NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Procalcitonin testing for Diagnosing and monitoring sepsis (ADVIA Centaur BRAHMS PCT assay, BRAHMS PCT Sensitive Kryptor assay, Elecsys BRAHMS PCT assay, LIAISON BRAHMS PCT assay and VIDAS BRAHMS PCT assay)

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 30 June 2015

THEME: GENERAL

Comment number	Name and organisation	Section number	Comment	Response
1	Roche	1.1	The Diagnostic Assessment Report (DAR) indicates the safe use of PCT guided algorithms for antibiotic prescribing in ICU and emergency units. PCT guided algorithms resulted in reduced prescribing and savings in health care resources leading to overall cost savings compared to standard care. In our view, these findings are robust as indicated by the sensitivity analysis in the DAR and in light of the experience with procalcitonin testing in the NHS.	Thank you for your comment which the Committee considered.
2	The British In Vitro Diagnostics Association (BIVDA)	General	BIVDA has been in discussion with its members relating to the Consultation document on Procalcitonin testing for diagnosing and monitoring sepsis. Members have indicated their disappointment that the clear benefits of Procalcitonin in enabling targeted antibiotic use have not been taken into account by the committee.	Thank you for your comment which the Committee considered.

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Diagnostics Advisory Committee date: 30 June 2015

THEME: GENERALISABILITY OF STUDIES TO THE NHS

Comment number	Name and organisation	Section number	Comment	Response
3	Thermo Fisher	6.6	*It further noted that many of the studies were conducted and published several years ago, and that clinical practice in terms of antibiotic stewardship has changed considerably in the last few years. The Committee therefore considered whether the results of these studies were generalisable to the NHS. The Committee heard from the External Assessment Group that many of the studies did not clearly report how treatment decisions were made in the control arms.* It is understood that the Committee is concerned that the standard of care reported within some of the included trials differs from current clinical practice in the UK. As a result, the Committee has questioned whether the inclusion of procalcitonin into UK care pathways would necessarily generate the claimed benefits and/or outcomes reported. In response to this concern, the principal investigators (PIs) of the included trials were contacted and asked to provide clarification on the exact protocols/methods used within the 'standard of care' or control arm, and how this compares to the current UK approach to antibiotic stewardship; please see Appendix A for all responses.	Thank you for your comment which the Committee considered. The Committee noted that although the survey provided some reassurance on the generalisability of included studies to the NHS, the questionnaire contained a generic description of the UK standard of care and a leading question was used to obtain details of the control arms in the studies. Therefore the survey findings were considered to be at risk of bias. The Committee concluded that the uncertainty around the generalisability of the studies and the additional benefit that procalcitonin testing would provide in the NHS still remains. This Committee consideration is detailed in section 6.9 of the guidance document.

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			The results of this PI consultation showed that, in most cases, the studies conformed to the UK approach to antibiotic stewardship and any reported deviations were minor. A summary of this survey's results is as follows: • Investigators from 13/18 trials responded to our request, which covers approximately 80% of the total patient cohort evaluated (Appendix A) • Overall, the majority of respondents (10/13) confirmed that the standard of care used within the control arm of the RCT, for which they were the PI, was equivalent to the UK standard of care approach. Within the question template sent to the PIs, the UK standard of care was defined as: 'In the UK, the standard of care adopted to support antibiotic stewardship in secondary care is based on the following principles: • Do not start antibiotics without clinical evidence of bacterial infection. If there is evidence or suspicion of bacterial infection, use local guidelines to start	

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			prompt, effective antibiotic treatment • Review the clinical diagnosis and the continuing need for antibiotics by 48 hours from the first antibiotic dose and make a clear plan of action. To support prescribing decisions, the following five options are considered: 1) Stop, 2) Switch intravenous to oral, 3) Change, 4) Continue, and 5) Outpatient Parenteral Antibiotic Therapy • Antibiotic stewardship should be considered daily during ward rounds, including input from a multidisciplinary team (eg, microbiologists and intensivists) • Document the following on the medicines chart and in the person's medical notes: clinical indication, duration and/or review date, route and dose • Obtain cultures – knowing the susceptibility of an organism can lead to narrowing of broad-spectrum therapy, changing therapy to treat resistant pathogens, and stopping antibiotics when cultures suggest infection is unlikely' In the three instances where deviations from the UK	

