

# **Diagnostic Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence – Protocol**

## **Title of project**

Procalcitonin (PCT) testing to guide antibiotic therapy for the treatment of sepsis in intensive care settings and for suspected bacterial infection in emergency department settings

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## **1 Plain English Summary**

Sepsis is a common, potentially life threatening condition which is caused by an extreme reaction of the body's immune system to infection. Many people admitted to intensive care units have severe sepsis and around half of these patients die in hospital. Recognition of sepsis and rapid treatment with appropriate antimicrobial drugs is important to maximise the chance of survival. It is also important to distinguish between sepsis and whole body immune responses which are not caused by infection, so that inappropriate treatment can be avoided. If sepsis is considered very likely, treatment may be started before the diagnosis has been confirmed to avoid potentially harmful delay. Where this occurs it is important to identify those people who do not have an infection as quickly as possible, so that antimicrobial treatment can be stopped and appropriate treatment identified. Where sepsis is present and antimicrobial treatment is appropriate, further testing may help to decide when to stop treatment because the infection has cleared, or when to change treatment because the current treatment is not working.

Symptoms which could be caused by less severe infections are a common reason for people to attend hospital emergency departments. In this situation, doctors need to be able to quickly decide whether an infection is present and, if so, whether that infection was caused by bacteria. This is important so that appropriate treatment can be given and inappropriate prescription of antibiotics can be avoided. Treatment of non-bacterial infections with antibiotics does not benefit the patient. In addition, prescribing fewer antibiotics is generally considered to be desirable because it may help conserve the effectiveness of existing drugs.

This projects aims to evaluate measurement of procalcitonin, a blood test which is associated with the body's immune response to infection, to help doctors decide on whether antibiotics are needed and the length of antibiotic treatment needed. The review will consider both clinical effectiveness (changes in the numbers of people being prescribed antibiotics, length of hospital stay and patients' outcomes associated with adding procalcitonin testing to the information available to doctors) and cost effectiveness (cost of different assessment strategies).

## **2 Decision problem**

### **2.1 Population**

The indications for this assessment are the management of antibiotic therapy in people with known or highly suspected sepsis who are being treated in intensive care units (ICUs) and in people who present to the emergency department (ED) with suspected bacterial infection.

For the ICU setting, the assessment will focus on people with confirmed or highly suspected sepsis; this is because sepsis is a common and serious problem amongst patients being treated in ICUs.<sup>1</sup> Sepsis is defined as probable or documented infection together with systemic manifestations of infection (sometimes described as systemic inflammatory response syndrome (SIRS)), severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction, and septic shock is defined as severe sepsis with hypotension which is not reversed by fluid resuscitation.<sup>2, 3</sup> Bacteria are the most common cause of sepsis; however, systemic viral and fungal infections can also occur. SIRS can also occur as a result of non-infectious challenge to the immune system and it is important for clinicians to be able to rapidly distinguish between infectious and non-infectious causes, as well as between different agents of infection, in order to guide appropriate therapy.

The most recent UK Hospital Episode Statistics (2012-2013) recorded 69,036 finished consultant episodes related to sepsis.<sup>4</sup> In addition, a recently published analysis of the 2001-2010 Office of National Statistics mortality data found that, during this period, 4.7% of all deaths recorded in England were 'definitely directly associated with sepsis.'<sup>5</sup> Ninety-nine percent of deaths definitely associated with sepsis had at least one of the ICD-10 codes A40 (sepsis due to pneumonia), A41 (other sepsis), or P36 (sepsis of newborn due to streptococcus group B) on the death certificate, however, only 8.6% of deaths definitely associated with sepsis in 2010 had a sepsis-related condition as the underlying cause of death.<sup>5</sup> Only 7.0% of deaths definitely associated with sepsis did not occur in hospital.<sup>5</sup> Incidence of sepsis is particularly high in patients admitted to ICUs. A large retrospective analysis of 56,673 admissions of adult patients to ICUs in England Wales and Northern Ireland, between 1995 and 2000, found that 27.1% met the criteria for severe sepsis with the first 24 hours of admission.<sup>1</sup> Thirty-five percent of these patients died before discharge from the ICU and 47% died in hospital.<sup>1</sup> Patients with severe sepsis accounted for 45% of intensive care bed days and 33% of hospital bed days used by all ICU admissions.<sup>1</sup> These data indicate that sepsis is a substantial healthcare problem with a high mortality rate, representing a major clinical challenge and associated with high resource use. Improving the management of sepsis, in particular in ICU settings is therefore an important healthcare goal.

