2 days and 3 days respectively. However, the study by Jensen et al. (2011) and Bouadma (2010) report increases in time spent in the ICU, of one day, for patients in the PCT-guided group. The other studies reported non-significant results.

MSAC and ESC noted that there were five RCTs in the GP / ED setting and eight in the ICU setting, with two studies reporting a statistically significant decrease in ICU length of stay and two studies reporting a statistically significant increase in ICU length of stay, compared to only one study identified by the applicant as reporting an increase, however, the remaining nine studies found no statistically significant differences.

Admission to ICU

Four RCTs undertaken in the ED reported on the need for admission to an ICU as a trial outcome. The use of PCT-guided therapy did not appear to result in an increase in the need for ICU admission.

MSAC and ESC noted that there was no statistically significant difference reported in ICU admission rates.

Days with Adverse Events with Antibiotics

The literature search identified two RCTs in the GP setting and 1 RCT in the ED setting. The Schuetz et al. (2009) trial, conducted in an ED, reported that patients in the PCT-guided arm had a statistically significant reduction in adverse events, such as diarrhoea, rash, nausea, compared to

patients in the standard therapy arm, reflecting the increased prescribing rate that was recorded in the control arm. Both of the studies conducted in a primary care setting reported on the median number of days patients suffered from adverse events from antibiotics. There was no statistical difference in the trials between those patients treated according to PCT-guided therapy and the control.

MSAC and ESC noted that in one RCT, it was reported to have a significant reduction in the number of days with adverse events in the ED setting, and a significant reduction in days with adverse events in the GP setting in another study, but no significant difference in the third study.

Disease Specific Complications / Organ Support

The Schuetz et al. (2009) and Jensen et al. (2011) trials reported on disease specific complications and both studies expressed some concern about the outcomes for the PCT-guided arm. The results from Schuetz et al. (2009) show that the trend is towards increased disease-specific complications and death in the PCT guided arm of the trial, although results did not reach significance. The results from Jensen et al. (2011) show that the need for organ support, such as mechanical ventilation, was significantly greater in the PCT-guided arm, but that the number of deaths did not differ between the two arms of the trial.

The requested listing is for measurement of PCT to be included alongside clinical assessment, other indirect biomarkers of infection (e.g. CRP) and other tests, and not as a stand-alone diagnostic test for bacterial infection. However, as background information the report includes evidence about the accuracy of PCT in the diagnosis of sepsis and in particular threshold cut-offs used in the studies to diagnose infection. The studies included are not exhaustive and are only studies conducted within the populations of interest in this assessment. The assessment of the clinical effectiveness of PCT is not based on these studies.

MSAC and ESC noted that there were no statistically significant differences in disease-specific complications although the direction of effect tended to be against PCT.

Analysis from the individual studies does not report any significant different in mortality between, the PCT-guided arm and the control arm. Pooling the mortality data from the four studies supports the conclusion that mortality was comparable between the two treatment groups. The study by Svoboda (2007) appears to show quite a strong trend towards lower deaths in the PCT-guided arm, but the confidence intervals are very wide due to the very small numbers in this study (information about whether the sample size was powered to detect a difference in mortality was not provided in the study report). The mortality endpoint reported by Schuetz (2009) forms part of composite primary endpoint of adverse events.

MSAC noted ESC advice that out of the seven outcome measures, strong evidence of a significant difference was only reported in one measure (antibiotic prescriptions) and this was in the GP / ED setting only. MSAC and ESC also noted that the consequences of a reduction in antibiotic prescriptions for patients' health are unclear.

10. Economic evaluation

A cost-effectiveness analysis was undertaken for this assessment.

Assessment of measurement of PCT will not substitute for any other direct or indirect measure of sepsis. A comparative cost analysis of measurement of PCT compared to no PCT is presented. Cost effectiveness analyses were undertaken based on the evidence of clinical effectiveness from the included studies in the primary care and ED settings but not in the ICU setting. This is because evidence of the clinical effectiveness of PCT-guided therapy in the ICU setting was lacking.