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			standard of care were reported by the PIs, the differences were minor:
			• Roh 2010[1]; Roh and Lee 2013[2]; the PI reported that the control arm of these two studies were 'almost the same' as the UK standard of care approach. The differences described were:
			  ○ That a patient's initial diagnosis and continuing need for antibiotics is assessed by 48-72 hours
			  ○ There is no option for outpatient parenteral antibiotic therapy
			  ○ There is no formal multidisciplinary team, however, problems are discussed with other specialist staff members (eg, pulmonary radiologist)
			• Tang et al 2013[3]; the PI reported that the UK standard of care 'does not reach the requirement of our [the local] department'. The PI stated culture and specificity (c/s) results from the laboratory, in combination with the general therapy process, clinical symptoms and image results were used to support an overall evaluation	

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			Studies in which deviations were reported by the PI represent a minority (n=551/5105) of the total randomised patient population. In addition, the majority (11/13) of respondents stated that either pre-defined protocols and/or international guidelines were used to support/drive the approach taken within the standard of care arms. References: 1Roh YH. Antibiotic therapy with the guidance of procalcitonin in patients with community-acquired pneumonia. Chest 2010; 138(4). 2Roh YH, Lee BJ. Treatment of elderly patients with community-acquired pneumonia with the guidance of procalcitonin. Chest 2013; 144(4). 3Tang J, Long W, Yan L et al. Procalcitonin guided antibiotic therapy of acute exacerbations of asthma: a randomized controlled trial. BMC Infect Dis 2013; 13:596.	
4	Thermo Fisher	6.6	*Further, intensive care units are often at maximum occupancy so clinicians have to work efficiently to discharge patients who no longer need intensive care. The Committee therefore concluded that in the intensive care unit setting, the reductions in resource use reported in the included*	Thank you for your comment which the Committee considered. The Committee noted that a reduction in length of stay for an individual patient benefits the NHS in

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			studies when procalcitonin was added to standard clinical practice were unlikely to be realised in the NHS. It is queried whether the argument of 'maximum occupancy' in the ICU is valid as a reason for not allowing reductions in resource use to be realised in the UK. It is argued that a reduction in length of stay for the individual patient still provides more efficient de-escalation of care and should be considered a reduction in resource use on a per-patient basis. Indeed, there are initiatives to help map and manage patient flow in an ICU setting, such as the 'Monitoring Patient Flows in Critical Care' by the Intensive Care Society1, which indicate there is still the potential to make efficiency improvements. Critical care outreach is a multidisciplinary organisational approach to ensure safe, equitable and quality care for all acutely unwell, critically ill and recovering patients irrespective of location or pathway.2 This approach is critical to ensure there is efficient escalation, and de-escalation, of care within hospitals. Such initiatives ensure patients are located within the most appropriate setting eg, a general admissions ward versus the ICU. It is requested the	terms of opportunity cost. That is, when a patient is discharged from an intensive care unit, the place can be taken by another patient who requires intensive care. The Committee also noted that reduction in length of stay for an individual patient does not have an impact on the NHS budget, but may improve overall patient outcomes. The Committee decided to change section 6.7 of the guidance document to reflect this consideration.

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			Committee considers the use of procalcitonin to support these critical care patient-flow decisions within hospitals. References: 1 Intensive Care Society – Patient Flow Steering Group. Managing Patient Flow. 2008 www.ics.ac.uk/EasySiteWeb/GatewayLink.aspx?alId=1158 (last accessed 24 June 2015) 2 National Outreach Forum Operational Standards and Competencies for Critical Care Outreach Services. NOrF 2012	
5	Roche Diagnostics	6.6	Although there might be some uncertainty on the transferability of ICU LOS or hospital LOS data, the sensitivity analysis reported in 5.69 indicates that PCT guided algorithms would still be cost effective in adults in ICU and ED even under the extreme assumption that there would be no difference in LOS with PCT compared to standard care in the NHS.	Thank you for your comment which the Committee considered. When no difference in hospital stay was assumed, ICERs varied between £3390 and £3948 per QALY gained for adults in the intensive care unit or in the emergency department. However, the changes in QALYs and costs upon which the ICERs are based are small. The Committee noted that the QALYs for the procalcitonin testing group and the standard clinical practice group could be considered broadly equal. It noted therefore that the ICERs were uncertain and that it was unclear whether savings

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				would be large enough to offset the cost of procalcitonin testing in the NHS.
6	Roche Diagnostics	6.7	We would like to emphasise that NHS sources on PCT guided antibiotic therapy cited above (comment 9) indicate significant difference in antibiotic prescribing compared to standard. This is in agreement with the results reported in randomised trials outside the UK. We therefore argue that the effects observed in these studies apply to the UK setting.	Thank you for your comment. The Committee considered whether there is a difference in antibiotic stewardship practices between different hospitals. The Committee noted the Public Health England report on the English surveillance programme for antimicrobial utilisation and resistance showed that combined GP and hospital antibiotic prescribing had increased 6% between 2010 and 2013, despite the publication of the “Start smart – then focus” toolkit for antimicrobial stewardship. The Committee concluded that improved antimicrobial stewardship and consequent reduction in antibiotic use was not currently being achieved in the NHS, and that this could reflect that guidance on antimicrobial stewardship was not being fully adhered to in all NHS hospitals.