For the emergency department setting, the assessment will consider a broader population, which will include people presenting with any suspected bacterial infection. This is because discussions at scoping suggested that inclusion of a broader population would be more clinically appropriate in this setting and that presentation to the ED with symptoms consistent with sepsis would be relatively uncommon. The most recent UK Hospital Episode Statistics (2012-2013) recorded a first ED diagnosis of 'infectious disease' in 141,308 out of a total of 18.3 million ED presentations; 'septicaemia' was recorded as the first ED diagnosis for 24,850 presentations.<sup>6</sup> Rapid and accurate determination of the presence or absence of bacterial infection is important to guide appropriate therapy and to reduce unnecessary exposure to antibiotics. Reduction of antibiotic exposure is increasingly a priority for the NHS, in the context of efforts to conserve the effectiveness of existing drugs. The Department of Health has set out actions to slow the development and spread of antimicrobial resistance in the UK Five Year Antimicrobial Resistance Strategy 2013 to 2018.<sup>7</sup> One of the aims of the strategy is to conserve and steward the effectiveness of existing antimicrobials by ensuring antibiotics are used responsibly and less often. NICE public health guidance (PHG89), 'Antimicrobial resistance – changing risk-related behaviours,' is currently under development.<sup>8</sup>

## **2.2 Intervention technologies**

Procalcitonin is a 116 amino acid precursor to calcitonin. In normal metabolism, calcitonin is produced solely by the C cells of the thyroid medulla and neuroendocrine cells in the lungs. Normal serum or plasma levels of PCT in healthy adults are  $\leq 0.05$  ng/mL.<sup>9</sup> Procalcitonin can also be produced by a variety of cell types in response to inflammatory stimuli (including systemic infection) and can be very high ( $>10$  ng/mL) in sepsis, severe sepsis and septic shock.<sup>9</sup> PCT modulates the immune response through induction of cytokine production and by affecting the migration of monocytes and parenchymal cells to the site of inflammation. A summary of the characteristics and clinical applications of PCT, produced by the Association for Clinical Biochemistry (ACB), lists the clinical uses of PCT measurement as:

- Diagnosis of bacterial infections of the lower respiratory tract and sepsis
- Monitoring progression of sepsis and response to antibiotic treatment
- Informing initiation, change or discontinuation of antibiotic therapy for sepsis

whilst cautioning that PCT can also be raised following surgery, trauma or severe burns, or in cases of severe pancreatitis, severe liver damage, severe multi-organ dysfunction syndrome, and severe fungal or viral infections.<sup>9</sup> The ACB document also notes that particular care is needed when interpreting PCT levels in neonates, as PCT levels can exceed 10 ng/mL in neonates in the absence of infection.<sup>9</sup>

All methods for the quantification of PCT are based on immunoassay and there are currently a number of CE marked automated assays available in the UK.

#### *Thermo Fisher Scientific BRAHMS PCT Sensitive Kryptor assay*

The BRAHMS PCT Sensitive Kryptor assay is an automated immunofluorescent sandwich assay for the determination of PCT in human serum and plasma. It is indicated for use with the BRAHMS Kryptor, BRAHMS Kryptor compact and BRAHMS Kryptor compact PLUS analysers. The assay has a measurement range of 0.02-5000 ng/mL, a functional assay sensitivity of 0.06 ng/mL, and an analytical sensitivity of 0.019 ng/mL. The time to result is 19 minutes.

A number of other companies have licensed the use of procalcitonin and its antibodies from Thermo Fisher Scientific. The main difference between these assays is the mechanism of detection of the antibody-PCT-antibody complexes.

All of the commercial assays have been standardised using the BRAHMS PCT LIA assay (the original manual PCT assay), which is no longer in widespread use in the UK. This assay was designed to be used in conjunction with a luminometer and results are calculated based on relative light units. The assay has a measurement range of 0.1-500 ng/mL, an analytical sensitivity of approximately 0.1 ng/mL, and a functional sensitivity of 0.3 ng/mL.

#### *Roche Elecsys BRAHMS PCT*

The Elecsys BRAHMS PCT is an electrochemiluminescent immunoassay for the determination of PCT in human serum and plasma. The assay is indicated for use on the Elecsys, Modular and Cobas e analysers. It has a measurement range of 0.02-100 ng/mL, a functional sensitivity of 0.06 ng/mL and an analytical sensitivity of <0.02 ng/mL. The time to result is 18 minutes.

#### *Siemens ADVIA Centaur BRAHMS PCT*

The ADVIA Centaur BRAHMS PCT is a chemiluminescent assay for the determination of PCT in human serum and plasma. The assay is indicated for use with the ADVIA Centaur/XP and ADVIA Centaur CP analysers. It has a measurement range of 0.02-75.00 ng/ml, a functional sensitivity of <0.05 ng/ml and an analytical sensitivity of <0.02 ng/ml. The time to result is 26-29 minutes, depending on which analyser is used.

#### *BioMérieux VIDAS BRAHMS PCT*

The VIDAS BRAHMS PCT is an Enzyme-Linked Fluorescent Assay for the determination of PCT in human serum and plasma. It is indicated for use with the VIDAS and miniVIDAS analysers. It has a measurement range of 0.05-200 ng/mL, a functional detection limit of 0.09 ng/mL and an analytical detection limit of 0.05 ng/mL. The time to result is 20 minutes.

#### *DiaSorin LIAISON BRAHMS PCT*

The LIAISON BRAHMS PCT is a sandwich chemiluminescent immunoassay for the determination of PCT in human serum and plasma. The assay is indicated for use with the LIAISON analyser. It has a measurement range of 0.1-500 ng/mL, a functional sensitivity of <0.24 ng/mL and an analytical sensitivity of <0.032 ng/mL. This assay is not currently marketed in the NHS. However, it will be included in the assessment so that, should the marketing situation change, any relevant data will have been evaluated.