A unit cost of $60.00 per measurement of PCT is assumed, based on information provided by the applicant. It is proposed that measurement of PCT will be an additional test alongside other laboratory tests and clinical judgement, incurring an additional cost to the treatment of infection.

Cost-effectiveness of the measurement of PCT in the Primary Care Setting

Of patients visiting their GP with the signs and symptoms of respiratory tract infection (RTI) who are tested for PCT, 23% will have antibiotics prescribed compared with 64% in the group who are not tested for PCT. The additional cost per course of antibiotics avoided in the PCT group is $117. Only the costs of the PCT test and antibiotics are included within this economic evaluation because additional information about health consequences and other cost consequences that may (or may not) occur from avoiding prescriptions for antibiotics were not available from the trials. To the extent that some patients in the control arm may require admission to hospital and parental therapy in the absence of PCT testing then the avoided cost of antibiotic therapy may be an underestimate of the cost-savings arising out of PCT testing. One patient in the control arm of the Burkhardt trial did require hospitalisation but this was not reported as being of significance.

Cost-effectiveness of the measurement of PCT in the Emergency Department Setting

Of patients visiting an ED with the signs and symptoms of RTI who are tested for PCT, 75.4% will have antibiotics prescribed compared with 87.6% in the group who are not tested for PCT. The additional cost per course of antibiotics avoided in the PCT group is $1409. To estimate these costs, the study by Schuetz (2009) was used as a basis because this study had been powered to detect a difference in the consequences of not prescribing antibiotics. Some costs could not be included. For example, the study reported that patients in the standard therapy arm had a greater likelihood of being admitted to an ICU, but the length of time patients were in an ICU was not reported in the trial. Length of hospital stay was reported and has therefore been used. This may favour the control arm. Another cost that was not included in the analysis above is that for disease specific complications. The study reported that these complications occurred more frequently in the PCT group, but the type of complications was not made clear in the study. This may favour the PCT guided arm.

Longer-term analysis, for example, of the possible benefit of reduced antibiotic prescribing for antibiotic resistance has not been done. This is primarily because it is difficult to separate out the role of the prescribing of antibiotics for non-bacterial RTI from other postulated causes of antibiotic resistance, such as the use of antibiotics in animal populations and patients not finishing their courses of antibiotics. In the event that it was possible to separate out the effects of the role of prescribing of antibiotics on the emergence of resistance, expert advice is that the measurement of PCT effect size on the emergence of resistance is likely to be very small, whereas the confounders are very large in these specific populations.

Measurement of PCT is not cost saving from a health care perspective compared to no measurement of PCT. The additional cost per antibiotic prescription avoided may range from $117 to $1,409, depending on the setting in which patients are being tested and taking into consideration assumptions about likely benefits in terms of number of antibiotic prescriptions avoided. Longer-term benefits in the form of hospitalisations avoided or mortality reductions were not included in the economic evaluation as these benefits were not demonstrated by the available evidence. These are not costs that are borne by the MBS.

MSAC agreed with ESC advice that it is unlikely there will be a significant benefit in the reduction of prescribed antibiotics in terms of reducing antibiotic resistance. The measurement of PCT is a strict add-on to the existing management pathway so no cost offsets arising from other tests/investigations avoided are included. The measurement of PCT will not be cost-saving as the cost of antibiotic prescriptions avoided will provide only a modest cost-offset to the cost of measuring PCT, and these cost savings have been shown to be less than the cost of PCT testing.

The application suggested a proposed fee for the measurement of PCT is $60, which includes the cost of the test (reagent, calibrators, QC); equipment component (depreciation, service etc); labour component (laboratory staff only); premises; and utilities.

The applicant has nominated a $60 schedule fee (75% MBS benefit of $45 and 85% benefit of $51). Given most pathology is bulk billed, out of pocket costs are likely to be at most minimal. MSAC and ESC noted that the expected co-payment / out of pocket costs were not considered in the report.

The Medicare Safety Net and Extended Medicare Safety Net are unlikely to have an impact.

11. Financial/budgetary impacts

MSAC and ESC noted that there are 4,489,500 LRTI problems (according to the Bettering the Evaluation and Care of Health (BEACH) data) managed by GPs in one year and agreed that the volume of PCT testing in this population could be substantial.