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				This Committee consideration is detailed in section 6.6 of the guidance document.
7	The British In Vitro Diagnostics Association (BIVDA)	General	We also feel that studies from outside the UK should have been considered applicable to the NHS â€“ member companies will individually reference these. More significantly we believe that there is enough use of Procalcitonin by the NHS to demonstrate the benefits of the test and again member companies will be able to provide reference sites for the usage.	Thank you for your comment which the Committee considered. The Committee concluded that despite the additional evidence from NHS sites submitted at consultation, the uncertainty around the generalisability of the studies and the additional benefit that procalcitonin testing would add to current NHS practice still remains.

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8	Thermo Fisher	1.1	Procalcitonin is already frequently used to support antimicrobial stewardship decisions in numerous centres across the UK (including, Manchester Royal Infirmary, Addenbrooke's Hospital, Medway Maritime Hospital, Ninewells Hospital in Dundee and Hampshire Hospitals NHS Foundation Trust [claim based on sales data]). Furthermore, the use of procalcitonin in the UK as part of the standard of care approach to antibiotic stewardship has been demonstrated in the following centres: 1. Hampshire Hospitals NHS Foundation Trust (Saeed *et al,* 2011[1] and Eddy *et al,* 2015[2]) – a manuscript by Saeed *et al,*[1] reported that procalcitonin use in a medical admissions unit (MAU) and intensive care unit (ICU) setting (n=141) resulted in a reduction in unnecessary antibiotic usage, without any adverse effects on patients and with cost reduction implications. Eddy *et al*[2] evaluated the use of procalcitonin in older patients (defined as over 65 years old; n=55) in a district general hospital setting in the UK. The authors concluded that the use of procalcitonin could assist antimicrobial stewardship in a complex population who are vulnerable to the	Thank you for your comment. The Committee considered the list of studies conducted in the UK. It heard from the External Assessment Group that these studies are not comparative studies and therefore cannot be used to assess the benefits of adding procalcitonin to standard clinical practice. The Committee concluded that although it was useful that more evidence had been submitted at consultation, the uncertainty around the generalisability of the studies and the additional benefit that procalcitonin testing would provide in the NHS still remains. This Committee consideration is detailed in section 6.9 of the guidance document.

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			development of *Clostridium difficile* and other antibiotic-resistant infections. 2. Brighton and Sussex University Hospital NHS Trust (Banerjee and Anumakonda, 2013)[3] – a pilot study that explored the role of procalcitonin in antibiotic prescribing in critically ill patients in an ICU setting. Based on 100 consecutive procalcitonin samples prospectively measured, antibiotic prescriptions were changed in 87 cases. The study concluded that judicious use of procalcitonin, when used to discontinue antibiotics, reduces antibiotic usage in adult ICU patients, both in a university and district hospital setting. 3. Northumbria Healthcare NHS Foundation Trust (Sarma *et al* 2014)[4] – an abstract reporting the role of procalcitonin (n=53; 74 tests) in either avoiding or stopping empirical therapy. Results showed that antibiotic use was avoided and stopped in 31 (58%) and 27 (61%) of cases, respectively. Cost saving implications were also realised. The authors concluded that procalcitonin could play an essential role in curbing avoidable exposure to antibiotics, with significant cost saving.	

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			4. James Paget University Hospital NHS Foundation Trust (Brodbeck *et al*, 2010)[5] – an abstract reporting the usefulness of procalcitonin in an ICU setting (n=27; 114 tests over 18 days). Antibiotics were discontinued or not initiated following low (<0.5 ng/ml) procalcitonin values in 38/49 samples, despite high C-reactive protein (CRP) levels; furthermore, in two patients already on antibiotic therapy, a rise in procalcitonin was noticed, which prompted a change in antibiotics. The authors concluded that regular assessment of procalcitonin, when interpreted in combination with the clinical context, was helpful, not only to decrease the duration of antibiotics but also to change the antibiotic regimen. 5. Wirral University Teaching Hospital NHS Foundation Trust (Clayton *et al,* 2012)[6] – a study that sought to establish what impact the knowledge of procalcitonin levels could have on antimicrobial prescribing and stewardship. Over a two-month period patients (n=27) were treated in a conventional manner based on clinical findings and standard investigations. Plasma samples from days 0 (respective to antimicrobial therapy) 1, 3, 5 and 7 were analysed for	