The ACB document states that PCT is 'not recommended as a routine screening test for infection, e.g. as part of an emergency department admission profile,'<sup>9</sup> i.e. it is not useful to rule out infection where there is a low pre-test probability. This proposition is supported by data from a randomised controlled trial, conducted in children (aged 1 to 36 months) presenting to the emergency department with fever of unknown origin, which compared diagnosis based on standard investigations, as directed by the attending physician, with and without information on the results of PCT testing.<sup>10</sup> This study found no difference in the overall rates of antibiotic use or hospitalisation between the groups.<sup>10</sup> When only patients without bacterial infection or neutropenia identified by other emergency department investigations (UTI, pneumonia, bacterial meningitis and neutropenia <500 x10<sup>6</sup>/L excluded) were considered, there were still no differences between groups in either rate of antibiotic use or rate of hospitalisation; the researchers calculated that if all patients in this group with a PCT indicative of moderate risk of infection had been treated with antibiotics, the rate of antibiotic use would have increased by 24%.<sup>10</sup> An alternative diagnostic application would be in differentiating patients with sepsis from those who have systemic inflammatory response syndrome (SIRS) without infection, i.e. diagnosing sepsis where there is a high pre-test probability. A recent systematic review and meta-analysis of 30 studies assessing procalcitonin for the diagnosis of sepsis in critically ill patients reported summary estimates of sensitivity and specificity of 77% (95% CI: 72 to 81%) and 79% (95% CI: 74 to 84%).<sup>11</sup> The reference standard for determination of sepsis was defined as microbiological confirmation, or one or more of the following: white blood cells in a normally sterile body fluid; perforated viscus; radiographic evidence of pneumonia and production of purulent sputum; syndrome associated with high risk of infection.<sup>11</sup> This level of sensitivity does not suggest that a negative PCT test results alone would be adequate to rule out bacterial infection in high risk population; the study authors concluded that whilst 'procalcitonin is a helpful biomarker for early diagnosis of sepsis in critically ill patients, the results of the test must be interpreted carefully in the context of medical history, physical examination, and microbiological assessment.'<sup>11</sup> This is in line with the ACB document, which states that: 'PCT results should be used to assist and guide clinicians towards a diagnosis or treatment strategy, but they should not be used to replace clinical judgement; treatment should not be withheld on the basis of PCT test results.'<sup>9</sup>

In order to provide information on the effectiveness of PCT testing, when used in an appropriate context alongside other clinical information, this assessment will summarise data from clinical trials comparing the management of patients with probable or confirmed sepsis based on standard practice plus PCT testing to management based on standard practice alone.

## **2.3 Care pathway**

There is currently no NICE clinical guideline covering the diagnosis and management of sepsis in general; NICE clinical guideline CG151 addresses the specific issue of prevention and management of neutropenic sepsis in cancer patients;<sup>12</sup> neutropenic sepsis is outside the scope of this assessment. A new NICE guideline, 'Sepsis: The recognition, diagnosis and management of severe sepsis,' is currently under development and publication is expected in July 2016.<sup>13</sup> There is also an ongoing study by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD), commissioned by the Health Quality Improvement Partnership (HQIP), which aims to 'identify and explore avoidable and remediable factors in the process of care for patients with known or suspected sepsis.'<sup>14</sup> This study will examine organisational issues, systems and processes, recognition or early signs of sepsis, appropriate management of established severe infection, communication with families and carers, and use of the 'acute' end of life pathway and ceilings of treatment; publication is expected in autumn 2015.

Comprehensive guidance on the diagnosis and management of sepsis is provided by the Surviving Sepsis Campaign (SSC), a joint collaboration of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine.<sup>2</sup> This guideline was last up-dated in 2012 and is currently undergoing revision. The guideline was developed following the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system; the quality of evidence was rated as high (A) to very low (D) and recommendations were classified as strong (1) or weak (2).<sup>15</sup>

### *Diagnosis and monitoring of sepsis*

The SSC guideline specifies the presence of some the following criteria, alongside the presence of proven or suspected infection, for the diagnosis of sepsis:<sup>2, 3</sup>

- Clinical criteria – fever  $>38.3^{\circ}\text{C}$ , hypothermia  $<36^{\circ}\text{C}$ , heart rate  $>90\text{ bpm}$  or  $>2\text{ SD}$  above the age-specific normal range, tachypnea, altered mental status, significant oedema or positive fluid balance ( $>20\text{ mL/kg}$  over 24 hrs), hyperglycaemia (plasma glucose  $>7.7\text{ mmol/L}$ ) in the absence of diabetes.
- Inflammatory markers – white blood cell count  $>12,000\text{ }\mu\text{L}^{-1}$  or  $<4,000\text{ }\mu\text{L}^{-1}$ , normal white blood cell count with  $>10\%$  immature forms, plasma C-reactive protein or PCT level  $>2\text{ SD}$  above the age-specific normal range.

- Haemodynamic status – arterial hypotension (systolic blood pressure <90 mm Hg, mean arterial pressure <70 mm Hg, or decrease in systolic blood pressure >40 mm Hg in adults or <2 SD below the age-specific normal range).
- Organ dysfunction signs – arterial hypoxemia ( $\text{PaO}_2/\text{FiO}_2 < 300$ ), acute oliguria (<0.5 mL/kg/hr for  $\geq 2$  hrs despite adequate fluid resuscitation, creatinine increase >44.2  $\mu\text{mol/L}$ , coagulation abnormalities (INR >1.5 or PTT >60 s), ileus (absent bowel sounds), thrombocytopenia (platelet count <100,000  $\mu\text{L}^{-1}$ ), hyperbilirubinemia (plasma total bilirubin >70  $\mu\text{mol/L}$ ).
- Tissue perfusion status – hyperlactatemia (>1 mmol/L), decreased capillary refill or mottling.

