National Institute for Health and Care Excellence

Final version

Sepsis

Sepsis: recognition, assessment and early management

NICE guideline 51

Appendices A to G

July 2016

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and, where appropriate, their guardian or carer.

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Appendix A: Scope

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SCOPE

1 Guideline title

Sepsis: the recognition, diagnosis and management of severe sepsis

1.1 Short title

Sepsis

2 The remit

The Department of Health has asked NICE: 'to produce a guideline on Sepsis: the recognition, diagnosis and management of severe sepsis'.

3 Need for the guideline

3.1 Epidemiology

a) Sepsis is a clinical syndrome caused by the body's immune and coagulation systems being switched on by the presence of an infection (bacteria, viruses or fungi). Severe sepsis is defined as organ dysfunction or tissue hypoperfusion (decreased blood flow) in addition to sepsis, usually requiring a stay in an intensive care unit (ICU). Septic shock is a life-threatening condition that is characterised by low blood pressure despite adequate fluid replacement in addition to organ dysfunction and sepsis. The UK Sepsis Trust estimates that 37,000 people die from sepsis in the UK every year.

b) According to the Parliamentary and Health Service Ombudsman Annual Report (2013), the most common causes of severe sepsis in adults are pneumonia, bowel perforation, urinary infection and

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severe skin infection. That report, based on example cases in children and adults, recommended that guidelines were needed to support the recognition and management of severe sepsis, particularly in its early stages, and they should cover areas such as initial recognition, timely use of antibiotics and fluid resuscitation.

3.2 *Current practice*

a) It can be difficult to identify cases of sepsis that need urgent treatment to prevent progression to severe sepsis. The current definitions of sepsis and severe sepsis were established in critical care and paediatric critical care to define whether people were eligible to join clinical trials. These definitions are used in International Critical Care guidelines and provide a framework for current intensive care management, but because sepsis is a variable syndrome affecting 1 or more organ systems, the existing critical care definitions and guidelines do not translate simply into diagnostic pathways for initial diagnosis and management.

b) Current standard practice varies according to the clinical experience of the physician or practitioner making the initial assessment, and the facilities immediately available. In secondary care, sepsis can present to any speciality involved in direct clinical care. Groups that are particularly at risk of missed diagnosis of sepsis are infants and young children, people who are immunocompromised for any reason (including those being treated for cancer), people who have recently had surgery, people with indwelling medical lines or devices and women following childbirth. These subgroups all have specific physiological factors that can lead to a missed or delayed diagnosis of sepsis.

c) Treatment involves immediate recognition, resuscitation, early treatment with antibiotics and continual monitoring and reassessment. Although many current guidelines include the assessment and management of sepsis in specific subgroups within their remit, most do not provide guidance for all healthcare

professionals in any situation to assess whether sepsis is present, and to guide initial assessment and treatment.

d) This guideline will provide recommendations for recognising sepsis and instituting treatment to prevent development of severe sepsis and septic shock in any person in any clinical environment, linking to other relevant existing NICE guidance. This guideline will not replicate the existing International Guidelines for Management of Severe Sepsis and Septic Shock: 2012, which cover the critical care management of sepsis in children or adults.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a)

Group	Rationale
• All populations will be included.	This guideline will include all populations. There are a number of different NICE guidelines that may cover aspects of recognition and management of sepsis and severe sepsis in subgroups of the population. We will cross-reference existing guidance when it makes sepsis-specific recommendations.

b) The following subgroups have been identified:

Group	Rationale
• Pregnant women • People at higher risk of infection.	People may be at higher risk of sepsis when they have other medical conditions. This includes immunodeficiency from various causes, for example, treatment for cancer, people with indwelling catheters or devices and people who have recently had surgery.

4.1.2 Groups that will not be covered

a) There are currently no groups that are excluded.

4.2 Setting

a) All healthcare settings.

4.3 Management

4.3.1 Key issues that will be covered

(a) Recognition and early assessment of sepsis and severe sepsis: clinical signs and symptoms.

Key clinical areas	Rationale
• Clinical risk assessment, including history and examination. • 'Red flags' for early identification of sepsis and severe sepsis. • Scoring tools.	Recognition of people at risk of severe sepsis allows appropriate treatment to be started quickly and this is likely to improve outcomes. Evidence indicates that delayed recognition of sepsis and severe sepsis is common. Initial assessment in primary and community settings and on hospital wards consists of evaluating physical signs and symptoms. Scoring systems may be used to predict which people are likely to develop severe sepsis and/or to help make a diagnosis in people with sepsis or severe sepsis.

a) Value of blood markers for predicting and detecting sepsis and severe sepsis.

Key clinical areas	Rationale
• Blood gas (arterial, venous or capillary). • Glucose.	Early identification of sepsis allows appropriate treatment to be started quickly. However, the

• Lactate. • Full blood count (haemoglobin, platelets, white cell count and differential). • Urea and electrolytes. • Clotting screen. • C-reactive protein (CRP).	use of markers of infection can be misleading in sepsis as apparently normal test results (such as for white cell count) may be associated with an overwhelmed immune response. Blood markers may be useful alone or in combination with other tests. Consideration will need to be given to the timing of tests and the feasibility of different tests in different settings.

b) Initial treatment for people with sepsis and with severe sepsis.

Key clinical issues	Rationale
(i) Intravenous fluids and electrolytes in early management of people with sepsis and with severe sepsis.	Sepsis can cause major systemic effects; severe sepsis with clinical shock is the worst of these. The products of the infecting organism (for example, endotoxin or exotoxin) cause the release and activation of inflammatory mediators which cause vasodilatation (the widening of blood vessels) and leakage from capillaries; this leads to people becoming hypovolemic (decreased blood volume). The initial choice of replacement fluid (that is, crystalloid, colloid or albumin), the timing of fluid treatment and the amount to be given will need to be considered. Note: NICE has developed guidelines on Intravenous fluid therapy in adults in hospital (CG174) and is developing guidance on Intravenous fluids therapy in children.
(ii) Empirical antimicrobial treatment strategies in early management of people with sepsis and severe sepsis.	It is not always possible to identify the cause of sepsis. Early use of antibiotics is part of the treatment for suspected meningococcal disease in all

	healthcare settings, and advice would be useful about how best to use antibiotics in suspected sepsis, due to any cause, in any setting (for example, pre-hospital treatment comparing immediate broad spectrum antibiotics to later targeted treatment). The incidence of different causes of sepsis in different populations and settings may be an important consideration.
(iii) Early treatment with oxygen and correcting the acid–base balance in people with sepsis and with severe sepsis.	There is increasing reference in the literature to optimal early treatment being within shorter time frames than the previous 'golden hour'. Correcting the acid–base balance and the delivery of oxygen may be appropriate once sepsis is suspected or has been diagnosed.

c) Escalating care for people with sepsis or with severe sepsis.

Key clinical issue	Rationale
• Timing of escalation of care in early management of sepsis. • Early treatment with inotropic agents in people with sepsis.	The care of a person with sepsis is a medical emergency and their care should be directed by senior specialists. The threshold

• Central venous access and arterial lines.	at which senior health professionals and/or critical care providers should be involved and central arterial or central venous access is needed will be considered. Inotropic drugs may be indicated for sepsis, and their use considered as soon as severe sepsis is suspected.

d) Identifying the source of infection.

Key clinical issues	Rationale
• The use of clinical symptoms and signs to identify the source of infection. • Tests, for example: - blood culture - lumbar puncture (clear contraindication criteria for lumbar puncture) - chest X-ray and other imaging.	Identifying the source of infection will allow treatment to be targeted in the management pathway. This may need appropriate healthcare staff (see 4.3.1.(d)) such as obstetricians and surgeons to be involved early on, depending on the clinical presentation. There may also be a need for prompt surgical treatment. Some investigations such as lumbar puncture may be contraindicated.

e) Early monitoring of people with sepsis.

Key clinical issue	Rationale
What parameters to continually assess, how often and by whom, for example: • heart rate • respiratory rate • blood pressure • blood gases • other blood markers, for example, lactate.	People with sepsis or suspected sepsis can deteriorate quickly, and appropriate monitoring can identify this deterioration and detect response to treatment.

f) Information and support for patients and carers.

Key clinical area	Rationale
Information and support.	Information and support is needed for: • people with sepsis or severe sepsis • people who are diagnosed as not having sepsis and are discharged from medical care • families and carers of people who have sepsis or severe sepsis • people who survive episodes of severe sepsis.

g) Training and education.

Key clinical area	Rationale
All healthcare providers.	Evidence indicates that sepsis is often not suspected or recognised. For some healthcare professionals the care of a person with severe sepsis will be an unusual event, but their suspicion of the diagnosis may be critical for that person.

4.3.2 Issues that will not be covered

Key clinical areas	Rationale
(i) Procalcitonin.	Assessment commissioned from NICE Diagnostics Assessment Programme.
(ii) Managing sepsis in neonates, children and adults in the ICU.	This is a specialist area for which speciality guidelines already exist. Specialist treatments of conditions that result from sepsis and experimental interventions within the ICU will also be excluded. These may include: • blood products • corticosteroids • supportive therapies • treating sepsis caused by ventilator-associated

	pneumonia • neuromuscular blockade • renal replacement therapy • venous thromboembolism prophylaxis • pressure ulcers • glucose control • immunoglobulins.
(iii) Treatment and care of secondary effects on other organs.	Sepsis can lead to multisystem failure; however, managing this requires specialist ICU care, which we propose is excluded.
(iv) Preventing sepsis.	The guideline will not cover measures to prevent sepsis. This includes vaccination programmes; infection control and prevention measures; personal protective equipment; use of particular types of catheters/feeding tubes; preventing sepsis arising from, for example, mechanical ventilation or surgery; antibiotic prophylaxis to prevent infection; screening for pathogens in at-risk populations.

4.4 Main outcomes

a) Mortality.

b) Progression to severe sepsis.

c) Duration of hospital stay.

d) Duration of ICU stay.

e) Number of organs supported.

f) Change in physical signs and symptoms.

g) Adverse events.

h) Health-related quality of life (for example, as assessed by SF-12 or EQ-5D).

i) Psychological outcomes.

j) Outcomes indicating severity of long-term disability/rehabilitation needs.

k) Patient-reported outcome measures.

4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in The guidelines manual.

4.6 Status

4.6.1 Scope

This is the final scope.

4.6.2 Timing

The development of the guideline will begin in July 2014.

5 Related NICE guidance

5.1 Published guidance

- Acute kidney injury. NICE clinical guideline CG169 (2013).
- Critical illness rehabilitation. NICE clinical guideline CG83 (2013).
- Intravenous fluid therapy in adults in hospital. NICE clinical guideline CG174 (2013).
- Feverish illness in children. NICE clinical guideline CG160 (2013).
- Patient experience in adult NHS services. NICE clinical guideline CG138 (2012).
- Antibiotics for early-onset neonatal infection. NICE clinical guideline CG149 (2012).
- Infection control. NICE clinical guideline CG139 (2012).
- Neutropenic sepsis. NICE clinical guideline CG151 (2012).
- Diabetic foot problems - inpatient management. NICE clinical guideline CG119 (2011).
- Bacterial meningitis and meningococcal septicaemia. NICE clinical guideline CG102 (2010).
- Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care. NICE clinical guideline CG108 (2010).
- Venous thromboembolism - reducing the risk. NICE clinical guideline CG92 (2010).
- Diarrhoea and vomiting in children under 5. NICE clinical guideline CG84 (2009).
- Induction of labour. NICE clinical guideline CG70 (2008).
- Intrapartum care. NICE clinical guideline CG55 (2008) (update due for publication October 2014).
- Surgical site infection. NICE clinical guideline CG74 (2008).
- Acutely ill patients in hospital. NICE clinical guideline CG50 (2007).
- Urinary tract infection in children. NICE clinical guideline CG54 (2007).

- Nutrition support in adults. NICE clinical guideline CG32 (2006).
- Postnatal care. NICE clinical guideline CG37 (2006).

5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Pneumonia. NICE clinical guideline. Publication expected December 2014.
- Intravenous fluids therapy in children. NICE clinical guideline. Publication expected October 2015.
- Antimicrobial stewardship guideline. NICE medicines practice guideline. Publication expected March 2015.
- Acute medical emergency guideline. NICE clinical guideline. Publication date to be confirmed.