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			procalcitonin. Nonparametric statistical analysis of procalcitonin levels was available for a retrospective multidisciplinary team review of case notes. The authors stated their experiences suggested the availability of the procalcitonin response between Days 0 and 5 would have been a useful adjunct in monitoring treatment of sepsis and would have facilitated timely de-escalation of, and hence exposure to, antimicrobial therapy. 6. Stockport NHS Foundation Trust (Stockport NHS Foundation Trust, 2013)[7] – based on audit data, the trust reported that procalcitonin usage led to a small reduction in antibiotic treatment duration. 7. Wye Valley NHS Trust (Boldger *et al,* 2014)[8] – a retrospective study to assess the CE of procalcitonin in an ICU setting (n=24) to guide antibiotic treatment concluded that the use of procalcitonin may be a cost-effective tool in deciding whether or not antibiotic treatment should be started. 8. Ninewells Hospital and Medical School (Christie *et al*, 2012)[9] – a procalcitonin-guided antibiotic treatment algorithm in the ICU showed that the use of procalcitonin would have resulted in a saving of	

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			£1,028, with a gain of 63 antibiotic-free days. 9. Medway NHS Foundation Trust – Medway Maritime Hospital has previously audited the savings derived from the routine implementation of procalcitonin testing, looking at a sample of 50 patients. The findings confirmed that the incremental saving in antibiotic costs alone averaged £34 per patient (personal communication). The critical care unit has recently installed a modern IT system and has the capability to interrogate drug, diagnostic and outcomes data in a useful timeframe to validate real-world experience within the UK NHS. The Committee may wish to consider engaging with the Medway NHS Foundation Trust to confirm the actual savings and impact on care that routine procalcitonin implementation in a UK setting have generated. While it is recognised the above usage is not based on a randomised controlled trial (RCT) setting, the results would suggest there is a place, and a need, for procalcitonin in the NHS for the purposes of medicines optimisation and achieving cost-efficiency savings. Hence, the existing use of procalcitonin within the NHS supersedes the current 'used	

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			only in research' recommendation wording. **References:** [1] Saeed K, Dryden M, Bourne S, Paget C, Proud A. Reduction in antibiotic use through procalcitonin testing in patients in the medical admission unit or intensive care unit with suspicion of infection *J Hosp Infect* 2011; **78:** 289–292. [2] Eddy F, Joyce A, Dryden M, Saeed K (2015) Procalcitonin in Older Patients; Promoting Antibiotic Stewardship in Complex Patients. *J Infect Non Infect Dis* 2015; **1:** 001. http://heraldopenaccess.us/fulltext/Infectious-and-Non-Infectious-Diseases/HINID-15-001.pdf (last accessed 18 June 2015) [3] Banerjee T, Anumakonda V. Role of procalcitonin (PCT) to guide antibiotic therapy in critically ill patients with suspected sepsis on a general intensive care units: a pilot study. European Society of Intensive Care Medicine 26th Annual Congress, Paris, 2013 (abstract 0243) http://poster-consultation.esicm.org/ModuleConsultationPoster/posterDetail.aspx?intIdPoster=5055 (last accessed 18 June 2015) [4] Sarma JB, Tait D, Marshall B, Oswald T, Banerjee S. Antimicrobial Stewardship: Role of ProCalcitonin (PCT). Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC), Washington DC, 2014 (abstract D-181) www.icaaconline.com/php/icaac2014abstracts/data/papers/2014/D-181.htm (last accessed 18 June 2015)	

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			[5] Brodbeck A, Elumogo N, Rajendran G. Evaluation of procalcitonin at James Paget Intensive Care Unit. *Critical Care* 2010; **14**(Suppl 1): S16 (P42). www.ncbi.nlm.nih.gov/pmc/articles/PMC2934078/pdf/cc8274.pdf (last accessed 18 June 2015) [6] Clayton J, White J, Wilson L, Leonard M, Cuniffe J. Would procalcitonin measurement aid antimicrobial stewardship in a UK district general hospital mixed adult critical care population? *Critical Care* 2012; **16**(Suppl 1): S11 (P30). www.ncbi.nlm.nih.gov/pmc/articles/PMC3363448/pdf/cc10637.pdf (last accessed 18 June 2015) [7] Stockport NHS Foundation Trust. Appendix 2: Audit Outcomes June/July 2012 – Evaluation of procalcitonin use to reduce antibiotic duration. In: *Board Quality Report*. 2013. www.stockport.nhs.uk/websitedocs/20130124-04.3%20-%20Board%20Quality%20Report%20-%20January%202013.pdf (last accessed 18 June 2015) [8] Boldger A, Davies J, Johnson A, Wheeler M. Procalcitonin in an intensive treatment unit (ITU): an economic evaluation. *Clin Chem Lab Med* 2014; **52**: eA361 (Th141). www.degruyter.com/dg/viewarticle.fullcontentlink:pdfeventlink/$002fj$002fcclm.2014.52.issue-11$002fcclm-2014-0890$002fcclm-2014-0890.pdf?format=INT&t:ac=j$002fcclm.2014.52.issue-11$002fcclm-2014-0890$002fcclm-2014-0890.xml (last accessed 18 June 2015)	