Definitions of sepsis in children are similar to adult definitions but depend on age-specific heart rate, respiratory rate and white blood cell count cut-off values. Special considerations for managing sepsis in paediatric patients are described in the SSC guidelines.<sup>2</sup>

The SSC guideline includes the specific recommendation (GRADE 1C – strong recommendation, low or very low quality evidence) that blood (and urine, cerebrospinal fluid, wounds, respiratory secretions, or other body fluids, as appropriate) cultures should be taken before initiating antimicrobial therapy, provided that this does not significantly delay (>45 min) the start of antimicrobial therapy.<sup>2</sup> It should be noted that, although the guideline includes elevated PCT in the list of criteria indicative of sepsis (see above), no specific recommendation is made for its use in the diagnosis of sepsis.

NICE clinical guideline CG160, on the assessment and management of feverish illness in children under five years,<sup>16</sup> included a research recommendation for a UK study on the performance characteristics and cost-effectiveness of procalcitonin versus C-reactive protein in identifying serious bacterial infection in children with fever of unknown origin. However, it should be noted that, whilst the guideline included a systematic review of studies assessing the diagnostic accuracy of these biomarkers, this review did not appear to have considered RCTs comparing the effectiveness of diagnostic strategies with and without PCT testing. Although the guideline cites later studies by the same authors, it does not include the RCT described above (pg. 4, Index test section).<sup>10</sup>

### *Treatment of sepsis*

The SSC guideline provides the following recommendations on antimicrobial therapy:<sup>2</sup>



- 'The administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (GRADE 1B – strong recommendation, moderate quality evidence) and severe sepsis without septic shock (GRADE 1C – strong recommendation, low or very low quality evidence) should be a goal of therapy.'
- 'Initial empiric anti-infective therapy should include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into the tissues presumed to be the source of sepsis.' (GRADE 1B – strong recommendation, moderate quality evidence).
- 'Combination empirical therapy for neutropenic patients with severe sepsis' (GRADE 2B – weak recommendation, moderate quality evidence) 'and for patients with difficult-to-treat, multidrug resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp' (GRADE 2B – weak recommendation, moderate quality evidence). 'For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is for *P. aeruginosa* bacteraemia' (GRADE 2B – weak recommendation, moderate quality evidence). 'A combination of beta-lactam and macrolide for patients with septic shock from bacteraemic *Streptococcus pneumoniae* infections' (GRADE 2B – weak recommendation, moderate quality evidence).
- 'Empiric combination therapy should not be administered for more than 3–5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known' (GRADE 2B – weak recommendation, moderate quality evidence).
- 'Duration of therapy typically 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteraemia with *S. aureus*; some fungal and viral infections or immunologic deficiencies, including neutropenia' (GRADE 2B – weak recommendation, low or very low quality evidence).
- 'Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin' (GRADE 2B – weak recommendation, low or very low quality evidence).
- 'Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of non-infectious cause' (ungraded recommendation).

The SSC guideline also includes a recommendation (GRADE 2C – weak recommendation, low or very low quality evidence) for the use of procalcitonin (PCT) or similar biomarkers to aid the clinician in discontinuation of empiric antibiotics, where there is no subsequent evidence of infection.<sup>2</sup>

This assessment will summarise the evidence on this use of PCT testing and on the use of PCT testing to guide the duration of therapy in patients who have been appropriately treated with antibiotics, as well as the evidence on the use of PCT testing to guide initiation of antibiotics. It should be noted that the SSC guideline found no evidence to suggest that the use of PCT testing reduces the prevalence of antibiotic resistance.<sup>2</sup>

### **3 Objectives**

The overall objectives of this project are:

1. To summarise the evidence on the clinical- and cost-effectiveness of adding PCT testing to the information used to guide antibiotic therapy for the treatment of confirmed or highly suspected sepsis in intensive care settings.
2. To summarise the evidence on the clinical- and cost-effectiveness of adding PCT testing to the information used to guide antibiotic therapy in people presenting to the emergency department with suspected bacterial infection.

We defined the following research questions to address the each review objective:

1.
  - For adults and children with confirmed or highly suspected sepsis, who are being treated in ICU settings, how does initiation of antibiotic therapy differ when PCT test results are added to the information available to treating clinicians?
  - For adults and children with confirmed or highly suspected sepsis, who are being treated in ICU settings, how does duration of antibiotic therapy and length of hospital/ICU stay differ when PCT test results are added to the information available to treating clinicians?
  - For adults and children with confirmed or highly suspected sepsis, who are being treated in ICU settings, how do clinical outcomes (e.g. septic shock, SOFA scores, in-hospital mortality) differ when PCT test results are added to the information available to treating clinicians?
  - Does the addition of procalcitonin testing to current clinical practice, to determine whether to initiate and when to discontinue antibiotic therapy, in

adults and children with confirmed or highly suspected sepsis who are being treated in an intensive care unit, represent a cost-effective use of NHS resources?