6 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

- How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS: 5th edition
- The guidelines manual.

Information on the progress of the guideline will also be available from the NICE website.

Appendix B: Declarations of interest

The May 2007 version (as updated October 2008) of the NICE code of practice for declaring and dealing with conflicts of interest policy was applied to this guideline.

Saul Faust

GDG meeting	Declaration of interest	Classification	Action taken
17/01/2014	For all commercial relationships I have received no personal payment of any kind from any organisation, all grants, honoraria and fees paid to University or Trust employer • Clinical Trial investigator for commercial clinical trials (acting on behalf of University of Southampton and University Hospital Southampton NHS Foundation Trust, no personal payments of any kind), all NIHR portfolio commercial studies. ○ 2006-14 clinical trials on behalf of Wyeth, Pfizer, GSK, Sanofi, Novartis for paediatric vaccines, Roche (antiviral agent in influenza), Alios (treatment for RSV infection) 2012-4 UK Chief Investigator for GSK quadrivalent influenza vaccine paediatric clinical trials (QIV004 and 009) ○ 2014-6 UK Chief Investigator for Cubist trial of antimicrobial agent in paediatric bone and joint infection • Grant funding to institution: co-investigator on Pfizer-funded investigator led	Non-personal pecuniary interest	Declared and participated

GDG meeting	Declaration of interest	Classification	Action taken
	study in pneumococcal molecular epidemiology (funds held by University of Southampton). ○ Pfizer Paediatric Vaccines Media Medics Lounge July 2013 • Meeting of experts (no personal payments as above) arranged by equal convenors: Astellas, Cubist & Actelion. April 2013 to discuss generic issues related to to C difficile in infants, NOT specific products. Meeting recommended further open discussions with EMA PDCO to discuss generic issues regarding age/case definition (took place on 15th Jan 2014) • Involved in sepsis research since 1996 as an investigator and co-investigator in MRC and pharma-funded clinical research and trials in paediatric sepsis. • Has recently been Chief Investigator on a UK AMRC Charity (Meningitis Research Foundation) funded, NIHR MCRN adopted, pilot phase 2 study of corticosteroids in paediatric sepsis, the analysis of which is currently being carried out and which will report in Q4 2014.	Personal non-pecuniary interest	
11th July 2014	No change		None
5th Sept 2014	No change		None

GDG meeting	Declaration of interest	Classification	Action taken
21st Oct 2014	No change		None
2nd Dec 2014	No change		None
16th Jan 2015	No change		None
4th Mar 2015	• Participation in Pfizer Meningococcal Vaccine Global Scientific Strategy Advisory Board 2015 (no personal payment of any kind from any organisation, all honoraria paid to University or Trust employer) • Clinical Trial investigator for 2014-5 commercial clinical trials in infants with RSV (Alios and Ablynx) (acting on behalf of University of Southampton and University Hospital Southampton NHS Foundation Trust, no personal payments of any kind),	• Non-personal pecuniary interest • Non-personal pecuniary interest	Declare and participate Declare and participate
28th Apr 2015	No change		None
2nd June 2015	No change		None
15th July	No change		None
8th September 2015	• Attended flu vaccine advisory board hosted by AstraZeneca. • Attended infectious Diseases Research Network meeting on sepsis biomarkers for children.	• Personal pecuniary interest • Personal non-pecuniary interest	• Declare and participate • Declare and participate
16th October	No change		None

Richard Beale

Date	Item declared	Classification	Action taken

Date	Item declared	Classification	Action taken
Initial declaration (2nd May 2014)	Small amount of industry consulting work - contracts are with Trust and fee is billed by Trust and goes to departmental research budget. No direct payment is received. $3,000 fee received by Trust for infection diagnostics for the Waters Corporation Current member of the Steering Committee of the Surviving Sepsis Campaign	Non-personal pecuniary interest Personal non-pecuniary interest	Declare and participate Declare and participate
14th June 2014	TSB grant in partnership with Edinburgh and Newcastle Universities and BD biosciences, to develop new sepsis biomarkers Membership of the steering committee of the Surviving Sepsis Campaign Chair of Research Committee of European Society of Intensive Care Medicine (2010 - 2013), and Executive Committee Member Waters Scientific Advisory Board meeting 10 12 13	Non-personal pecuniary interest Personal non-pecuniary interest	Declare and participate
11th July 2014	No change		None
5th Sept 2014	No change		None
21st Oct 2014	No change		None
2nd Dec 2014	No change		None
16th Jan 2015	No change		None
4th March 2015	Research grant for sepsis biomarkers. TSB/ BD biosciences via King's College London	Personal non-pecuniary interest	Declare and participate
28th Apr 2015	No change		None
2nd June 2015	No change		None
15th July 2015	No change		None
8th September 2015	No change		None

Date	Item declared	Classification	Action taken
18th September 2015	No change		None
16th October 2015	No change		None

John Butler

Date	Item declared	Classification	Action taken
Initial declaration (2nd June 2014)	Member of the Faculty of Intensive Care Board, as the College of Emergency Medicine Representative, with full voting rights. Member of the UK Sepsis Trust for about five years and has utilised their Survive Sepsis educational material to conduct Sepsis study days within Trust. Membership is voluntary and unpaid. Attended a Houses of Parliament meeting in September 2013 following an invitation from the UK Sepsis Trust, to Lobby MPs on the importance of sepsis as a major healthcare issue. Evaluated the use of biomarker PCT in critical care unit about 4 years ago. Following its successful evaluation and implementation, has presented departmental experience at meeting and has received travel and accommodation expenses from Thermofisher. The only meeting in the last year was on 28 January and was sponsored by Thermofisher. Talk was about biomarkers and experience with PCT in clinical practice. At request of Trust, attended two meetings in March 2014, organised by Advancing Quality Alliance. Attended Sepsis group and worked with a group of multi-disciplinary clinicians to produce a set of clinical standards which could be used to assess clinical performance in the management of patients with sepsis. This work was unfunded and attended in own time.	Personal non-pecuniary interest	Declare and participate
11th July 2014	No change		None
5th Sept 2014	No change		None

Date	Item declared	Classification	Action taken
21st Oct 2014	No change		None
2nd Dec 2014	No change		None
16th Jan 2015	No change		None
5th Feb 2015	No change		None
4th March 2015	No change		None
28th Apr 2015	No change		None
2nd June 2015	No change		None
15th July 2015	No change		None
8th September 2015	No change		None
18th September 2015	No change		None
16th October 2015	No change		None

Enitan Carrol

Date	Item declared	Classification	Action taken
Initial declaration (9th May 2014)	None		None
11th July 2014	1) TSB grant holder for development of a point of care test for sepsis with two UK SMEs. 2) My institution has filed a patent on my behalf, for a biomarker combination for sepsis. 3) Existing collaboration with Biomerieux and Brahms but have never received any payments to myself or my institution. Biomerieux has hosted collaborative visits, but expenses are in line with what would be considered reasonable.	1) Non-personal pecuniary interest 2) Non-personal pecuniary interest 3) Personal non-pecuniary interest	1) Declare and participate 2) Declare and participate 3) Decl

Date	Item declared	Classification	Action taken
	4) Member of two NIHR panels ; RfPB and i4i 5) Personal experience of septicaemia 6) Co-opted member of a NICE diagnostic assessment committee, which is looking at Procalcitonin.	4) Personal non-pecuniary interest 5) N/A 6) Personal non-pecuniary	are and participate 4) Declare and participate 5) N/A 6) Declare and participate
5th Sept 2014	No change		None
7th Oct 2014	No change		None
16th Jan 2015	No change		None
6th Feb 2015	I have been invited to join the Scientific Advisory Board for Biomerieux (BioFire- Film Array) for development of a diagnostic panel for infections in children. Meeting will take place on 16-18 March. All honorarium will be paid directly to my institution (University of Liverpool) and the contract is between my institution and Biomerieux. I will not personally receive any financial or other benefits from the contract.	Non-personal pecuniary interest	Declare and participate
22nd April 2015	No new declarations I have worked on biomarkers of infection in the past 12 months (procalcitonin, NGAL, resistin, S100A100 , MMP8/9 and many others) I filed a patent for the combination of biomarkers of bacterial infection in 2012; UK Patent Application No 1201918.8, Biomarkers for sepsis, International Patent Application No PCT/GB2012/051251	Non-personal pecuniary interest	
2nd June	No change		None

Date	Item declared	Classification	Action taken
2015			
15th July 2015	I am on Steering group of Infectious Diseases Research Network I received an MRC Confidence in Concept award in 2014 on identifying biomarkers of sepsis using peptide arrays with a company called Avacta Life Sciences I received a Knowledge Transfer Partnership with Avacta from Innovate UK. The Knowledge Transfer Partnership (KTP) scheme allows UK Universities to help UK Industry by utilising knowledge which exists within the University. The scheme is partly funded by the Business itself (~33%) with the remainder being funded by government grants. The academic's institution receives financial remuneration for this, to be used for any academic purpose on any project.	Personal non-pecuniary	Declare and participate
8th September 2015	No change		None
18th September 2015	No change		None
16th October 2015	No change		None

Simon Nadel

Date	Item declared	Classification	Action taken
Initial declaration (16th Oct 2014)	Consultant and advisory board member for Novartis Vaccines	Personal pecuniary interest	Declare and participate
14th July 2014	Advisory boards for Novartis, Pfizer, Baxter and Abbvie – money paid for expenses and travel. Educational grant Pfizer Research grant Pfizer Scientific committee for Meningitis Research Foundation and Meningitis Now	Personal pecuniary interest Non-personal pecuniary interest Personal non-pecuniary interest	Declare and participate Declare and participate Declare and participate

Date	Item declared	Classification	Action taken
	charities. Scientific committee for British Paediatric Surveillance Unit Writing Committee for American Academy of Pediatrics, Sepsis Guidelines Group. Secretary of European Society for Paediatric and Neonatal Intensive Care		
5th Sept 2014	No change		None
21st Oct 2014	No change		None
2nd Dec 2014	No change		None
16th Jan 2015	No change		None
4th March 2015	No change		None
28th Apr 2015	No change		None
2nd June 2015	No change		None
15th July 2015	No change		None
8th September 2015	Been invited to the German Sepsis Society conference.	Personal non-pecuniary interest	None
18th September 2015	No change		None
16th October 2015	No change		None

Julian Newell

Date	Item declared	Classification	Action taken
Initial declaration (5th May 2014)	None		None
11th July 2014	Advisor to NCEPOD Study: Sepsis Volunteer for UK Sepsis Trust Has attended one meeting regarding an NHS England (Patient Safety Division) patient study.	Personal non-pecuniary interest	Declare and participate
5th Sept 2014	No change		None
21st Oct	No change		None

Date	Item declared	Classification	Action taken
2014			
2nd Dec 2014	No change		None
16th Jan 2015	No change		None
4th March 2015	No change		None
28th Apr 2015	No change		None
2nd June 2015	No change		None
15th July 2015	No change		None
8th September 2015	No change		None
18th September	No change		None
16th October	No change		None

Jenny O'Donnell

Date	Item declared	Classification	Action taken
Initial declaration	Lead volunteer for UK Sepsis Trust	Personal non-pecuniary interest	Declare and participate
1st July 2014	Family experience of sepsis	Personal non-pecuniary interest	Declare and participate
5th Sept 2014	No change		None
21st Oct 2014	No change		None
2nd Dec 2014	No change		None
16th Jan 2015	No change		None
4th March 2015	No change		None
28th Apr 2015	No change		None
2nd June 2015	Attended the UK Sepsis Trust Parliamentary Reception in September 2014.	Personal pecuniary interest	Declare and participate