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			[9] Christie S, McCann R, Bartlett R *et al*. Procalcitonin testing to guide antibiotic therapy in the intensive care unit. *Anaesthesia* 2012; **67:** 89. http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2044.2012.07158.x/pdf (last accessed 18 June 2015)	
9	Roche Diagnostics	5.1	As the committee did place a significant emphasis on the question of transferability of the findings from randomised interventional studies from other countries to the UK setting, the evidence considered should have included a review of all available evidence in the UK and included real-world data or local NHS audits. These reports support the transferability of the RCT findings to the UK setting. Sources from the NHS that report use of PCT guided algorithms in ICU and acute admissions setting are listed below: 1. K. Saeed & MS Dryden (Winchester and Eastleigh Healthcare NHS Trust) report PCT use in a medical admission unit (MAU) with suspected infection and patients in intensive care unit (ICU) w. signs of infection. They report a reduction in unnecessary antibiotic usage without any adverse effects on patients with cost reduction implications. (Source: K. Saeed, MS Dryden ,S. Bourne, C Paget, A. Proud. Reduction in antibiotic use through procalcitonin	Thank you for your comment. The Committee considered the list of studies conducted in the UK. It heard from the External Assessment Group that these studies are not comparative studies and therefore cannot be used to assess the benefits of adding procalcitonin to standard clinical practice. The Committee concluded that although it was useful that more evidence had been submitted at consultation, the uncertainty around the generalisability of the studies and the additional benefit that procalcitonin testing would provide in the NHS still remains. This Committee consideration is detailed in section 6.9 of the guidance document.

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			testing in patients in the medical admission unit or intensive care unit with suspicion of infection, Journal of Hospital Infection (2011), doi:10.1016/j.jhin.2011.03.018) 2. F Eddy, A Joyce, M Dryden, K Saeed (Southmead Hospital, North Bristol NHS Trust & Hampshire Hospitals NHS Foundation Trust) report PCT in elderly in MAU and concluded that "Clinicians are using this tool in patients with a doubtful suspicion of bacterial infection, as evidenced by the fact that 64% had not started antibiotics pending results. Other biomarkers such as WCC and CRP were elevated in the majority of cases, supporting the case that PCT adds an extra dimension to tests currently used." (Source: http://www.fis-infection.org.uk/0001-0022-Diagnostics.pdf, https://www.bristolccg.nhs.uk/media/medialibrary/2014/05/govbody_6i_25mar2014.pdf) 3. T. Banerjee & V. Anumakonda (Brighton and Sussex University Hospital NHS Trust & Maritime hospital NHS trust) report use of PCT guidance in adults in ICU. They report reduction in antibiotic use when used to discontinue antibiotics in adult ICU patients in	

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			both university and district general hospitals settings and concluded cost effectiveness of PCT (Source: http://poster-consultation.esicm.org/ModuleConsultationPoster/posterDetail.aspx?intIdPoster=5055) 4. J. B. Sarma (Northumbria Health Care NHS Foundation Trust) reported that PCT use in elderly with signs and symptoms of infection led to reduced AB prescribing and net cost saving (http://www.icaaconline.com/php/icaac2014abstracts/data/papers/2014/D-181.htm). 5. A Brodbeck (James Paget University Hospital NHS Foundation Trust, Great Yarmouth) reports that regular assessment of PCT in ICU patients, when interpreted with clinical context, was helpful not only to decrease the duration of antibiotics but also to change the antibiotic regimen (Source: Evaluation of procalcitonin at James Paget Intensive Care Unit A Brodbeck, N Elumogo, G Rajendran Critical Care 2010, 14(Suppl 1):P42 http://ccforum.com/content/pdf/cc8274.pdf). 6. J Clayton (Wirral University Teaching Hospital NHS Foundation Trust) report that their experience	

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Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 30 June 2015