2.

- For adults and children presenting to the emergency department with suspected bacterial infection, how does initiation of antibiotic therapy differ when PCT test results are added to the information available to treating clinicians?
- For adults and children presenting to the emergency department with suspected bacterial infection, how does duration of antibiotic therapy and number and length of hospital admissions differ when PCT test results are added to the information available to treating clinicians?
- For adults and children presenting to the emergency department with suspected bacterial infection, how do clinical outcomes (e.g. complications of infection) differ when PCT test results are added to the information available to treating clinicians?
- Does the addition of procalcitonin testing to current clinical practice, to determine whether to initiate and when to discontinue antibiotic therapy, in adults and children presenting to the emergency department with suspected bacterial infection, represent a cost-effective use of NHS resources?

#### **4 Methods for assessing clinical effectiveness**

Systematic review methods will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care<sup>17</sup> and NICE Diagnostic Assessment Programme manual.<sup>18</sup>

##### **4.1 Inclusion and exclusion criteria**

###### *Population*

1. Adults and children with confirmed or highly suspected sepsis, in whom antibiotic therapy is indicated, who are being treated in intensive care units.
2. Adults and children presenting to the emergency department with suspected bacterial infection.

Studies of neonates or immunosuppressed neutropenic patients on chemotherapy, immunosuppressant drugs or transplant programmes will be excluded.

###### *Intervention/Index test*

Treatment decisions based on laboratory-based procalcitonin testing, using any of the tests described in section 2.2, in addition to standard practice (as reported in individual studies).

Point-of-care tests will be excluded.

#### *Comparator*

Treatment decisions based on standard practice (as reported in individual studies), without procalcitonin testing.

#### *Outcomes*

Resource use (initiation/duration of antibiotic therapy, number of hospital admissions, length of hospital/ICU stay), acute clinical outcomes (SOFA scores, in-hospital mortality).

#### *Study design*

Randomised controlled trials (RCTs), or controlled clinical trials (CCTs) where no RCTs are available. Where no controlled trials (RCTs or CCTs) are available for a specified population, studies which assess the change in diagnostic accuracy associated with the addition of PCT testing to standard diagnostic work-up will be eligible for inclusion; such studies will be required to use adjudication of infection by independent panel as the reference standard.

Studies that assess the diagnostic accuracy of PCT testing alone, or that use culture alone as the reference standard will be excluded.

## **4.2 Search strategy**

Development of search strategies will follow the recommendations of the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care<sup>17</sup> Strategies will be based on procalcitonin assays, target condition (sepsis) and population(s) of interest (people being treated in ICU), and will initially include a sensitive filter for RCTs.<sup>19</sup> If initial searches identify no RCTs for one or more of the specified populations, searches will be re-run without a study design filter and may be further modified to focus on the specified population(s).

Candidate search terms will be identified from target references, browsing database thesauri (e.g. Medline MeSH and Embase Emtree), existing reviews identified during the rapid appraisal process and initial scoping searches. These scoping searches will be used to generate test sets of target references, which will inform text mining analysis of high-frequency subject indexing terms using Endnote reference management software. Strategy development will involve an iterative approach testing candidate text and indexing terms across a sample of bibliographic databases, aiming to reach a satisfactory balance of sensitivity and specificity. Search strategies will be developed specifically for each database

and the keywords associated with procalcitonin, sepsis and intensive care settings will be adapted according to the configuration of each database.

The following databases will be searched for relevant studies from 1995 to the present:

- MEDLINE (OvidSP)
- MEDLINE In-Process Citations and Daily Update (OvidSP)
- EMBASE (OvidSP)
- CINAHL (Cumulative Index to Nursing & Allied Health Literature) (EBSCO)
- Cochrane Database of Systematic Reviews (CDSR ) (Internet)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Internet)
- Database of Abstracts of Reviews of Effects (DARE) (Internet)
- Health Technology Assessment Database (HTA) (Internet)
- Science Citation Index (SCI) (Web of Science)
- LILACS (Latin American and Caribbean Health Sciences Literature) (Internet)  
(<http://regional.bvsalud.org/php/index.php?lang=en>)
- NIHR Health Technology Assessment Programme (Internet)

Completed and ongoing trials will be identified by searches of the following resources:

- NIH ClinicalTrials.gov (<http://www.clinicaltrials.gov/>)
- Current Controlled Trials (<http://www.controlled-trials.com/>)
- WHO International Clinical Trials Registry Platform (ICTRP)  
(<http://www.who.int/ictRP/en/>)

Key conference proceedings, to be identified in consultation with clinical experts, will be screened for the last five years. References in retrieved articles and relevant systematic reviews will be checked.

No restrictions on language or publication status will be applied. Searches will take into account generic and other product names for the intervention. An example of the initial search strategies to be used (including a sensitive RCT filter) is presented in Appendix 1; these will be adapted as necessary following consultation with clinical experts. The main Embase strategy for each search will be independently peer reviewed by a second Information Specialist, using the CADTH Peer Review checklist.<sup>20</sup> Identified references will be downloaded in Endnote X6 software for further assessment and handling. References in retrieved articles will be checked for additional studies.