Date	Item declared	Classification	Action taken
	Attended the UK Sepsis Trust Ball in September 2014 (paid £200 for the ticket) and won auction prize of a holiday (paid £1250 for this). The holiday included a week (2-9 April 2015) at the CEO of UK Sepsis Trust's apartment in Spain and £300 towards flights. Attended two West of England Academic Health Science Network Sepsis Masterclass sessions (one in Q1 2015, one in Q2 2015). Also in the process of setting up a Sepsis Support Group in Bristol on behalf of the UK Sepsis Trust.		
15th July 2015	No change		None
14th September 2015	I attended the Sepsis Parliamentary Reception in conjunction with the UK Sepsis Trust (UKST). As previously stated, I am organizing a Sepsis Support Group in Bristol on 22nd October 2015 on behalf of the UK Sepsis Trust. The UKST will also fund my Cruse training on 21st October 2015 to help me prepare for the support group.	Personal non-pecuniary interest	Declare and participate
18th September 2015	No change		None
16th October 2015	No change		None

Rachel Rowlands

Date	Item declared	Classification	Action taken
Initial declaration (18th June 2014)	Department audit lead and paediatric governance lead.	Personal non-pecuniary interest	Declare and participate
11th July 2014	No change		None
5th Sept 2014	No change		None
21st Oct 2014	No change		None

Date	Item declared	Classification	Action taken
2nd Dec 2014	No change		None
16th Jan 2015	No change		None
4th March 2015	No change		None
28th Apr 2015	Won £500 from UK Sepsis Trust from competition to pitch ideas to improve sepsis care. Funding received by organisation, not RR personally.	Non-personal pecuniary interest	Declare and participate
2nd June 2015	No change		None
15th July 2015	No change		None
8th September 2015	No change		None
18th September 2015	No change		None
16th October 2015	No change		None

Mark Simmonds

Date	Item declared	Classification	Action taken
Initial declaration (1st May 2014)	None		None
6th Aug 2014	Developing electronic sepsis screening tool with NerveCentre Software as part of wider electronic observations work at Nottingham University Hospitals.	Non-personal pecuniary interest	Declare and participate
5th Sept 2014	No change		None
21st Oct 2014	No change		None
2nd Dec 2014	No change		None
16th Jan 2015	No change		None
4th March 2015	No change		None
3rd April 2015	No change		None

Date	Item declared	Classification	Action taken
28th Apr 2015	No change		None
2nd June 2015	No change		None
15th July 2015	No change		None
8th September 2015	Developing automated sepsis screening with Nervecentre Software. Attended and spoke at Sepsis UK conference 2015.	Personal non-pecuniary interest	Declare and participate
18th September 2015	No change		None
16th October 2015	No change		None

Alison Tavaré

Date	Item declared	Classification	Action taken
Initial declaration	Dr Tavaré's husband is in receipt of grants from the Wellcome Trust, Cancer Research UK, EPSRC and Diabetes UK. He is director of the Elizabeth Blackwell Institute for health research at the University of Bristol.	Personal family interest	Declare and participate
11th July 2014	Personal experience of sepsis. Involved in raising awareness of sepsis amongst clinicians at North Bristol Trust, GP practices in Bristol and Eastwood Park Prison, Gloucs.	Personal non-pecuniary interest	Declare and participate
5th Sept 2014	Uses educational material from the UK Sepsis Trust and has attended a reception at the Houses of Parliament as part of this role.	Personal non-pecuniary interest	Declare and participate
21st Oct 2014	No change		None
2nd Dec 2014	No change		None
16th Jan 2015	No change		None
4th Mar 2015	No change		None
3rd April 2015	No change		None
2nd June 2015	Member of the West of England AHSN (Academic health science network) working group looking at improving methods of detecting and managing sepsis in the	Personal non-pecuniary interest	Declare and participate

Date	Item declared	Classification	Action taken
	community		
15th July 2015	Asked to review the NCEPOD report and recommendations on sepsis and speak at the launch of the report	Personal non-pecuniary interest	Declare and participate
8th September 2015	Attended a Sepsis Trust reception at the Houses of Parliament in September 2015.	Personal non-pecuniary interest	Declare and participate
18th September 2015	No change		None
16th October 2015	Contacted by the Health Science Network to work on a project improving communication in principal setting. Not committed as of yet.	Personal pecuniary interest	Declare and participate

Louella Vaughan

Date	Item declared	Classification	Action taken
Initial declaration (6th May 2014)	Collaborator in research project which has received non-financial support from Brahms (manufactures biomarkers which may be of use in sepsis).	Non-personal pecuniary interest	Declare and participate
13th Aug 2014	1) Working on research projects that have received funding from industry partners (Thermofisher) – no money directly to myself 2) Council Member of the Society for Acute Medicine and have publicly supported the National Early Warning System (NEWS)	1) Non-personal pecuniary interest 2) Personal non-pecuniary	Declare and participate
5th Sept 2014	No change		None
21st Oct 2014	No change		None
2nd Dec 2014	No change		None
16th Jan 2015	No change		None
4th March 2015	No change		None
28th Apr 2015	No change		None
2nd June	No change		None

Date	Item declared	Classification	Action taken
2015			
15th July 2015	No change		None
8th September 2015	No change		None
18th September 2015	No change		None
16th October 2015	No change		None

James Wenman

Date	Item declared	Classification	Action taken
Initial declaration (30th May 2014)	None		
31st July 2014	In 2012/13 South Western Ambulance Service (SWASFT) embarked on a joint project with Daiichi Sankyo (pharmaceutical company) developing the first electronic referral pathway for patients with atrial fibrillation. This project was funded partly by Daiichi Sankyo (£10k) matched with the equivalent of professional managerial input and training by SWASFT. The £10k was spent directly on the project, purchasing the licence for the required software to facilitate to the pathway. The payment was made directly to the Trust.	Non-personal pecuniary interest	Declare and participate
5th Sept 2014	No change		None
21st Oct 2014	No change		None
2nd Dec 2014	No change		None
16th Jan 2015	No change		None
4th March 2015	No change		None
28th Apr 2015	No change		None
2nd June 2015	No change		None

Date	Item declared	Classification	Action taken
15th July 2015	I have been approached by the UK Sepsis Trust to support the dissemination of the new pre-hospital sepsis tool kits (time scales to be confirmed).	Non-personal pecuniary interest	Declare and participate
8th September 2015	No change		None
18th September 2015	No change		None
16th October 2015	No change		None

Catherine White

Date	Item declared	Classification	Action taken
Initial declaration	None		None
11th July 2014	No change		None
15th Sept 2014	1) Volunteers for ICUsteps as the Information Manager and a Trustee. This role involves reviewing research trials to provide a patient perspective. 2) Helped produce a patient information booklet with the UK Sepsis Trust. 3) Independent paid lay member on the leoPARDs (Levosimendan for the Prevention of Acute oRgan Dysfunction in Sepsis) clinical trial. Role is to present the patient view. 4) Paid lay member on the NIHR Health Technology Assessment Clinical Evaluation and Trials Board. Occasionally the board is asked to consider funding a sepsis trial. 5) Lay reviewer for the NIHR, which occasionally involves reviewing sepsis trials. 6) Volunteer lay member on the NCEPOD	1) Personal non-pecuniary interest 2) Personal non-pecuniary 3) Personal pecuniary interest 4) Personal pecuniary interest 5) Personal non-pecuniary 6) Personal non-pecuniary	Declare and participate

Date	Item declared	Classification	Action taken
	current sepsis investigation.		
21st Oct 2014	No change		None
2nd Dec 2014	No change		None
16th Jan 2015	No change		None
4th March 2015	No change		None
28th Apr 2015	No change		None
2nd June 2015	No change		None
15th July 2015	No change		None
8th September 2015	No change		None
18th September 2015	No change		None
16th October 2015	No change		None

Appendix C: Clinical review protocols

C.1 Signs and symptoms

Table 1: Review protocol: signs and symptoms for identification of sepsis

Component	Clinical signs and symptoms for identification of sepsis
Review question	In people with suspected sepsis suspected sepsis how accurate are physiological signs and symptoms to identify whether sepsis is present?
Objectives	To identify the clinical signs and symptoms that would assist in the recognition and early assessment of people with sepsis.
Population	All people with suspected (or under investigation for) sepsis, including the following groups: • Adults • Young people aged 12-18 years • Children including infants and neonates (pre- term neonates excluded) • People aged over 70years • People at higher risk of infection • Pregnant women and recently pregnant women Immunocompromised people.
Index tests: sign(s) or symptom(s)	1. heart rate 2. respiratory rate 3. systolic blood pressure, pulse pressure, mean arterial pressure 4. level of consciousness 5. altered mental state: – (possible descriptors - delirium, hypoactive, for children- no response to social cues, does not wake or if roused does not stay awake) 6. low oxygen saturation 7. fever (including history of fever) 8. hypothermia 9. reduced urine output 10. appearing ill to a healthcare professional/or relative 11. history of falls 12. rigor 13. skin rash 14. pain, including pleuritic pain, limb pain 15. diarrhoea/ watery diarrhoea/ vomiting 16. abdominal pain/vaginal discharge 17. shock/hypoperfusion (prolonged capillary refill time, cold hands and feet , reduced skin turgor, pale/mottled/ashen/blue skin, lips or tongue) 18. altered breathing (for example, nasal flaring, grunting, chest indrawing) 19. weak, high-pitched or continuous cry 20. bulging fontanelle
Reference standards	• Blood culture proven infection • American College of Chest Physicians/ Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference definition of sepsis • Other composite definitions of sepsis based on clinical biochemistry tests and signs and symptoms • All-cause mortality at 28-days (or closest time point) • Onset of organ failure
Statistical	Sensitivity

Component	Clinical signs and symptoms for identification of sepsis
measures	Specificity Positive Predictive Value Negative Predictive Value ROC curve or area under the curve Odds ratio: univariate analyses only included if no multivariate analyses reported
Key confounders	For studies reporting ORs: no pre-specified confounders
Study design	Cross-sectional studies Prospective and retrospective cohorts Systematic reviews of the above
Exclusions	Non-English language Studies published before 1990
Search Strategy	Databases: Medline, Embase, the Cochrane library Date: post 1990 data Language: restrict to English language only
The review strategy	Appraisal of methodological quality: • The methodological quality of each study will be assessed using the QUADAS-2 checklist (per target condition). Synthesis of data: • Diagnostic meta-analysis will be conducted where appropriate using hierarchical methods.

C.2 Scoring systems

Table 2: Review protocol: sepsis scoring systems

Component	Scoring systems for identification of sepsis
Review question	What is the most accurate and cost-effective assessment tool to identify patients with sepsis?
Objectives	To identify the most accurate and cost-effective scoring system to: • identify patients with sepsis • prognosis • assess severity of the disease
Population	All populations, including the following subgroups: Adults Children People at higher risk of infection Pregnant women and recently pregnant women
Index test: Severity assessment tools	Scoring systems, for example: PEWS, MEWS, NEWS, early warning scores, triage scoring, MTS (Manchester triage), emergency severity index, POP score, CURB65, APACHE, SOFA, PIRO Note: only tools used in ED or ward are included (exclude critical care context)
Reference standard or target condition/patient outcomes	Patient outcomes: • mortality • hospital admission • health-related quality-of-life (measured by CAP symptom questionnaire, EQ5D or SF-36). • escalation of care

Component	Scoring systems for identification of sepsis
	• unplanned critical care admission • composite unexpected patient death/cardiac arrest/admission to critical care Note: exclude critical care outcomes Other outcomes: • test practicality.
Outcomes	If thresholds are established/pre-defined: • relative risk (RR) or odds ratio (or) (and ultimately risk difference) for patient outcomes listed above for those in higher or lower risk groups • area under the curve (AUC) (through ROC analysis). Supplementary information only if no other data (RRs, ORs, AUCs) available through: • sensitivity • specificity • positive predictive value (PPV) • negative predictive value (NPV).
Study design	Systematic reviews (SRs), RCTs and non-RCTs comparative study including any of the above severity tools. External validation studies.
Exclusions	Non-English language Case-control studies and internal validation studies
Setting	Community settings in which NHS care is received
Search Strategy	To be added
The review strategy	Appraisal of methodological quality The methodological quality of each study will be assessed using NICE checklists. Synthesis of data: Meta-analysis will not be conducted. Priority will be given to results as presented by AUCs (discriminatory analysis) and results of multivariate analysis (or or RRs (95% CI). When the studies report the raw data of outcome of interest by low/intermediate/high risk groups as defined by tools, this information will be summarized in RRs and corresponding absolute effect measures.
Notes	Only tools that are externally validated will be assessed As non-RCTs studies are prone to publication bias, results from the largest studies will be highlighted. As some of the tools have already incorporated some of the confounding factors, results from the univariate analysis will be equally presented. Test practicality will also be considered by the GDG in deciding which tool is 'best'.