MSAC and ESC noted that the frequency of use per patient per year over a lifetime is not reported.

To estimate the financial implications for the government of listing the measurement of PCT on the MBS, surrogate measures were used to try to estimate the number of tests that may be ordered. The focus was on general practice because expert clinical advice holds that this setting would likely use measurement of PCT most widely. However, estimates of the likely use of the test in the private hospital setting are also included.

To estimate the potential number of PCT tests that may be requested if measurement of PCT were listed on the MBS, an attempt was made to estimate the number of patients who may visit their GP with the signs and symptoms of a LRTI as well as those with a diagnosis of chronic obstructive airways disease (COAD).

The estimates of the number of patients seen with LRTI by GPs and the numbers and rates of pathology ordering by GPs for respiratory conditions are derived from data obtained from the (BEACH) program. The BEACH study does not record a diagnosis of LRTI, but does record specific diagnoses, (e.g. bronchitis). Rates of community acquired pneumonia (CAP) are recorded in a category of other respiratory infections, rather than separately, as the rates are too low.

The following table estimates the number of respiratory problems that would be seen by GPs, separated into the relevant individual respiratory conditions that fall within the definition or symptoms of LRTI or COPD.

Estimates of the number of problems seen by GPs and the number of problems that fall within the definition of LRTI 1998-99 and 2007-08

	1998-99		2007-08	
	Rate per encounters	Number of problems	Rate per encounters	Nos. of problems
National	145.3	149,100,000	151.3	165,673,500
Respiratory	24.3	24,920,136	19.4	21,243,000
Acute bronchitis	3.3	3,384,216	2.4	2,628,000
COAD	0.8	820,416	0.8	876,000
cough	0.6	615,312	0.5	547,500
Other respiratory infections	0.5	512,760	0.4	438,000

Note: The number of general practice professional services claimed from Medicare Australia for the financial year 1998-99 was 102.6 million and for 2007-08 it was 109.5 million

MSAC and ESC noted that patient numbers per year (prevalence or incidence or mix over time) is not reported, but is likely to be less than the number of problems managed as some patients may have less than one test per year.

MSAC and ESC noted the total cost of the proposed intervention to the MBS at 100% of LRTI encounters ($269 million), 20% of LRTI encounters ($54 million), with the most likely being 3% of LRTI encounters ($8 million), with an additional $9m to be included if listed to includes patients with signs / symptoms of sepsis. MSAC and ESC agreed that if the test became available under the MBS, there is a risk of overuse of the item.

Total cost of the charges to the public were not reported.

The estimates in the following table are the likely cost to the MBS of requests for PCT tests in the general practice setting, with ESC noting that there are no cost offsets.

Likely costs to the MBS based on the estimate of the number of problems seen by general practitioners that fall within the definition of LRTI 2007-08

	Nos of problems	Cost of PCT test	If 100% of patients visiting GP referred for test# $	If 20% of patients visiting GP referred for test $	If 3%* of patients visiting GP referred for test $
Acute bronchitis	2,628,000	$60	157,680,000	31,536,000	4,730,400
COAD	876,000	$60	52,560,000	10,512,000	1,576,800
cough	547,500	$60	32,850,000	6,570,000	985,500
Other respiratory infections	438,000	$60	26,280,000	5,256,000	788,400
Total	4,489,500				8,081,100

#in the trials conducted in the general practice setting, all patients presenting with a respiratory tract infection were ordered a PCT test. Therefore, these figures would grossly underestimate the likely number of tests if following these trials because upper respiratory tract infections would also need to be included. *The likelihood of pathology being ordered in the management of respiratory problems was 3.2% in 2006-2008- Britt and Miller 2009 p. 73.

The table above indicates that if measurement of PCT were listed on the MBS for use in the general practice setting for patients who present to their GP with the signs and symptoms of LRTI then the likely financial implications to the MBS may be approximately $8,608,000.

In the event that measurement of PCT were listed on the MBS for patients with the signs and symptoms of sepsis, another setting for which there is likely to be a financial implications for the MBS is inpatients in a private hospital.