THEME: ADDITIONAL EVIDENCE

Comment number	Name and organisation	Section number	Comment	Response
			suggests the availability of PCT response between days 0 and 5 would have been a useful adjunct in monitoring treatment of sepsis on their unit and would have facilitated timely de-escalation and hence exposure to antimicrobial therapy (Source: J Clayton, J White, L Wilson, M Leonard, J Cuniffe Critical Care 2012, 16(Suppl 1):P30 (doi: 10.1186/cc10637) http://ccforum.com/content/pdf/cc10637.pdf) 7. C Chadrasekaran (Stockport NHS Foundation Trust) reported that PCT usage led to a small reduction in antibiotic course duration (Source: https://www.stockport.nhs.uk/websitedocs/20130124-04.3%20-%20Board%20Quality%20Report%20-%20January%202013.pdf) 8. A Boldger, J Davies, A Johnson, M Wheeler (Wye Valley NHS Trus) report that PCT in an ITU setting may be a cost effective tool in deciding whether or not antibiotic treatment should be started. It may also be a valuable in limiting unnecessary antibiotic usage (Source: Clin Chem Lab Med 2014; 52(11): eA205–eA379) 9. S. Chrsitie, R. McCann (Ninewells Hospital and Medical School, Dundee) report that their analysis	

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THEME: ADDITIONAL EVIDENCE

Comment number	Name and organisation	Section number	Comment	Response
			indicated that the use of PCT would have resulted in a saving of £1028, with a gain of 63 antibiotic-free days in ICU. They demonstrated high compliance with the PCT-guided treatment algorithm. (Source: Anaesthesia 2012, 67, 807–810)	

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THEME: SAPS STUDY

Comment number	Name and organisation	Section number	Comment	Response
10	Thermo Fisher	6.14	*The Committee requested further information on both of these studies [SAPS and Australian] to be available for discussion at the second Committee meeting*. While the results of the *Stop Antibiotics on guidance of Procalcitonin Study* (SAPS) are currently unpublished, it is likely the results of this large (n=1,800) RCT will be published within the timeframe of this Diagnostics Assessment Programme (DAP) – the estimated date for the final published guidance is October 2015. The Committee may wish to consider the parallel timings of these two publications/processes. Should the Committee choose to consider the data from the *Australian* study (Shehabi *et al* 2014)[1] as part of this DAP, it is requested that any conclusions from the study are evaluated in the context that an atypical procalcitonin algorithm cut-off value was used in this study (a 0.1 ng/ml cut-off determined antibiotic cessation) when compared with other RCTs; for example, Bouadma *et al* 2010[2] employed a cut-off value of <0.25ng/ml to strongly discourage use of antibiotics.	Thank you for your comment which the Committee considered. The Committee noted that the population in the SAPS study were adults in an intensive care unit setting. The Committee noted that this is an important study, but that the results are expected to be available after publication of this guidance. The Committee agreed the Shehabi 2014 study used a lower threshold for determining discontinuation of antibiotics compared with the studies included in the systematic review (0.1 nanograms per millilitre compared with 0.25 nanograms per millilitre), which would likely impact on the results.

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THEME: SAPS STUDY

Comment number	Name and organisation	Section number	Comment	Response
			References: [1] Shehabi Y, Sterba M, Garrett PM *et al.* Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis. A randomized controlled trial. *Am J Respir Crit Care Med*. 2014; **190:** 1102–1110. [2] Bouadma L, Luyt CE, Tubach F *et al.* Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* 2010; **375:** 463–474.	
11	Roche Diagnostics	6.14	If the committee were of the opinion that the results of the SAPS study are important evidence to consider before making a final recommendation on the use of PCT in the NHS, we would support a suspension of this Diagnostic Assessment until availability or publication of the study results.	Thank you for your comment which the Committee considered. The Committee noted that the population in the SAPS study were adults in an intensive care unit setting. The Committee noted that this is an important study, but that the results are expected to be available after publication of this guidance.

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THEME: EVIDENCE BASE, CLINICAL AND COST EFFECTIVENESS

Comment number	Name and organisation	Section number	Comment	Response
12	Thermo Fisher	6.4	*The Committee also noted that most studies included a small number of patients and reported low event numbers; they were not sufficiently powered to detect a difference.* It is requested the Committee qualifies this statement with the actual cohort numbers included in the studies that were evaluated. In total, 18 studies were included in the evaluation, which comprised of n=5,105 randomised patients (ranging from n=62 to n=1,381 per study). When compared with the evidence base for other diagnostics/devices, it is contested that the data available for procalcitonin actually include a large patient cohort. Furthermore, while data from the SAPS are currently not included within the DCD (as the trial results are still unpublished), this study will provide data from a further 1,800 randomised patients.	Thank you for your comment which the Committee considered. The Committee agreed that the number of patients included in the studies was greater than seen in some other diagnostic assessments. It noted that the issue lies more with the heterogeneity between the studies and their applicability to the UK. The Committee decided to change section 6.4 of the guidance document to better reflect its thoughts.
13	Roche Diagnostics	6.19	The observation that the average QALY gain for patients in PCT guided algorithms is relatively small compared to standard care is likely to be true for any antibiotic stewardship programme. This is because the main patient benefits considered in this cost-effectiveness analysis associated with reduced antibiotic prescribing are reduced	Thank you for your comment which the Committee considered. The Committee noted that outcomes relating to antibiotic stewardship were not included in the model. The Committee considered the potential