C.3 Blood tests

Table 3: Review protocol: blood tests

Review question 6a	In people with suspected sepsis how accurate are blood tests to identify whether sepsis is present?
Objectives	To identify the blood tests that would assist in the recognition and early assessment of people with sepsis.
Population	All people with suspected (or under investigation for) sepsis

Index tests	All of the following, alone or in combination: • blood gas (arterial, venous or capillary): pH, bicarbonates, base deficit • glucose • lactate • full blood count (haemoglobin, platelets or thrombocytopenia, white cell count or leucocyte (TLC) or neutrophil (ANC), Immature to Total Neutrophil Ratio (I/T ratio) bands or Toxic granulations, polymorph); • biochemical tests (urea/electrolytes (sodium, potassium)/renal/liver function, creatinine, haematocrit); • clotting screen; prothrombin time PT/INR, APTT/APTR, TT and fibrinogen • C-reactive protein (CRP).
Reference standards	• blood culture proven infection • American College of Chest Physicians/ Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference definition of SIRS, sepsis, severe sepsis and septic shock • other composite definitions based on clinical biochemistry tests and signs and symptoms • clinical outcome of all-cause mortality at 28 days (or nearest time point)
Statistical measures	Sensitivity Specificity Positive Predictive Value Negative Predictive Value ROC curve or area under the curve Odds ratio
Study design	• RCTs • prospective and retrospective cohort studies • cross-sectional studies • case-control studies (if there is no other evidence)
Exclusions	Procalcitonin (PCT) Erythrocyte sedimentation rate (ESR) Gram-stained gastric aspirate cytology (GAC) Endotoxin Interleukin (IL) Activators adenosine diphosphate (ADP) Arachidonic acid (AA) Collagen (Col) Thrombin receptor activating peptide (TRAP) Tumour necrosis factor (TNF) Microalbuminuria Studies conducted in developing countries Date: studies published before 1999
Key confounders for studies reporting ORs	No pre-specified confounders
Search Strategy	Databases: Medline, Embase, the Cochrane library, Language: restrict to English language only Population search strategy:

	exp Sepsis/ Sepsis.ti,ab. blood-borne pathogens/ (blood adj2 (pathogen* or poison*)).ti,ab. exp Systemic Inflammatory Response Syndrome/ systemic inflammatory response syndrome'.ti,ab. SIRS.ti,ab. (septicaemi* or septicemi*).ti,ab. (Septic adj2 shock).ti,ab. (pyaemi* or pyemi* or pyohemi*).ti,ab. (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab. or/1-11
Review Strategy	Stratification – groups that cannot be combined: • adults • children • neonates (not pre-term, not NICU, not SCBU) • immunocompromised adults including those on immunosuppressive drugs (including corticosteroids) • immunocompromised children including those on immunosuppressive drugs (including corticosteroids) • pregnant and recently pregnant women Subgroups where diagnostic tests may be more or less accurate – to investigate heterogeneity: • Different ethnic groups Appraisal of methodological quality: • The methodological quality of each study will be assessed using the QUADAS-2 checklist (per target condition). Synthesis of data: • Diagnostic meta-analysis will be conducted where appropriate using hierarchical methods.

C.4 Lactate

Table 4: Review protocol: What is the predictive value of lactate in people with sepsis for the recognition and early assessment of worsening sepsis?

Review question	In people with suspected sepsis how accurate is blood lactate to identify worsening sepsis?
Objectives	To determine the accuracy of initial blood lactate and blood lactate clearance in predicting worsening sepsis
Population	People with suspected sepsis or severe sepsis
Index test	Lactate
Reference standards	These were intended to be reference standard measures that a worsening of sepsis had taken place: • all-cause mortality at 28 days(or nearest time point) • ICU admission • hospitalisation

	• length of hospital stay
Statistical measures	Sensitivity Specificity
Study design	Observational studies that included diagnostic accuracy analyses
Exclusions	• studies conducted in developing countries • studies published before 1999
Search strategy	Databases: Medline, Embase, the Cochrane library, Language: restrict to English language only 3 populations: • sepsis • HTA • meningococcal disease Search • lactate AND 3 populations
Review strategy	Diagnostic accuracy data. If papers only presented AUC data then the authors were contacted for more information Appraisal of methodological quality: • The methodological quality of each study will be assessed using the QUADAS-2 checklist (per target condition). Synthesis of data: • Diagnostic meta-analysis will be conducted where appropriate using hierarchical methods.

C.5 Creatinine

Table 5: Review protocol: serum creatinine

Review question	In people with suspected sepsis how accurate is serum creatinine to identify worsening sepsis?
Objectives	To determine the accuracy of initial serum creatinine in predicting worsening sepsis
Population	People with suspected sepsis, severe sepsis or septic shock
Index test	Serum creatinine
Reference standards	These were intended to be reference standard measures that a worsening of sepsis had taken place: • all-cause mortality at 28 days (or nearest time point) • ICU admission • hospitalisation • length of hospital stay
Statistical measures	Sensitivity Specificity Positive Predictive Value Negative Predictive Value ROC curve or area under the curve Odds ratio
Study design	Observational studies that included diagnostic accuracy analyses
Key confounders for studies reporting odds ratios	No pre-specified confounders
Exclusions	Studies conducted in developing countries

Review question	In people with suspected sepsis how accurate is serum creatinine to identify worsening sepsis?
	Study published before 1999
Search strategy	Databases: Medline, Embase, the Cochrane library, Language: restrict to English language only 3 populations: • sepsis • HTA • meningococcal disease Search • creatinine AND (3 populations AND acute kidney injury)
Review strategy	Stratification – groups that cannot be combined: Adults Children Neonates (not pre-term, not NICU, not SCBU) Immunocompromised adults including those on immunosuppressive drugs (including corticosteroids) Immunocompromised children including those on immunosuppressive drugs (including corticosteroids) Pregnant and recently pregnant women Subgroups where prognosis may be more or less accurate – to investigate heterogeneity: Different ethnic groups Appraisal of methodological quality: • The methodological quality of each study will be assessed using the QUADAS-2 checklist (per target condition). Synthesis of data: • Diagnostic meta-analysis will be conducted where appropriate using hierarchical methods.

C.6 Disseminated intravascular coagulation and sepsis

Table 6: Review protocol: Disseminated intravascular coagulation

Review question	In people with suspected sepsis what is the extent to which disseminated intravascular coagulation (DIC) affects clinical outcomes?
Objectives	To determine the accuracy of disseminated intravascular coagulation in predicting worsening sepsis
Population	People with suspected sepsis, severe sepsis or septic shock
Index test	Disseminated intravascular coagulation (DIC)
Reference standards	These were intended to be reference standard measures that a worsening of sepsis had taken place: • all-cause mortality at 28 days (or nearest time point) • ICU admission • hospitalisation • length of hospital stay
Statistical measures	Odds ratio
Key confounders	No pre-specified confounders
Study design	Observational studies

Review question	In people with suspected sepsis what is the extent to which disseminated intravascular coagulation (DIC) affects clinical outcomes?
Exclusions	Studies conducted in developing countries Study published before 1999
Search strategy	Databases: Medline, Embase, the Cochrane library, Language: restrict to English language only 3 populations: • sepsis • HTA • meningococcal disease Search • disseminated intravascular coagulation AND 3 populations
Review strategy	Stratification – groups that cannot be combined: • adults • children • neonates (not pre-term, not NICU, not SCBU) • immunocompromised adults including those on immunosuppressive drugs (including corticosteroids) • immunocompromised children including those on immunosuppressive drugs (including corticosteroids) • pregnant and recently pregnant women Subgroups where prognosis may be more or less accurate – to investigate heterogeneity: • different ethnic groups Appraisal of methodological quality: • The methodological quality of each study will be assessed using the QUADAS-2 checklist (per target condition). Synthesis of data: • Meta-analysis will be conducted where appropriate using hierarchical methods.

C.7 Empiric antimicrobials

Table 7: Review protocol: empiric antimicrobial treatment

Component	Description
Review question	What are the most clinically and cost effective timings of IV or IM (parenteral) empiric antimicrobial treatments in patients with a) septic shock b) severe sepsis without shock c) sepsis?
Objectives	The aim of this review is to identify the most appropriate timing for antimicrobial treatment; it is known that the earliest the treatment is initiated, the better. The aim is also to establish whether treatment can be initiated in primary care or in ambulance service.
Population	People with or at risk of developing sepsis or severe sepsis
Subgroups	The following groups will be considered separately if data are available: • children • adults • pregnant women • people at higher risk of infection

	• different settings
Intervention	Empiric antimicrobial treatment
Comparison	Early versus late initiation of treatment
Outcomes	Critical: • all-cause mortality at 28 days (or nearest time point) • health-related quality of life (for example, as assessed by SF-12 or EQ-5D). • . Important: • duration of hospital stay. • duration of critical care stay. • number of organs supported (change is SOFA score). • adverse events (inability to tolerate drugs).
Study design	Systematic reviews, RCTs and cohort studies
Setting	All settings in which NHS care is provided
Search Strategy	
Review Strategy	Data analysis • meta-analysis will be conducted wherever possible (i.e., where similar studies can be combined) • if heterogeneity is found, the influence of subgroups will be examined by: ○ Severity infection (sepsis/severe sepsis/septic shock) ○ Different countries which might have a different resistance profile (for example, in Africa antibiotic resistance is low, so efficacy of treatment might be higher, while in India the antibiotic resistance is high, so efficacy treatment might be lower). ○ Year in which the study was conducted (the resistance profile of the antibiotics might change over time, influencing efficacy of treatment) ○ Different settings (primary care, ED, hospital ward, ICU) • if heterogeneity cannot be explained, a random effects analysis will be performed in place of fixed • mortalities at different time points (in-hospital, 28-days and 30-days mortality) will be meta-analysed as "Mortality" • studies that did not report multivariable analysis (adjusted OR for mortality) will be excluded from the analysis.
Key papers	None

C.8 IV fluid administration

Table 8: Review protocol: IV fluid administration

Component	Description
Objectives	To identify which patients with sepsis need IV fluid resuscitation: i.e. to identify which patients with a) septic shock, b) severe sepsis without shock, or c) sepsis would benefit from immediate/bolus IV fluid resuscitation To identify which fluid is prescribed, to who and when, in early sepsis, suspected sepsis, sepsis or severe sepsis
Review question	What is the most clinical and cost effective a) immediate/bolus IV fluid, b) volume/dosage of immediate/bolus IV fluid resuscitation, and c) rate of administration of immediate/bolus IV fluids in patients with sepsis?