Expert advice is that PCT is most likely to mimic the CRP pathology test in terms of requests. MBS item 66500 includes CRP but also includes a suite of other measures. It is not possible to separate out the number of requests for CRP alone. Direct measures of infection for patients with sepsis are blood cultures, and for CAP, sputum cultures. Expert advice is that in the general practice setting, GPs are unlikely to order blood cultures or sputum cultures, for query LRTI (although they may order a chest x-ray) because these tests are deemed to be hospital-based tests and GPs usually diagnose and start antibiotics rather than run patients through a diagnostic regimen. Information about the frequency of requests for sputum or blood cultures could not be obtained from BEACH statistics reports of the most frequently requested pathology tests. Given the infrequency with which blood and sputum cultures appear to be requested by a GP, the Medicare statistics reporting the number of blood and sputum culture services are assumed to be for patients in a private hospital setting.

The PCT-guided algorithms, used in the clinical trials, recommend multiple measurements of PCT to indicate when to initiate antibiotic therapy, as a gauge of whether the antibiotic therapy is appropriate and as an indicator to cease antibiotic therapy. If the MBS listing and use of measurement of PCT were in accordance with these PCT-guided antibiotic algorithms then each patient suspected of sepsis may have multiple tests.

Using the number of services requested for blood and sputum cultures, the following Table shows estimates of the likely number of tests that may be requested for measurement of PCT. In estimating these figures it is assumed that one set of blood cultures will equate to one request for measurement of PCT. Multiple blood cultures, up to a maximum of three, may be ordered for each episode of suspected bacteraemia but they attract different MBS item numbers. If following the PCT-guided algorithms used in the trials, multiple tests for PCT measurement may be ordered for each episode of suspected sepsis, with some studies requiring daily PCT measurements. Therefore, the number of blood cultures is likely to be an underestimate of the number of PCT tests that may be requested. Trying to extrapolate from the number of sputum cultures to the likely number of PCT tests, has not been attempted, as it is not likely to be meaningful because the relevant MBS item may refer to one test multiple tests or multiple specimens.

Estimates of the potential number of tests to measure PCT levels

MBS item		Services 2010	Level at which PCT may be requested	Cost of PCT test	Likely cost if listed on MBS
69354	Blood cultures 1 set of cultures	148,605	148,605	$60	$8,916,300
69318	Sputum cultures 1 or more tests on 1 or more specimens	132,213	132,213	$60	$7,932,780

From these estimates, the likely financial implications for the government of the listing of measurement of PCT for patients presenting to their GP with the signs and symptoms of LRTI may be approximately $8 million dollars per year. If the listing also includes patients with the signs and symptoms of sepsis, the likely financial implications may be an additional $9 million per year. The likely number of tests may be 283,290 or greater at a potential cost to the MBS of $17 million per year. This may be an underestimate as it is possible that multiple tests of PCT may be done for each episode of sepsis or LRTI to guide antibiotic therapy.

12. MSAC key issues

MSAC found no key uncertainties around the evidence and conclusions for safety.

Routine measurement of PCT, with corresponding obligatory guidelines for antimicrobial therapy, for patients presenting to the ED with query LRTI or exacerbation of chronic obstructive pulmonary disease (ECOPD), alongside clinical assessment and other measures of sepsis, usually resulted in a reduction in the use of antibiotics. However, only one of the trials set in the ED was powered to address the question of whether this reduction in antibiotic therapy had any consequences for patients' health, and it reported non-significant increases in mortality and disease specific complications. The routine use of a PCT test for every person with a query LRTI in the emergency department would result in a large number being requested. The available evidence does not justify the routine measurement of PCT and use of a PCT-guided algorithm for antimicrobial therapy in the ED, as used in these trials.

The routine measurement of PCT, with corresponding obligatory guidelines for antimicrobial therapy, as an indicator of sepsis alongside clinical assessment for patients in an ICU setting may

not result in a reduction in antibiotic therapy. It was unclear whether following a PCT-guided algorithm for initiating or ceasing antibiotic therapy would have consequences for patients, as the majority of the studies in the ICU setting were not powered to answer this question. The one study that was powered to detect 28-day mortality reported no difference in survival, but did report that patients in the PCT-guided arm suffered increased rates of organ-related harm and had prolonged admission to ICU. The routine use of a PCT test in the ICU setting, often recommended on a daily basis, would result in a large number being requested. The available evidence does not justify the routine measurement of procalcitonin, and use of a PCT-guided algorithm for antimicrobial therapy in the ICU setting.