### **4.3 Review strategy**

Two reviewers will independently screen titles and abstracts of all reports identified by searches and discrepancies will be discussed. Full copies of all studies deemed potentially relevant, after discussion, will be obtained and two reviewers will independently assess

these for inclusion; any disagreements will be resolved by consensus or discussion with a third reviewer.

Where available, data will be extracted on the following: study design/details; participants characteristics (e.g. age, gender, primary diagnosis and/or co-morbidities, other concomitant treatments (e.g. mechanical ventilation, TPN)); details of procalcitonin test (e.g. method, decision threshold, timing); details of standard practice (information, other than the procalcitonin test result, available to the treating clinician); resource use outcomes (e.g. numbers receiving antibiotic therapy, duration of antibiotic therapy, number of hospital admissions, length of hospital stay, length of ICU stay); acute clinical outcomes (e.g. complications of infection, SOFA score, in-hospital mortality). Data will be extracted by one reviewer, using a piloted, standard data extraction form. A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

#### **4.4 Quality assessment strategy**

The methodological quality of included RCTs will be assessed using the Cochrane Risk of Bias Tool.<sup>21</sup> Any included diagnostic accuracy studies will be assessed using QUADAS-2.<sup>22</sup> The results of the quality assessment will be used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of recommendation for design of any future studies. Quality assessment will be undertaken by one reviewer and checked by a second reviewer, any disagreements will be resolved by consensus or discussion with a third reviewer.

#### **4.5 Methods of analysis/synthesis**

We will provide a narrative synthesis involving the use of text and tables to summarise data. These will allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed. Studies will be organised by participant age (adults, children, or neonates), setting (medical or surgical ICU), outcome measure and PCT assay used. A detailed commentary on the major methodological problems or biases will also be included, together with a description of how this may have affected the individual study results. Recommendations for further research will be made based on any gaps in the evidence or methodological limitations of the existing evidence base.

If sufficient data are available meta-analyses will be used to calculate summary effect estimates (e.g. hazard ratios, odds ratio, relative risks, weighted mean differences) together with 95% CIs, using DerSimonian and Laird random effects models.<sup>23</sup> Forest plots will be used to display results from individual studies and summary estimates to allow visual assessment of heterogeneity. Heterogeneity will be assessed statistically using the tau<sup>2</sup> and I<sup>2</sup> statistics. If sufficient data are available, any observed heterogeneity will be investigated using meta-

regression or stratified analyses. Variables that may be investigated as possible sources of heterogeneity include patient demographics (age, gender), primary diagnosis and/or co-morbidities, other concomitant treatments (e.g. mechanical ventilation, TPN), PCT assay type, and risk of bias domains.

If diagnostic accuracy studies are included and where available data allow, summary estimates of the sensitivity and specificity together with 95% confidence intervals (CIs) and prediction regions will be calculated for PCT in addition to standard diagnostic work-up compared to standard diagnostic work-up. We will use the bivariate/hierarchical summary receiver operating characteristic (HSROC) random effects model to generate summary estimates and an HSROC curve.<sup>24-26</sup>

## **5 Methods for synthesising evidence of cost-effectiveness**

### **5.1 Identifying and reviewing published cost-effectiveness studies**

Exploration of the literature regarding published economic evaluations, utility studies and cost studies will be performed. A review of published economic evaluations will be undertaken on the following databases, utilising a methodological study design filter where appropriate:

- MEDLINE (OvidSP)
- MEDLINE In-Process Citations and Daily Update (OvidSP)
- EMBASE (OvidSP)
- NHS Economic Evaluation Database (NHS EED) (Wiley)
- Health Economic Evaluation Database (HEED) (Wiley)
- EconLit (EBSCO)
- Research Papers in Economics (REPEC) (Internet) (<http://repec.org/>)

Supplementary searches may be undertaken to focus on original papers that report on cost, cost-effectiveness, or cost-utility analyses that study PCT testing. For our assessment cost studies, utility studies and full economic evaluations, i.e. those that explicitly compare different decision options will be selected. Clinical trials as well as modelling studies and cohort studies will be relevant within the frame of our project. The intention is not to perform a systematic review, but to use the studies identified to support the development of an economic model and estimation of model input parameters that will aim to answer the research questions of this project.

The results and the methodological quality of the studies selected will be summarised. Assessment of methodological quality will follow the criteria for economic evaluations in health care as described in the NICE methodological guidance.<sup>27</sup> Data extraction will focus on technologies compared, indicated population, main results in terms of costs and consequences of the alternatives compared, and the incremental cost-effectiveness, but also on methods of modelling used (if applicable), analytical methods and robustness of the study findings.

## **5.2 Evaluation of costs, quality of life and cost-effectiveness**

Decision analytic modelling will be undertaken to determine the cost-effectiveness of adding PCT test results to the information available to clinicians treating 1) patients with confirmed or highly suspected sepsis in intensive care settings and 2) patients presenting to the emergency department with suspected bacterial infection. More specifically, the following research question will be addressed:

1. Does the addition of procalcitonin testing to current clinical practice, to determine whether to initiate and when to discontinue antibiotic therapy, in adults and children with confirmed or highly suspected sepsis who are being treated in an intensive care unit, represent a cost-effective use of NHS resources?
2. Does the addition of procalcitonin testing to current clinical practice, to determine whether to initiate and when to discontinue antibiotic therapy, in adults and children presenting to the emergency department with suspected bacterial infection, represent a cost-effective use of NHS resources?