Component	Description
Review population	People at risk of developing or diagnosed with severe sepsis Strata (by severity disease): • sepsis • severe sepsis • septic shock
Subgroups	The following groups will be considered separately if data are available: • children • adults • pregnant women • people at higher risk of infection
Intervention/ comparison	Studies in the following fluids will be considered: • crystalloid • colloid • albumin • blood or blood product (haemoglobin, packed cells, fresh/frozen plasma, platelets) Comparisons: • immediate initiation vs. none/later • high volume vs. low volume • fast vs. slow rate of administration
Outcomes	• all-cause mortality at 28 days (or nearest time point) • health-related quality of life (critical) • admission to critical care as a proxy for progression to severe sepsis (critical) • duration of hospital stay (important) • duration of critical care stay (important) • number of organs supported (important) • time to reversal of shock (important) • adverse events (long term disability; short-term heart failure) (important)
Study design	Systematic reviews RCTs Cohort studies
Setting	All settings in which NHS care is provided
Review Strategy	Data analysis: Meta-analysis will be conducted wherever possible (i.e., where similar studies can be combined). If heterogeneity is found, it will be explored by performing a sensitivity analysis and eliminating papers that have high risk of bias. If heterogeneity is still present, the influence of subgroups will be examined by: • pregnant women • people at higher risk of infection. If heterogeneity cannot be explained, a random effects analysis will be performed in place of fixed.
Key papers	None
Search criteria	Databases: Medline, Embase Date limits for search: none Language: English only

C.9 Escalation of care

Table 9: Review protocol: Escalation of care

Component	Review protocol: When is the most appropriate time for care of people with sepsis to be directed to a) a senior healthcare professional, and b) critical care providers?
Objectives	To determine when to escalate care to senior healthcare professionals and/or critical care providers
Review question	When is the most appropriate time for care of people with sepsis to be directed to a) senior healthcare professionals, and b) critical care providers?
Population	People at risk of developing severe sepsis
Subgroups	The following groups will be considered separately if data are available: • children • adults • pregnant women • people at higher risk of infection
Intervention/ comparison	Early vs. late escalation
Outcomes	• all-cause mortality at 28 days (or nearest time point) (critical) • • health-related quality of life (critical) • admission to critical care (critical) • duration of hospital stay (important) • duration of critical care stay (important) • number of organs supported (important) • adverse events (important)
Study design	Systematic reviews RCTs Cohort studies
Setting	All settings in which NHS care is provided
Search Strategy	Date limit: 1999 Country: data from UK only (but indirect data to be assessed)
Review Strategy	Data analysis Meta-analysis will be conducted wherever possible (i.e., where similar studies can be combined). If heterogeneity is found, it will be explored by performing a sensitivity analysis and eliminating papers that have high risk of bias. If heterogeneity is still present, the influence of subgroups will be examined by: • Pregnant women • People at higher risk of infection • If heterogeneity cannot be explained, a random effects analysis will be performed in place of fixed
Key papers	Ninis N, Phillips C, Bailey L et al. The role of healthcare delivery in the outcome of meningococcal disease in children: case-control study of fatal and non-fatal cases. British Medical Journal 2005; 330:(7506)1475.

C.10 Supplemental oxygen

Table 10: Review protocol: supplemental oxygen

Component	Description
Review question	Is the use of supplemental oxygen clinically and cost effective in patients with sepsis?
Objectives	The aim of this review is to determine the impact of treatment with oxygen in people with suspected sepsis.
Population	People with or at risk of developing sepsis or severe sepsis: • hypo-oxygenated people • not hypo-oxygenated people
Subgroups	The following groups will be considered separately if data are available: • children • adults • pregnant women • people at higher risk of infection • different settings
Intervention/ comparison	Treatment with oxygen versus no treatment with oxygen
Outcomes	Critical: • all-cause mortality at 28 days (or nearest time point)health-related quality of life (for example, as assessed by SF-12 or EQ-5D) • admission to critical care as a proxy for progression to severe sepsis Important: • duration of hospital stay • duration of critical care stay • number of organs supported • time to reversal of shock • adverse events (long term disability; short-term heart failure)
Study design	Systematic reviews and RCTs. If no RCTs are found, multivariable observational studies and comparative observational studies (including retrospective) which investigate the prognostic role of treatment with oxygen on the outcomes will be considered.
Setting	All settings in which NHS care is provided
Search Strategy	
Review Strategy	Data analysis Meta-analysis will be conducted wherever possible (i.e., where similar studies can be combined) If heterogeneity is found, it will be explored by performing a sensitivity analysis and eliminating papers that have high risk of bias. If heterogeneity is still present, the influence of subgroups will be examined by: Pregnant women People at higher risk of infection. If heterogeneity cannot be explained, a random effects analysis will be performed in place of fixed For observational data, a summary of effects reported across studies will be included. If confounded factors differ between studies, then an individual relative effect (RR or OR) will be presented.
Key papers	

C.11 Use of bicarbonate

Table 11: Review protocol: acid-base balance (use of bicarbonate)

Component	Description
Review question	Is acid-base balance (that is, the use of bicarbonate) clinically and cost effective in people with sepsis?
Objectives	The aim of this review is to determine the impact of acid-base balance correction in people with suspected sepsis.
Population	People with or at risk of developing sepsis or severe sepsis
Subgroups	The following groups will be considered separately if data are available: • children • adults • pregnant women • people at higher risk of infection • different settings
Intervention/ comparison	Bicarbonate versus no bicarbonate
Outcomes	Critical: • all-cause mortality at 28 days (or nearest time point) • health-related quality of life (for example, as assessed by SF-12 or EQ-5D). • admission to critical care as a proxy for progression to severe sepsis. Important: • duration of hospital stay • duration of critical care stay • number of organs supported • time to reversal of shock • adverse events (long term disability; short-term heart failure)
Study design	Systematic reviews and RCTs. If no RCTs are found, multivariable observational studies and comparative observational studies (including retrospective) which investigate the prognostic role of timing of acid-base balance correction on the outcomes will be considered.
Setting	All settings in which NHS care is provided
Search Strategy	
Review Strategy	Data analysis Meta-analysis will be conducted wherever possible (i.e., where similar studies can be combined) If heterogeneity is found, it will be explored by performing a sensitivity analysis and eliminating papers that have high risk of bias. If heterogeneity is still present, the influence of subgroups will be examined by: • pregnant women • people at higher risk of infection If heterogeneity cannot be explained, a random effects analysis will be performed in place of fixed For observational data, a summary of effects reported across studies will be included. If confounded factors differ between studies, then an individual relative effect (RR or OR) will be presented.
Key papers	None

C.12 Early goal-directed therapy

Table 12: Review protocol: Early goal-directed therapy

Component	Description
Review question	Is acid-base balance (that is, the use of bicarbonate) clinically and cost effective in people with sepsis?
Objectives	To determine the clinical and cost effectiveness of implementing early goal-directed therapy (EGDT)
Outcomes	Critical: • all-cause mortality at 28 days (or nearest time point)health-related quality of life (for example, as assessed by SF-12 or EQ-5D) • admission to critical care as a proxy for progression to severe sepsis Important: • duration of hospital stay • duration of critical care stay • number of organs supported (for example, SOFA score) • time to reversal of shock • adverse events (long term disability; short-term heart failure)
Study design	Systematic reviews RCTs
Setting	All settings in which NHS care is provided
Search Strategy	Search estimate:
Review Strategy	Data analysis Meta-analysis will be conducted wherever possible (i.e., where similar studies can be combined) If heterogeneity is found, it will be explored by performing a sensitivity analysis and eliminating papers that have high risk of bias. If heterogeneity is still present, the influence of subgroups will be examined by: • pregnant women • people at higher risk of infection. If heterogeneity cannot be explained, a random effects analysis will be performed in place of fixed
Key papers	Angus 2015
Notes	No search was carried out

C.13 Monitoring

Table 13: Review protocol: monitoring – scoring systems

Component	Description
Objectives	The aim of this review is to determine, in patients with sepsis or severe sepsis: the predictive accuracy of clinical observations (heart rate, respiratory rate, blood pressure) and blood markers (lactate, blood gases) how often do tests need to be repeated and when should testing stop?
Review question	In people with sepsis or severe sepsis, what is the clinical and cost effectiveness of scoring systems, and specified blood markers (trends in lactate) in monitoring response

Component	Description
	to treatment?
Population	People with suspected sepsis or severe sepsis.
Subgroups	The following groups will be considered separately if data are available: • children • adults • pregnant women • people at higher risk of infection
Prognostic factors/tests	1) Use of scoring systems (PEWS, MEWS, NEWS, early warning scores) 2) Lactate
Outcomes	1) Use of scoring systems (PEWS, MEWS, NEWS, early warning scores) Critical outcomes: • mortality • clinical resolution (up to and including end of treatment) • health-related quality-of-life (up to 30 days) • critical care admission Important outcomes: • treatment failure • appropriate or inappropriate use of antibiotics • duration of treatment • hospital re-admission (30 days) • length of hospital stay • complications (including relapse; 30 days) 2) lactate • all-cause mortality at 28 days (or nearest time point) • ICU admission • hospitalisation • length of hospital stay
Study design	Systematic reviews cohort studies
Population size and directness	Minimum number of patients: 2000. Studies with indirect populations will not be considered.
Setting	All healthcare settings in which NHS care is provided
Search Strategy	
Review Strategy	Appraisal of methodological quality The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data Meta-analysis will be conducted where appropriate.

C.14 Inotropic agents and vasopressors

Table 14: Review protocol: Inotropic agents

Component	Description
Objectives	To identify which treatment is prescribed and when in people with early sepsis,

Component	Description
	suspected sepsis, sepsis or severe sepsis.
Review question	a. What is the most clinical and cost effective inotropic agent or vasopressor for early management of people with severe sepsis? b. What are the most clinically and cost effective timings of inotropic agents and vasopressors in patients with severe sepsis?
Review population	People at risk of developing severe sepsis Strata (by severity disease): • sepsis • severe sepsis • septic shock
Subgroups	The following groups will be considered separately if data are available: • children • adults • pregnant women • people at higher risk of infection
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Inotropic agents and vasopressors: • milrinone • enoximone • dobutamine • dopamine • dopexamine • adrenalin/epinephrine • noradrenaline/norepinephrine • vasopressin • metaraminol Comparison: • inotropic agents and vasopressors compared to each other • early versus late initiation
Outcomes	• all-cause mortality at 28 days (or nearest time point) (critical) • health-related quality of life (critical) • admission to critical care as a proxy for progression to severe sepsis (critical) • duration of hospital stay (important) • duration of critical care stay (important) • number of organs supported (important) • adverse events (long term disability; short-term heart failure) (limportant)
Study design	Systematic Review RCT Prospective cohort study (if “not enough” RCT evidence is found) Retrospective cohort study (if “not enough” RCT evidence is found)
Setting	All settings in which NHS care is provided
Review strategy	Data analysis: Meta-analysis will be conducted wherever possible (i.e., where similar studies can be combined). If heterogeneity is found, it will be explored by performing a sensitivity analysis and eliminating papers that have high risk of bias. If heterogeneity is still present, the influence of subgroups will be examined by:

Component	Description
	• pregnant women • people at higher risk of infection. If heterogeneity cannot be explained, a random effects analysis will be performed in place of fixed.
Key papers	None
Search criteria	Databases: Medline, Embase Date limits for search: none Language: English only

C.15 Patient education, information and support

Table 15: Review protocol: Patient education, information and support

Component	Description
Review question	What information, education and support would be useful for: • people assessed for possible sepsis but discharged from medical care • people at high risk of sepsis • people who have sepsis or severe sepsis, families and carers • people who survive episodes of severe sepsis
Objectives	To provide a systematic narrative review of the relevant literature that will aid the GDG towards consensus recommendations.
Population	People assessed for possible sepsis but discharged from medical care People at high risk of sepsis People who have sepsis or severe sepsis, families and carers People who survive episodes of severe sepsis
Interventions	Information, education and support useful for: • people assessed for possible sepsis but discharged from medical care • people at high risk of sepsis • people who have sepsis or severe sepsis, families and carers • people who survive episodes of severe sepsis Delivered by all health care professionals involved in assessment, diagnosis, management and monitoring of sepsis (e.g. doctors, nurses, ambulance staff, paramedics, physiotherapists, pharmacists, 111/999 call.
Outcomes / themes	Patient satisfaction, including understanding Reduction in time to diagnosis Themes or views based on patients'/carers'/families' experiences on what they perceived as important elements of information and support needs
Study design	Cohort (high quality prospective and retrospective cohorts), quasi-experimental, RCT if available. Qualitative research relating to sepsis. Exclusions: Editorials/commentaries/opinion pieces (other than large consensus surveys)
Settings	All settings in which NHS care is provided (note: no geographical restrictions on the studies considered)
Search strategy	Databases: Medline, Embase, the Cochrane library, CINAHL, PsycInfo, Date: post 1990 data Language: restrict to English language only

Component	Description
Review strategy	Studies will be evaluated to assess their relevance to the question asked. The review will start with focusing on studies which are conducted in a setting directly relevant to the NHS setting and the scope of the guideline. Analysis of studies that are most relevant to the review question in terms of population, setting (situation), context and objectives will be carried out. Thematic analysis will be conducted, and common themes across studies will be extracted and reported. The review will be considered as complete when no new themes are found within the area (theme saturation reached). For observational/surveys/audits, the key findings will be summarised and presented. Search for literature to include septicaemia/septicaemia/septic. Critical care follow-up literature where specified that a high proportion of patients have had sepsis.