The routine measurement of PCT, with corresponding obligatory guidelines for antimicrobial therapy, for patients presenting to their GP with symptoms of respiratory tract infection (RTI), alongside clinical assessment, resulted in a reduction in the use of antibiotics in the two studies evaluated. However, neither of the trials was powered to measure any consequences to patients that may result from a reduction in antibiotic therapy. The routine use of a PCT test for every person who presents to their GP with the symptoms of RTI would result in a large number being requested. The evidence does not justify the routine measurement of PCT and use of a PCT-guided algorithm for antimicrobial therapy in the general practice setting.

Consistent information regarding the accuracy of levels of PCT needed to reliably differentiate between infectious and non-infectious SIRS appears to be lacking.

MSAC agreed with ESC that there is only strong evidence of effect on one of seven outcome measures (antibiotic prescriptions avoided), the implications of reduced antibiotic prescriptions for patients' health is not clear, and there is little chance of the reduction in antibiotic prescriptions having an impact on antibiotic resistance.

There is some clinical uncertainty regarding the extent of adoption of PCT measurement in clinical practice if listed on the MBS.

MSAC found that the measurement of PCT will not be cost-saving and patient health benefits are not clear.

MSAC and ESC agreed that if the measurement of PCT is listed on the MBS, financial outlays are subject to some uncertainty and the most likely net financial impact on MBS outlays will be $8 million to $20 million (but could be a lot higher). Members discussed at length that this test will not alter the clinical management pathway for the patient.

13. Other significant factors

MSAC agreed with ESC that:

- there are no intermediate outcomes in the primary care setting;
- there is a risk that GPs may order PCT for any type of RTI and not just for the severe cases;
- the evidence on diagnostic performance suggests there is a risk involved in relying on the test outcome for the treatment of a patient;
- the exclusion criteria for studies are unclear;
- details of trial design are not always available;
- trials were designed to show the effect on patients and not just diagnostic performance;
- there is no evidence that measurement of PCT has either a beneficial or adverse effect on health outcomes; and
- there is no reference standard for diagnostic accuracy, making it difficult to interpret the evidence in terms of comparative diagnostic performance.

MSAC and ESC noted the item descriptor does not constrain the use of the test to patient groups for whom evidence of effectiveness is available, for example, patients in an ICU setting with signs and symptoms of sepsis and patients presenting to a GP / ED setting with sign and symptoms of LRTI.

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

The applicant originally requested MBS listing of a commercial immunoluminometric assay (ILMA) used to determine the concentration of procalcitonin (PCT) in human serum and plasma for diagnosing life threatening infections and sepsis in patients and monitoring the course and control of antibiotic therapy. On the basis of advice from the Advisory Panel, the assessment was broadened to 'measurement and determination of procalcitonin' - that is, the assessment was not limited to consideration of the BRAHMS commercial products. The applicant originally requested public funding for the measurement and determination of PCT in biological fluids in hospitalised patients and in the primary care setting for the diagnosis and management of bacterial infections and sepsis. The Advisory Panel considered that the populations with the greatest capacity to benefit from the measurement of PCT included patients in intensive care units (ICUs) who have the signs and symptoms of sepsis; and patients who present to a General Practitioner (GP) or the Emergency Department (ED) with the signs and symptoms of lower respiratory tract infections (LRTI).

MSAC considered the strength of the evidence, relating to the measurement and determination of PCT for diagnosing life threatening infections and sepsis as well as monitoring the course and control of antibiotic therapy. MSAC recognised that there is a clear need for early accurate diagnosis of sepsis and severe bacterial infection to improve patient outcomes. MSAC noted that sepsis is currently managed based on a composite of clinical judgement according to the nature of a patient's presentation in conjunction with results of existing testing (such as erythrocyte sedimentation rate, C-reactive protein, chest x-ray, white cell count). MSAC noted that the introduction of PCT testing aims to supplement (not substitute for) the existing battery of tests ordered in the context of a clinical presentation where sepsis is suspected.