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THEME: EVIDENCE BASE, CLINICAL AND COST EFFECTIVENESS

Comment number	Name and organisation	Section number	Comment	Response
			complications of antibiotic therapy. However, these complications are relatively minor or rare, as antibiotics are well tolerated, resulting in a small average QALY gain for the individual. The committee should therefore also consider the additional benefits of better antibiotic stewardship to support the antibiotic resistance agenda that are not captured in this analysis.	contribution that procalcitonin testing could make to improving antimicrobial stewardship and the consequent reduction in the incidence of antibiotic-resistant infections. The Committee noted its earlier conclusions about the uncertainty of whether the reductions in resource use reported in the studies would be realised in clinical practice in the NHS and concluded that procalcitonin testing may contribute to improving antibiotic stewardship in the NHS if it leads to a reduction in antibiotic use. This Committee consideration is detailed in section 6.20 of the guidance document.
14	The British In Vitro Diagnostics Association (BIVDA)	General	Overall, for many diagnostic tests, the use of the QALY will result in low savings to the system as a diagnostic test in itself can only be part of a clinical process to improve health outcomes. We remain optimistic that methodologists, especially with evidence from the Diagnostic Evidence Co-operatives, will identify a more effective mechanism for evaluating IVD tests.	Thank you for your comment which the Committee considered.
15	Roche Diagnostics	6.20	Reports 1, 3, 4. & 9 in comment 9 reported a costs analysis of introducing PCT guided algorithms in the NHS and	Thank you for your comment which the Committee considered.

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THEME: EVIDENCE BASE, CLINICAL AND COST EFFECTIVENESS

Comment number	Name and organisation	Section number	Comment	Response
			source 1, 4.& 9 report cost reductions/savings. This is in line with the conclusions of the economic analysis and demonstrates that savings in an NHS setting can be achieved.	

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THEME: ECONOMIC MODEL

Comment number	Name and organisation	Section number	Comment	Response
16	Thermo Fisher	6.17	*The Committee requested clarification on the number of procalcitonin tests per day for discussion at the second meeting*. The published protocols associated with the clinical trials evaluated can provide further information in relation to the number of procalcitonin tests completed per day; for example, as described in the PRORATA trial (Bouadma *et al* 2010[1]), procalcitonin testing for each patient was completed as follows: • Day 1: baseline procalcitonin was measured to determine whether antibiotic initiation should be discouraged or encouraged. When antibiotics were initially withheld, physicians were advised to repeat clinical assessments and procalcitonin measurements 6–12 hours later • Day 2 onwards: for patients who subsequently received antibiotics, procalcitonin concentrations were assessed daily until treatment was finished. Local UK protocols can range from daily procalcitonin measurements to procalcitonin testing every other day.	Thank you for your comment which the Committee considered. The Committee heard from External Assessment Group that using a value of 30 tests per laboratory per day increased the cost of procalcitonin testing by £4 in the emergency department setting and £7 in the intensive care unit setting, but that this did not impact the model results. Section 6.21 of the guidance document has been changed to reflect the results of changing this outcome.

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THEME: ECONOMIC MODEL

Comment number	Name and organisation	Section number	Comment	Response
			According to recent sales data, the major users of procalcitonin in the UK typically use 10-20 procalcitonin tests per hospital per day (data from a range of NHS centres; average over a three-month period). This average value is primarily built on usage within an ICU setting. Hence, it is anticipated the average daily usage could reach 30-40 tests per hospital per day to encompass usage across all settings (eg, the emergency department and medical admissions unit). **References:** [1] Bouadma L, Luyt CE, Tubach F *et al.* Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* 2010; **375:** 463–474.	