### *Diagnosis and treatment strategies*

The economic analyses will consider two populations in two settings: children and adults in ICU and emergency department settings. For these patient groups, the proportion of patients receiving antibiotic treatment, the duration of antibiotic therapy, and length of hospital/ICU stay, as well as clinical outcomes, may differ when PCT test results are added to the information available to treating clinicians. Moreover, differences may occur due to the use of different tests to quantify PCT. Therefore, whenever possible, test specific costs and effects will be considered. However, if this is not feasible, the PCT tests will be assessed as a group (comparing PCT testing versus no PCT testing), assuming equal costs and effects for all tests listed in the scope.

### *Model structure*

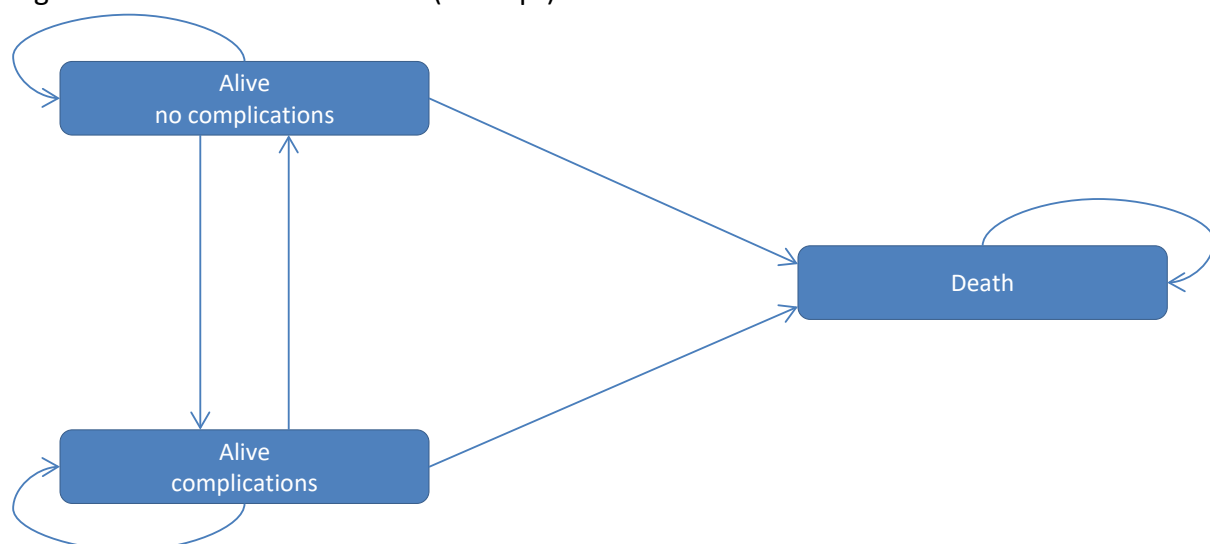
The model structure will be similar for both populations and settings and will distinguish complications and mortality (Figure 1). Complications may include septic shock, persistence



or development of pneumonia, lung abscess, empyema and acute respiratory distress syndrome. A short-term model (28 days) will take into account antibiotic exposure and the different settings (ICU, general ward or discharged). If the evidence suggests that mortality and complications differ between the technologies being compared, and these differences impact the cost-effectiveness result, we will explore the long term consequences of these differences by extrapolating the short-term results to a long-term time horizon using a state-transition model (i.e. Markov model)

Necessary choices and definitions regarding the final structure of the model will depend on the findings from the literature review and consultation with clinical experts. Hence, the draft model structure, presented in the section below, may be developed/expanded. If evidence is lacking for a specific setting and/or (sub)population, no health economic model will be developed for this case.

Figure 1: State-transition model (concept)\*



\* Taking into account antibiotic exposure (intravenous or oral) and setting (ICU, general ward, discharged)

#### *Health outcomes*

Utility values, based on literature or other sources, will be incorporated in the economic model. QALYs will be calculated from the economic modelling.

#### *Costs*

Resource utilisation will be estimated for PCT testing, treatments and hospital/ICU admission. Data for the cost analyses will be drawn from routine NHS sources (e.g. NHS reference costs, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF)), discussions with individual hospitals and with the manufacturers of the PCT tests.

### *Issues relevant to analyses*

- Longer term costs and consequences will be discounted using the UK discount rates of 3.5% of both costs and effects.
- One way sensitivity analyses will be performed for all key parameters, especially for parameters in the models which are based on expert opinion.
- Probabilistic sensitivity analyses will be performed using parameter distributions.
- Decision uncertainty regarding mutually exclusive alternatives will be reflected using cost-effectiveness planes and cost-effectiveness acceptability curves.