MSAC noted that there were no data on the accuracy of the test given there is no reference standard. MSAC found that there was little evidence that PCT rises earlier or is more accurate in predicting serious bacterial infection. MSAC agreed with the conclusion from the assessment report that PCT testing was safe but appeared to have no impact on hospitalisation or a significant impact on overall mortality. MSAC also noted across the studies looking at length of stay (LOS) in ICU, most suggested that PCT testing had no significant impact in reducing LOS.

MSAC noted there was some evidence suggesting a possible reduction in antibiotic prescribing in the PCT group but there was significant heterogeneity in results making it difficult to infer whether this had a downstream impact on the prevalence of antibiotic resistance in the community. MSAC agreed that adherence to established guidelines on appropriate antibiotic prescribing was more likely to impact on antibiotic resistance than introducing PCT testing.

MSAC noted that a cost effectiveness analysis was undertaken based on studies derived in a primary care or emergency department setting as there was no evidence of clinical effectiveness of PCT guided therapy in an ICU setting. This analysis was primarily based on the cost for avoided antibiotics and that other costs were difficult to identify. As a result, the analysis was unable to quantify the impact and possible cost saving from reducing antibiotic resistance by avoiding antibiotic exposure. MSAC agreed that it was difficult to justify the proposed fee of $60 per test compared with the low costs associated with existing tests.

Measurement of PCT is not cost saving from a health care perspective compared to no measurement of PCT. MSAC agreed that there was potential for high volume use with current wording of the proposed item descriptor and that the number of repeat tests outlined in the assessment report is likely to be an underestimation of the number of tests that may actually be ordered (particularly in an ICU setting). MSAC also agreed that the GP BEACH data used to estimate the likely volume of use/year was also likely to be an underestimation. MSAC therefore concluded that the total cost of $17 million per year was considered to be a gross underestimate especially given PCT testing has the potential to be used in a wider range of clinical scenarios than was originally considered in the assessment report.

MSAC noted that the turnaround time to receive test results in a general practice setting may be up to 24 hours compared to a hospital setting in which a result may only take up to 1-5 hours.

In relation to claims of PCT testing changing antibiotic prescribing, MSAC noted that the delay in obtaining results in the GP setting meant that the likelihood of the test result changing antibiotic prescribing / utilisation habits was reduced. MSAC noted the potential for point of care testing to affect this analysis, but also noted that no evidence was presented in this regard.

MSAC concluded that there were limitations highlighted in the study data on the accuracy of the test, even though the studies measured clinically relevant outcomes such as changing length of stay. MSAC noted the applicant comment about quality of data which was addressed in committee discussions. MSAC considered it likely that in an ICU setting, patients would be tested more than once per day.

MSAC acknowledged the potential for use of PCT in the right clinical setting. MSAC also noted that the point was made that there could be a place for PCT done as a point of care test in GP/ED setting as this had the potential to assist in diagnosis and reduce antibiotic prescribing.

15. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the safety, effectiveness and cost-effectiveness of measurement of procalcitonin in serum or plasma for diagnosing life threatening infections and sepsis, and monitoring the course and control of antibiotic therapy, MSAC considered there was currently insufficient evidence to support public funding for measurement of procalcitonin.

16. Context for decision

This advice was made in accordance with MSAC Terms of Reference.

MSAC is to:

Advise the Minister for Health and Ageing on medical services that involve new or emerging technologies and procedures and, where relevant, amendment to existing MBS items, in relation to:

- the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
- whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
- the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
- the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;
- other matters related to the public funding of health services referred by the Minister.

Advise the Australian Health Ministers' Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to effectively undertake its role. MSAC may delegate some of its functions to its Executive sub-committee.

17. Linkages to other documents

MSAC's processes are detailed on the MSAC Website at: www.msac.gov.au.

The Assessment Report is available at
http://www.msac.gov.au/internet/msac/publishing.nsf/Content/app1139-1