C.16 Training and education

Table 16: Review protocol: training and education

Component	Description
Review question	What education and training programmes improve early recognition, diagnosis and management of sepsis and severe sepsis?
Objectives	• main objective: To examine qualitative and qualitative evidence of education for sepsis recognition and management to aid the GDG towards consensus recommendations
Population	All healthcare professionals involved in the diagnosis, management and monitoring of sepsis (for example, doctors, nurses, ambulance staff, paramedics, physiotherapists, pharmacists and 111/999 call handlers [note: include non-UK specific terms])
Interventions	• education programmes to raise awareness of sepsis (sepsis identification and the management of the condition)
Outcomes for quantitative studies	• identifying patients who needs intervention • process outcomes such as timely initiation of management • patient outcomes – morbidity and mortality
Study design	(1) Quantitative studies: RCT,cohort, quasi-experimental, (2) Qualitative research relating to understanding learning needs, barriers to recognition of sepsis and experience of education programmes for sepsis (3)Thematic synthesis of findings from (1) and (2) above
Settings	All settings in which NHS care is provided (note: no geographical restrictions on the studies considered)
Search strategy	Databases: Medline, Embase, the Cochrane library, CINAHL, PsycInfo, ERIC Date: post 1990 data Language: restrict to English language only
Review strategy	(1)Qualitative data analysis • meta-analysis will be conducted wherever possible (i.e., where similar studies can be combined). If heterogeneity is found, it will be explored by performing a sensitivity analysis and eliminating papers that have high risk of bias. • for observational data, a summary of effects reported across studies will be included. If confounded factors differ between studies, then an individual relative effect (RR or OR) will be presented. (2) Qualitative analysis

Component	Description
	• thematic analysis will be conducted, and common themes across studies will be extracted and reported. The review will be considered as complete when no new themes are found within the area (theme saturation reached). (3) Thematic synthesis from (1 and (2) Search for literature to include septicaemia/septicaemia/septic. Search for literature to include septicaemia/septic.
Key papers:	1. Intensive Care Med. 2014 Feb;40(2):182-91. doi: 10.1007/s00134-013-3131-5. Epub 2013 Oct 22. Implementation of a multifaceted sepsis education program in an emerging country setting: clinical outcomes and cost-effectiveness in a long-term follow-up study. Noritomi DT(1), Ranzani OT, Monteiro MB, Ferreira EM, Santos SR, Leibel F, Machado FR. 2. J Healthc Qual. 2013 Mar 27. doi: 10.1111/jhq.12006. [Epub ahead of print] An Interprofessional Process to Improve Early Identification and Treatment for Sepsis. Palleschi MT, Sirianni S, O'Connor N, Dunn D, Hasenau SM. 3. Int J Clin Pract. 2012 Jul;66(7):705-10. doi: 10.1111/j.1742-1241.2012.02939.x. Implementation of sepsis management guideline in a community-based teaching hospital - can education be potentially beneficial for septic patients? Nguyen HM(1), Schiavoni A, Scott KD, Tanios MA. 4. Shock. 2012 May;37(5):463-7. doi: 10.1097/SHK.0b013e31824c31d1. Improvements in compliance with resuscitation bundles and achievement of end points after an educational program on the management of severe sepsis and septic shock. Jeon K(1), Shin TG, Sim MS, Suh GY, Lim SY, Song HG, Jo IJ. 5. Semin Respir Crit Care Med. 2010 Feb;31(1):19-30. doi: 10.1055/s-0029-1246286. Epub 2010 Jan 25. Using protocols to improve patient outcomes in the intensive care unit: focus on mechanical ventilation and sepsis. Kollef MH(1), Micek ST. 6. Crit Care Nurs Q. 2008 Jul-Sep;31(3):251-69. doi: 10.1097/01.CNQ.0000325050.91473.0b. The effect of nurse champions on compliance with Keystone Intensive Care Unit Sepsis-screening protocol. Campbell J. 7. Crit Care Med. 2007 May;35(5):1257-62. Economic implications of an evidence-based sepsis protocol: can we improve outcomes and lower costs? Shorr AF(1), Micek ST, Jackson WL Jr, Kollef MH. 8. Crit Care Nurs Clin North Am. 2006 Dec;18(4):469-79, ix. Developing and implementing quality initiatives in the ICU: strategies and outcomes.

Component	Description
	9. Am J Infect Control. 2005 Mar;33(2):83-7. Impact of an educational program and policy changes on decreasing catheter-associated bloodstream infections in a medical intensive care unit in Brazil. Lobo RD(1), Levin AS, Gomes LM, Cursino R, Park M, Figueiredo VB, Taniguchi L, Polido CG, Costa SF. 10. Ann Intern Med. 2000 Apr 18;132(8):641-8. Education of physicians-in-training can decrease the risk for vascular catheter infection. Sherertz RJ(1), Ely EW, Westbrook DM, Gledhill KS, Streed SA, Kiger B, Flynn L, Hayes S, Strong S, Cruz J, Bowton DL, Hulgan T, Haponik EF. 11. This is a useful summary of the Headsmart work- their intervention of a symptom card has reduced diagnosis times- sure they would be happy to provide further info http://www.health.org.uk/public/cms/75/76/6270/3930/CtGtCC%20HeadSmart%20final%20report.pdf?realName=UT94qs.pdf 12. Mackintosh, BMJ Qual Saf. 2012 Feb;21(2):135-44. 13. Shearer. What stops hospital clinical staff from following protocols? An analysis of the incidence and factors behind the failure of bedside clinical staff to activate the rapid response system in a multi-campus Australian metropolitan healthcare service. BMJ Qual Saf. 2012 Jul;21(7):569-75. doi: 10.1136/bmjqs-2011-000692. Epub 2012 May 23. 14. Winters. Rapid response systems: should we still question their implementation? J Hosp Med. 2013 May;8(5):278-81. doi: 10.1002/jhm.2050 15. Liaw SY1, Scherpbier A, Klainin-Yobas P, Rethans JJ. A review of educational strategies to improve nurses' roles in recognizing and responding to deteriorating patients. Int Nurs Rev. 2011 Sep;58(3):296-303. doi: 10.1111/j.1466-7657.2011.00915.x. Epub 2011 Jul 6. 16. DeVita MA, Bellomo, R. (2007) The case of rapid response systems: Are randomized clinical trials the right methodology to evaluate systems of care? Crit Care Med, 35, 1413-14. 17. McGaughey J, et al. (2010) Realistic Evaluation of Early Warning Systems and the Acute Life-threatening Events--Recognition and Treatment training course for early recognition and management of deteriorating ward-based patients: research protocol. J Adv Nurs, 66, 923-32. 18. Gerdtz MF. Evaluation of a multifaceted intervention on documentation of vital signs at triage: a before-and-after study. Emerg Med Australas. 2013 Dec;25(6):580-7. doi: 10.1111/1742-6723.12153. Epub 2013 Nov 8. 19. Benning A, et al. (2011a) Large scale organisational intervention to improve patient safety in four UK hospitals: mixed method evaluation. BMJ, 342, d195. 20. Leach LS, et al. (2010) How RNs rescue patients: a qualitative study of RNs'

Component	Description
	perceived involvement in rapid response teams. Qual Saf Health Care, 19, doi: 10.1136/qshc.2008.030494.

Appendix D: Health economic review protocol

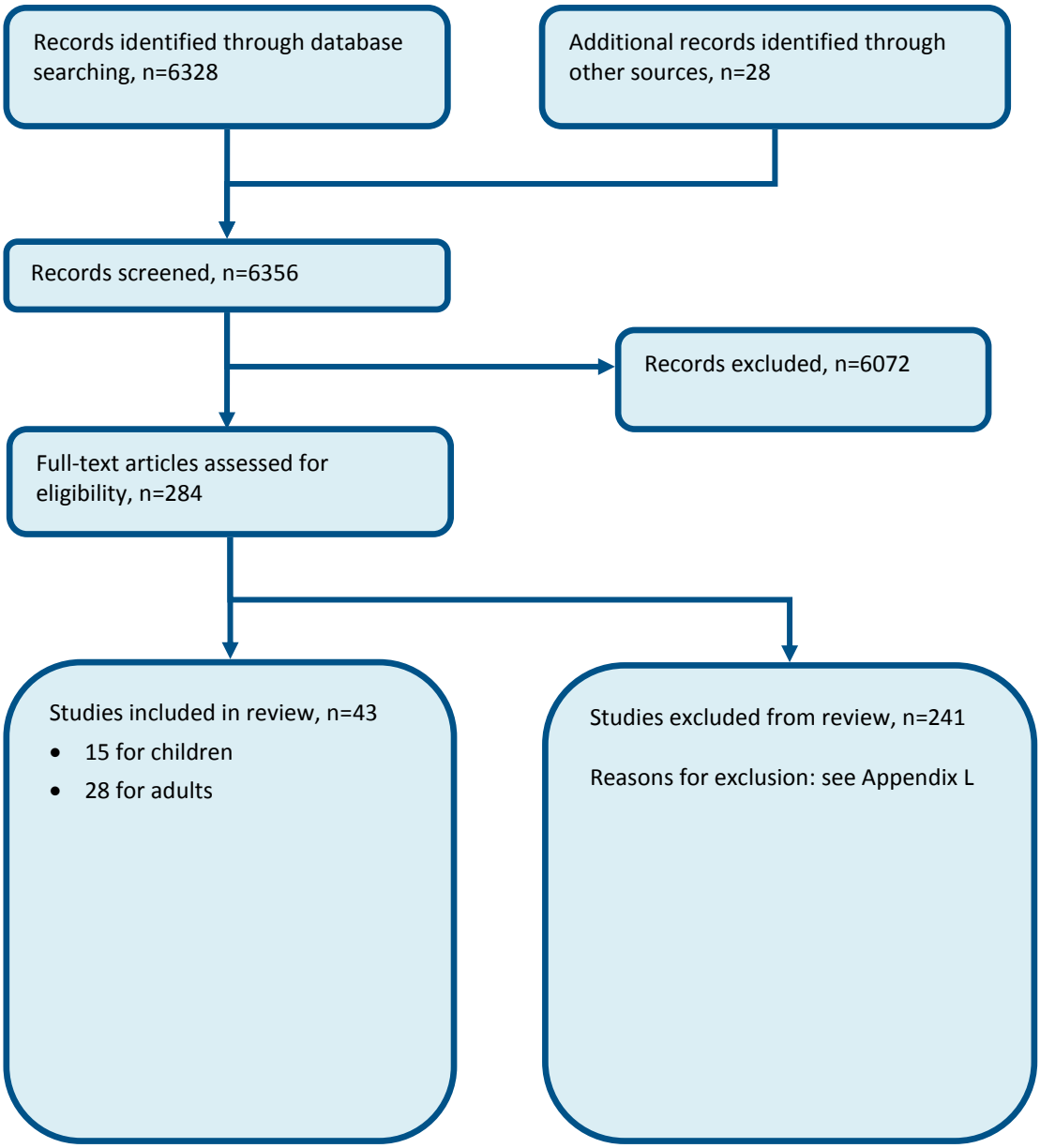
Review question	All questions – health economic evidence
Objectives	To identify economic evaluations relevant to any of the review questions.
Search criteria	(4) Populations, interventions and comparators must be as specified in the individual review protocol above. (5) Studies must be of a relevant economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). (6) Studies must not be a letter, editorial or commentary, or a review of economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) (7) Unpublished reports will not be considered unless submitted as part of a call for evidence. (8) Studies must be in English.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix G [in the Full guideline].
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 1999, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the NICE guidelines manual (2012).[1] **Inclusion and exclusion criteria** (9) If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. (10) If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile. (11) If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the GDG if required. The ultimate aim is to include studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the GDG if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix M. The health economist will be guided by the following hierarchies. *Setting:*