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THEME: USE IN CHILDREN

Comment number	Name and organisation	Section number	Comment	Response
17	Thermo Fisher	6.13	*The Committee was concerned that without robust evidence the introduction of procalcitonin testing into standard clinical practice may not reduce the use of antibiotic therapy, but could potentially increase antibiotic exposure and hospital admissions.* It is requested that further evidence and explanation is provided to support the Committee's concern that the introduction of procalcitonin testing for use in children could potentially increase antibiotic exposure and hospital admissions.	Thank you for your comment which the Committee considered. The Committee clarified that their concern arose from the study by Baer et al. (2013) which reported a trend towards increased antibiotic use when procalcitonin test results were added to standard clinical practice. The Committee also noted that there was no agreed threshold for procalcitonin which should be used to encourage or discourage antibiotic use in children with suspected bacterial infection. The Committee concluded that more robust evidence on the use of procalcitoinin testing with standard clinical practice in children presenting to the emergency department with suspected bacterial infection is required. Section 6.16 of the guidance document has been changed to better reflect the considerations of the Committee.

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THEME: RECOMMENDATIONS AND FURTHER RESEARCH

Comment number	Name and organisation	Section number	Comment	Response
18	Royal College of Pathologists	1.1	The line "*Procalcitonin test… are recommended for use only in research for guiding decisions*". From the later sections on Research (7) the intention is made clear that further research in all areas of the application and impact of the test is desirable, but this recommendation may be very restrictive.	Thank you for your comment which the Committee considered. The Committee agreed that use of the word 'only' could be restrictive. The Committee decided to change the wording of the recommendation in section 1.1 of the guidance.
19	Roche Diagnostics	1.1	We ask the committee to take the experience from NHS hospitals (see comment 9 for sources) and the data from the unpublished SAPS study into account before making a final recommendation.	Thank you for your comment which the Committee considered.
20	Thermo Fisher	1.1	While the current recommendation that procalcitonin has a place in the NHS in a research context is welcomed, it is requested that the committee considers extending the recommendations to include the use of procalcitonin to support antibiotic stewardship in routine clinical practice. This request is based on the following: 1. Procalcitonin is already routinely being used as part of the standard of care approach to antibiotic stewardship in the NHS (see comment 8) 2. The evidence base, as concluded in the cost-	Thank you for your comment which the Committee considered. The Committee thought that the procalcitonin tests show promise, but there is insufficient evidence to recommend their routine adoption in the NHS. The Committee decided to change the wording of the recommendation in section 1.1 of the guidance document to reflect this.

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THEME: RECOMMENDATIONS AND FURTHER RESEARCH

Comment number	Name and organisation	Section number	Comment	Response
			effectiveness (CE) base case analysis of the Diagnostics Assessment Report, indicated procalcitonin testing with standard clinical practice dominates standard clinical practice alone for all populations evaluated within the CE analysis; that is, it was both cost-saving and more effective 3. Information has been provided as part of this consultation in response to several of the concerns described within the Diagnostics Consultation Document (DCD) in relation to the quality and generalisability of the evidence base to a UK setting (see comments 3, 4, 8, 10, 12 and 16)	
21	Roche Diagnostics	7.1	We would like to highlight that randomised interventional studies, such as the studies considered in the systematic review, are difficult to conduct in the ICU and A&E settings. With a significant number of interventional studies and NHS audit data (comment 9) available, it is arguable if such a study is required.	Thank you for your comment which the Committee considered.
22	Thermo Fisher	6.21	'The Committee encourages centres currently using procalcitonin testing to take part in relevant research.' The encouragement from the Committee that centres currently using procalcitonin testing should continue using	Thank you for your comment which the Committee considered.

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THEME: RECOMMENDATIONS AND FURTHER RESEARCH

Comment number	Name and organisation	Section number	Comment	Response
			the assay and take part in relevant research is welcomed. It is requested the statement is extended to also encompass centres that are not currently using procalcitonin but have a local need and/or priority to evaluate antimicrobial stewardship practices/protocols.	

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THEME: OTHER

Comment number	Name and organisation	Section number	Comment	Response
23	Royal College of Pathologists	3.2	The mention of C diff diarrhoea in the untoward outcome may be important in relation to the use of antibiotics. This must have been discussed but I cannot recollect, or not aware of, the outcome of the such discussion.	Thank you for your comment which the Committee considered.
24	Roche Diagnostics	6.9	NHS sources on PCT guided antibiotic therapy cited in comment 9 included not only ICU but also Acute Medical Unit (AMU) patients, indicating that reduced initiation or length of antibiotic therapy can be achieved in the NHS setting in these pathways when using PCT guided algorithms compared to standard care.	Thank you for your comment which the Committee considered.
25	Thermo Fisher	8	Input from NICE to support the implementation of its guidance is welcomed. In addition to the activities described within the implementation section of the DCD report, we would also welcome the support of NICE to produce relevant tools (e.g. a clinical audit tool) to be included within the resources pages of this guidance, to support implementation by the NHS, as observed with other DAP-led guidance; for example, the NICE diagnostics guidance 15 [DG15] (www.nice.org.uk/guidance/dg15/resources).	Thank you for your comment.