## **6 Handling of information from the companies**

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than 02/10/2014. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

## **7 Competing interests of authors**

None

## **8 Timetable/milestones**

<b>Milestones</b>	<b>Completion data</b>
Draft protocol	12/06/2014
Final protocol	07/07/2014
Progress report	02/10/2014
Draft assessment report	02/12/2014
Final assessment report	08/01/2015
Final executable economic model	12/01/2015



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## Appendix 1

### Clinical effectiveness search – example search strategy

Database: Embase <1974 to 2014 June 27>

Date searched: 30.6.14

Records found: 1210

- 
- 1 exp systemic inflammatory response syndrome/ (172787)
  - 2 exp bacterial infection/ (745043)
  - 3 (systemic inflammatory response syndrome\$ or SIRS).ti,ab,ot,hw. (10736)
  - 4 (sepsis\$ or septic\$ or sepsis).ti,ab,ot,hw. (191638)
  - 5 (bacill?emia\$ or bacter?emia\$ or endotox?emia\$ or pyoh?emia\$ or py?emia\$).ti,ab,ot,hw. (48133)
  - 6 (fusobacterium adj2 necrophorum).ti,ab,ot,hw. (1164)
  - 7 (Lemierre\$ adj2 (disease\$ or syndrome\$)).ti,ab,ot,hw. (798)
  - 8 (necrobacillosis or necrobacillosis or meningococc?emia or urosepsis).ti,ab,ot,hw. (3762)
  - 9 (Neisseria adj2 meningitidis adj2 bacter?emia).ti,ab,ot,hw. (19)
  - 10 tetanus.ti,ab,ot,hw. (34768)
  - 11 ((bacter?emic or bacterial or endotoxi\$ or toxi\$) adj3 shock\$).ti,ab,ot,hw. (11163)
  - 12 (toxic adj2 forward adj2 failure).ti,ab,ot,hw. (0)
  - 13 (blood adj2 poison\$).ti,ab,ot,hw. (257)
  - 14 infect\$.ti,ab,ot. (1461612)
  - 15 (bacterial adj2 (meningitis or pneumonia or peritonitis or endocarditis or superinfection or disease\$)).ti,ab,ot,hw. (60674)
  - 16 (bartonellosis or bordetellosis or Bordetella or pertussis or botryomycosis or brucellosis or campylobacter\$ or legionnaire\$ disease or listeriosis or mycoplasmosis or pyomyositis or pyonephrosis or Staphylococc\$ or Streptococc\$ or "e coli").ti,ab,ot,hw. (475125)
  - 17 or/1-16 (2327414)
  - 18 Procalcitonin/ (4820)
  - 19 PCT.ti,ab,ot. (6593)

20 (procalcitonin or pro-calcitonin or 56645-65-9 or (calcitonin adj2 precursor\$)).ti,ab,ot,hw,rn,tn.  
(5087)

21 brahms.af. (915)

22 KRYPTOR.af. (221)

23 b r a h m s.af. (11)

24 or/18-23 (10280)

25 17 and 24 (4786)

26 Random\$.tw. or clinical trial\$.mp. or exp health care quality/ (3261790)

27 25 and 26 (1231)

28 animal/ (1569119)

29 animal experiment/ (1782343)

30 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or  
pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or  
sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5658580)

31 or/28-30 (5658580)

32 exp human/ (14900947)

33 human experiment/ (326401)

34 or/32-33 (14902376)

35 31 not (31 and 34) (4528206)

36 27 not 35 (1218)

**37 limit 36 to yr="1995 -Current" (1210)**



## Appendix 2

### Related NICE guidance: published guidance

Intravenous fluid therapy in adults in hospital NICE Clinical Guideline CG174 (December 2013) Available from: <http://guidance.nice.org.uk/CG174> Date for review: TBC

Feverish illness in children: Assessment and initial management in children younger than 5 years. NICE Clinical Guideline CG160 (May 2013) Available from: <http://guidance.nice.org.uk/CG160> Date for review: TBC

Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients. NICE Clinical Guideline CG151 (September 2012) Available from: [www.nice.org.uk/guidance/CG151](http://www.nice.org.uk/guidance/CG151) Date for review: TBC

Antibiotics for early-onset neonatal infection: antibiotics for the prevention and treatment of early-onset neonatal infection. NICE Clinical Guideline CG149 (August 2012) Available from: <http://guidance.nice.org.uk/CG149> Date for review: TBC

The management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. NICE Clinical Guideline CG102 (June 2010) Available from; <http://guidance.nice.org.uk/CG102> Date for review: June 2013

Management of acute diarrhoea and vomiting due to gastroenteritis in children under 5. NICE Clinical Guideline CG84 (April 2009) Available from: <http://guidance.nice.org.uk/CG84> Date for review: June 2012 – decided not to review at this time

Prevention and treatment of surgical site infection. NICE Clinical Guideline CG74 (October 2008) Available from: <http://guidance.nice.org.uk/CG74> Date for review: August 2014

Urinary tract infection: diagnosis, treatment and long-term management of urinary tract infection in children. NICE Clinical Guideline CG54 (August 2007) Available from: <http://guidance.nice.org.uk/CG54> Date for review: August 2013

### Related NICE guidance: under development

[Intravenous fluids therapy in children](#). NICE Clinical Guideline. Expected publication: October 2015

[Major trauma services: service delivery for major trauma](#). NICE Clinical Guideline. Expected publication: October 2015

[Major trauma: assessment and management of airway, breathing and ventilation, circulation, haemorrhage and temperature control](#). NICE Clinical Guideline. Expected publication: April 2016

[Sepsis: the recognition, diagnosis and management of severe sepsis](#) NICE Clinical Guideline. Expected publication date: July 2016