	(12) UK NHS (most applicable). (13) OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). (14) OECD countries with predominantly private health insurance systems (for example, Switzerland). (15) Studies set in non-OECD countries or in the USA will have been excluded before being assessed for applicability and methodological limitations. *Economic study type:* (16) Cost–utility analysis (most applicable). (17) Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). (18) Comparative cost analysis. (19) Non-comparative cost analyses including cost-of-illness studies will have been excluded before being assessed for applicability and methodological limitations. *Year of analysis:* (20) The more recent the study, the more applicable it will be. (21) Studies published in 1999 or later but that depend on unit costs and resource data entirely or predominantly from before 1999 will be rated as 'Not applicable'. (22) Studies published before 1999 will have been excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the economic analysis:* (23) The more closely the effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix E: Clinical article selection

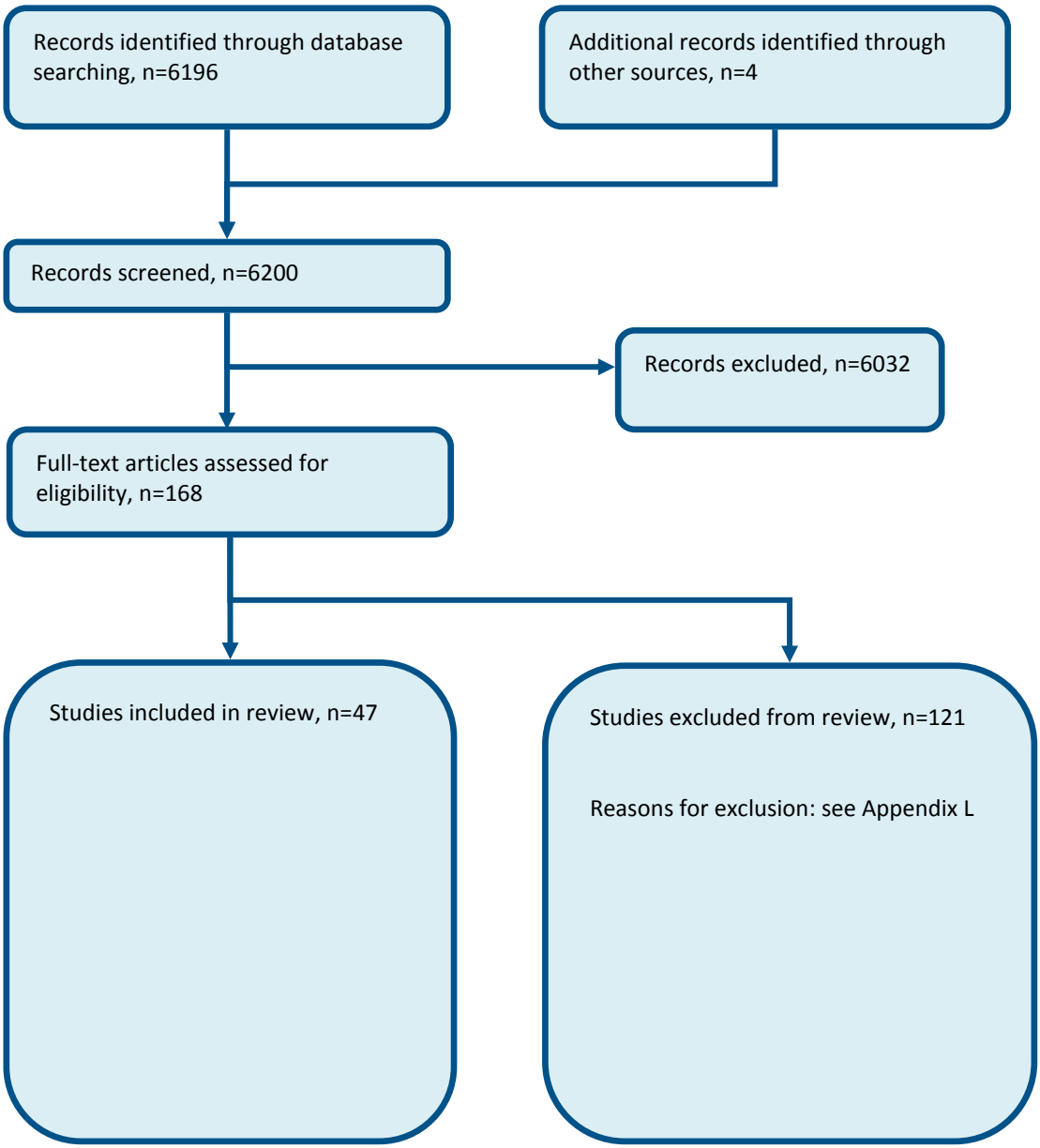
E.1 Signs and symptoms

Figure 1: Flow chart of clinical article selection for the review of signs and symptoms



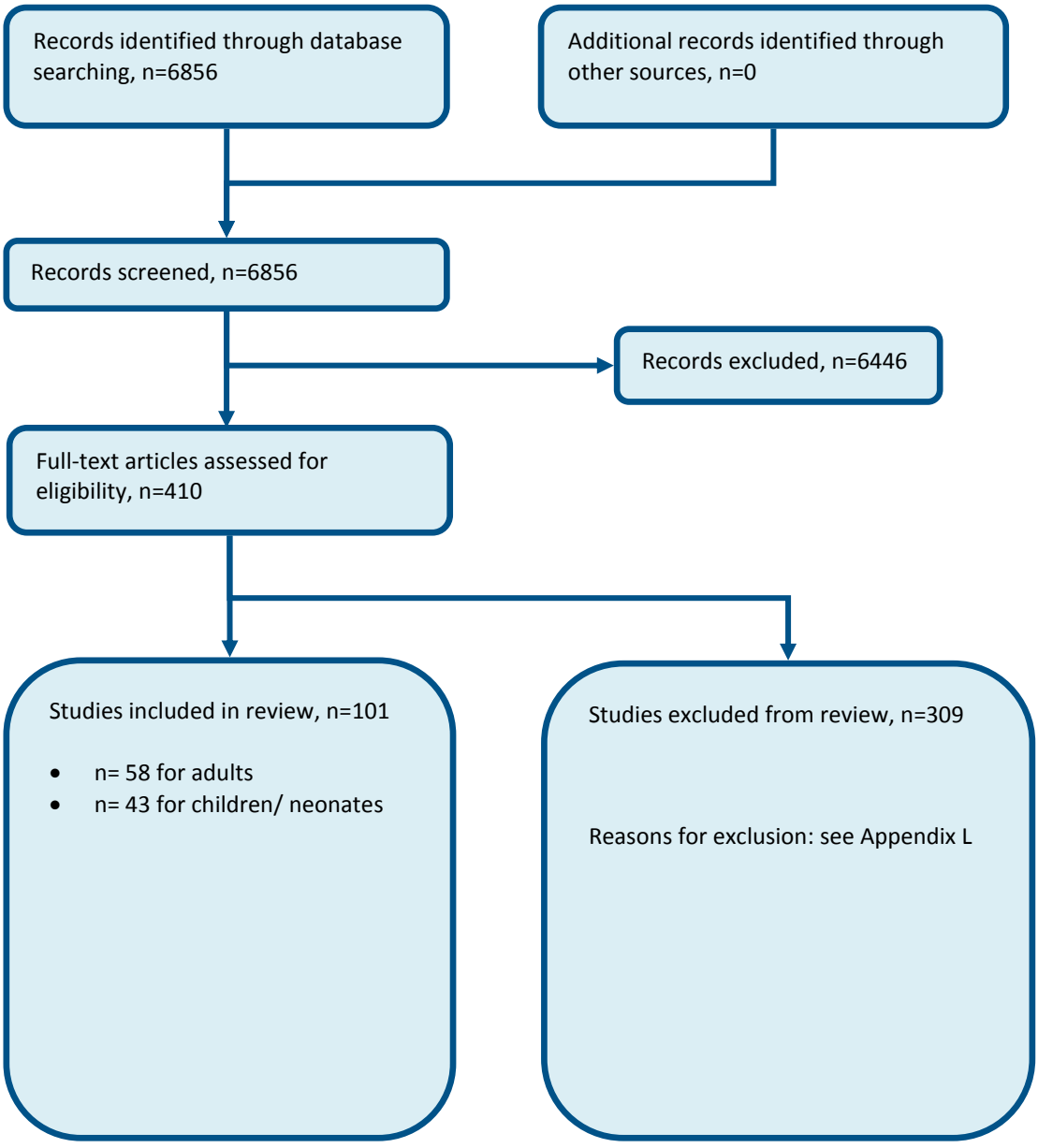
E.2 Scoring systems

Figure 2: Flow chart of clinical article selection for the review of scoring tools



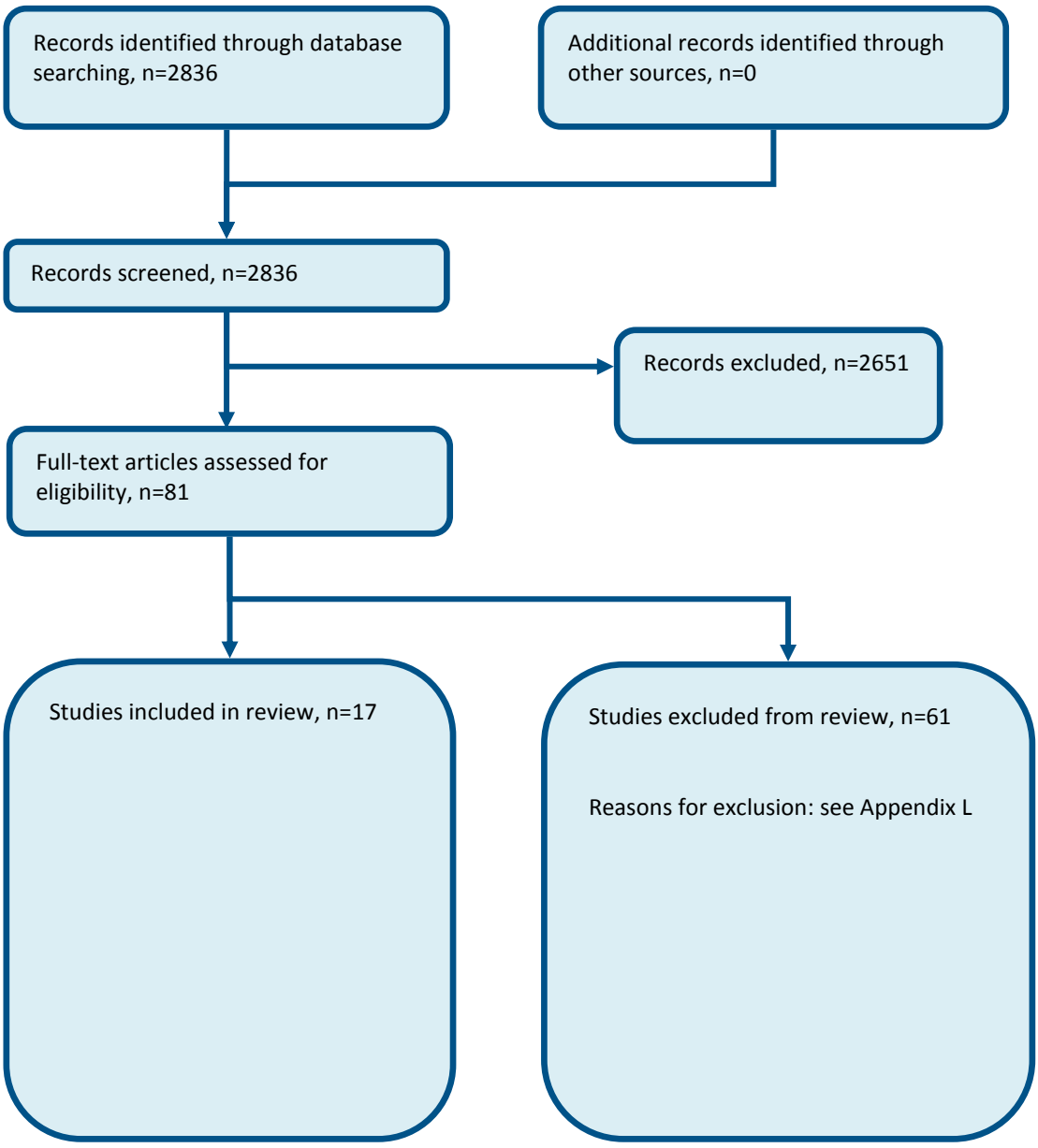
E.3 Blood tests

Figure 3: Flow chart of clinical article selection for the review of blood tests



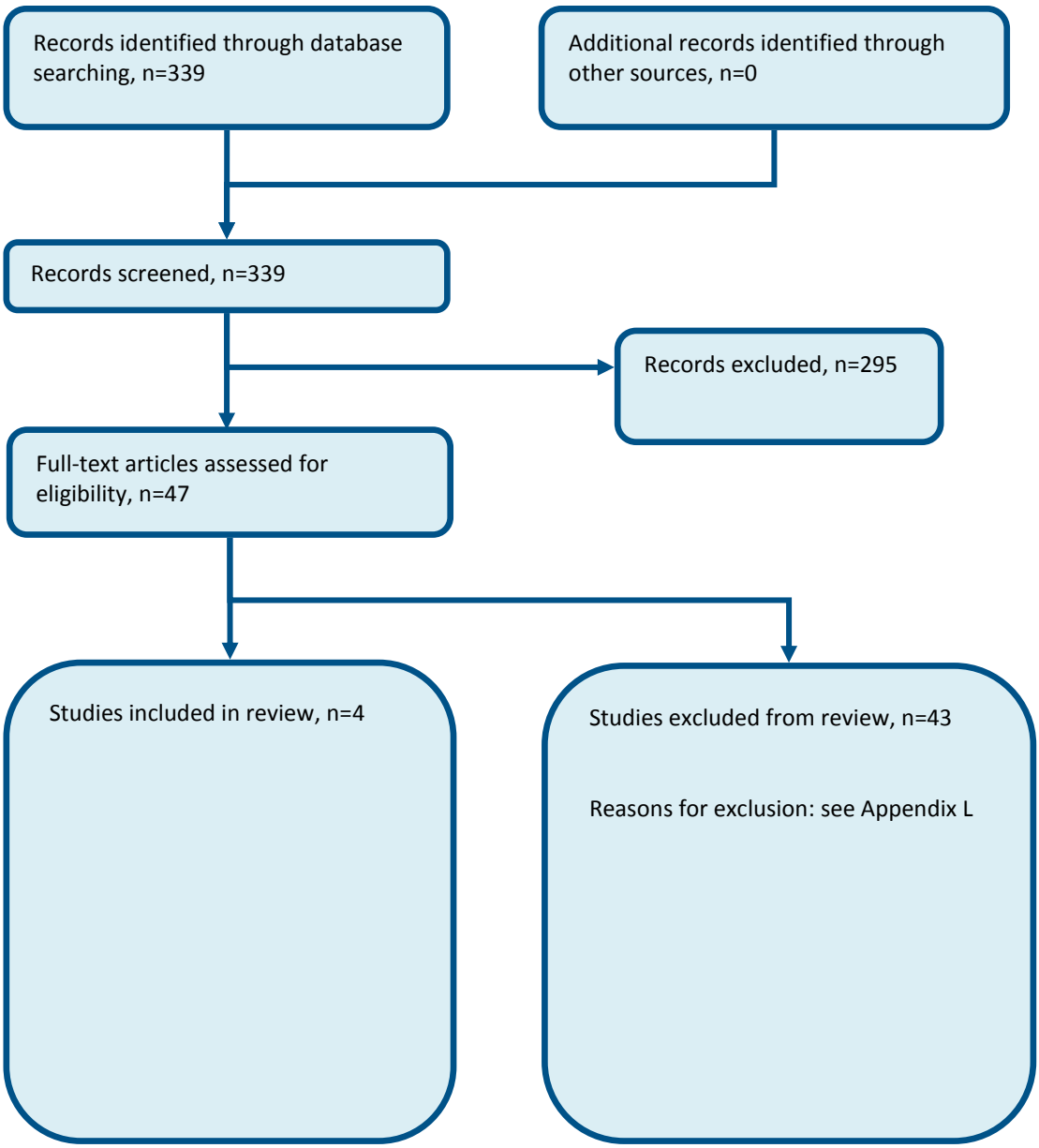
E.4 Lactate

Figure 4: Flow chart of clinical article selection for the review of initial lactate for the recognition and early assessment of worsening sepsis



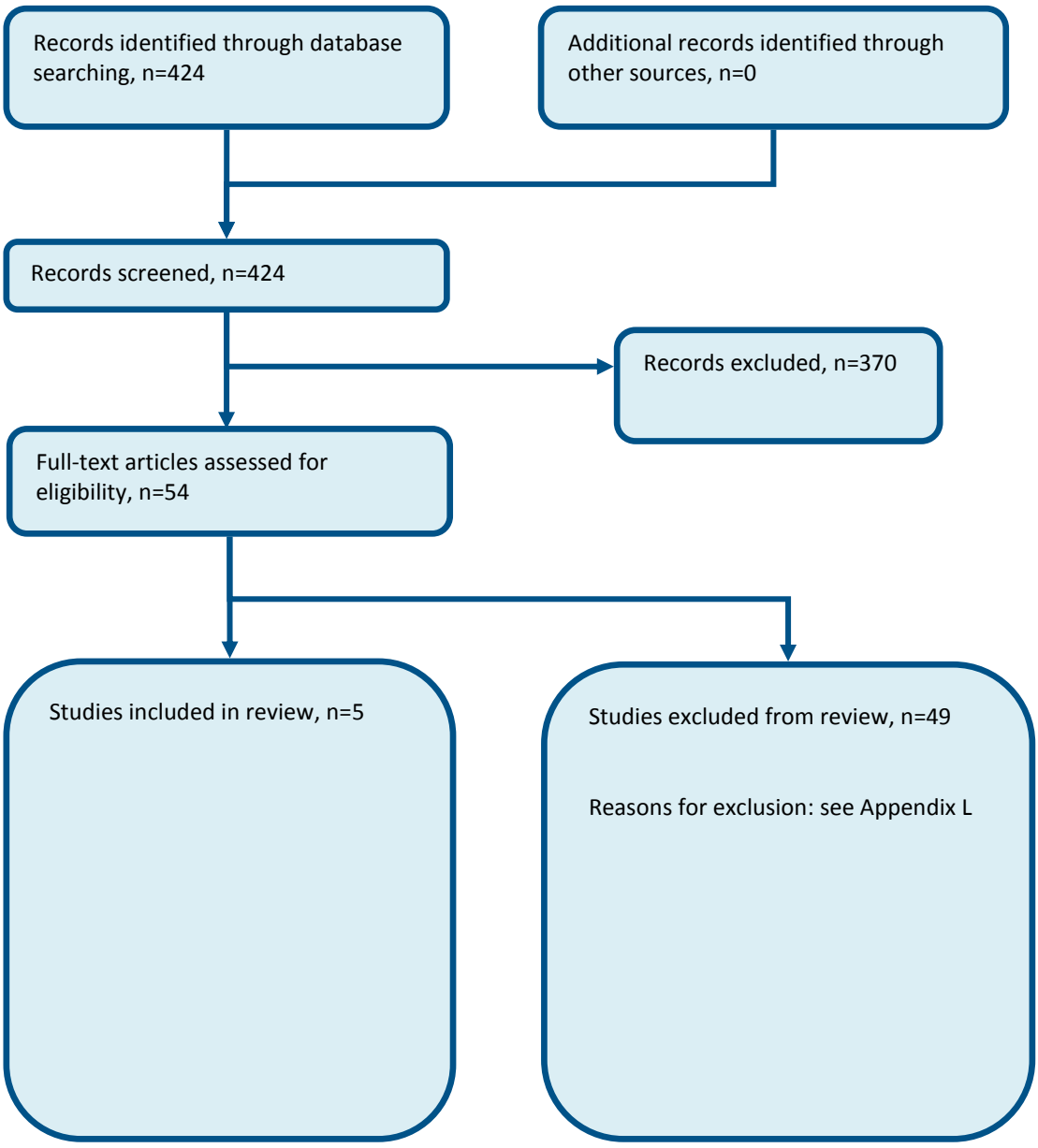
E.5 Serum creatinine

Figure 5: Flow chart of clinical article selection for the review of serum creatinine



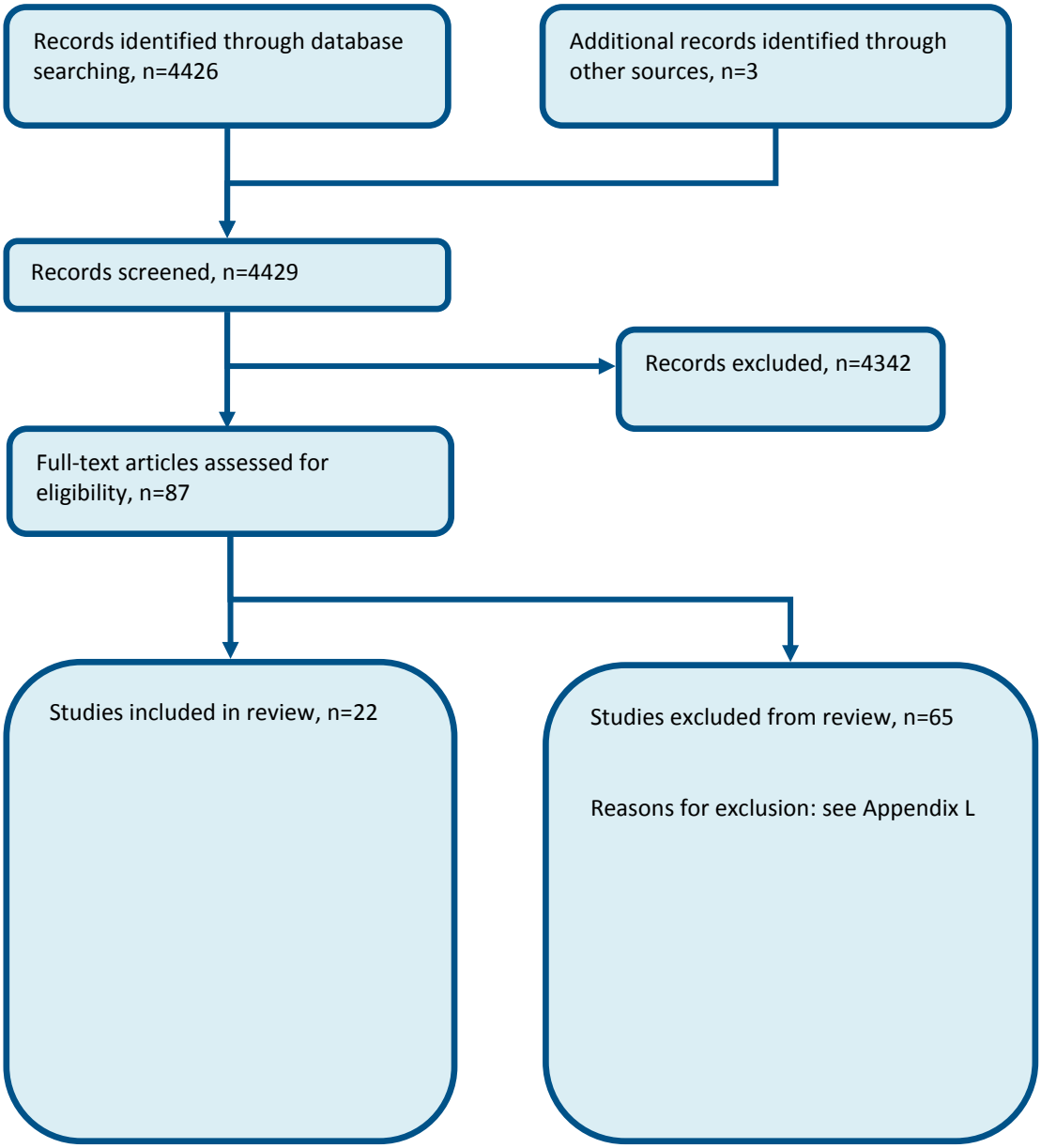
E.6 Disseminated intravascular coagulation

Figure 6: Flow chart of clinical article selection for the review of disseminated intravascular coagulation



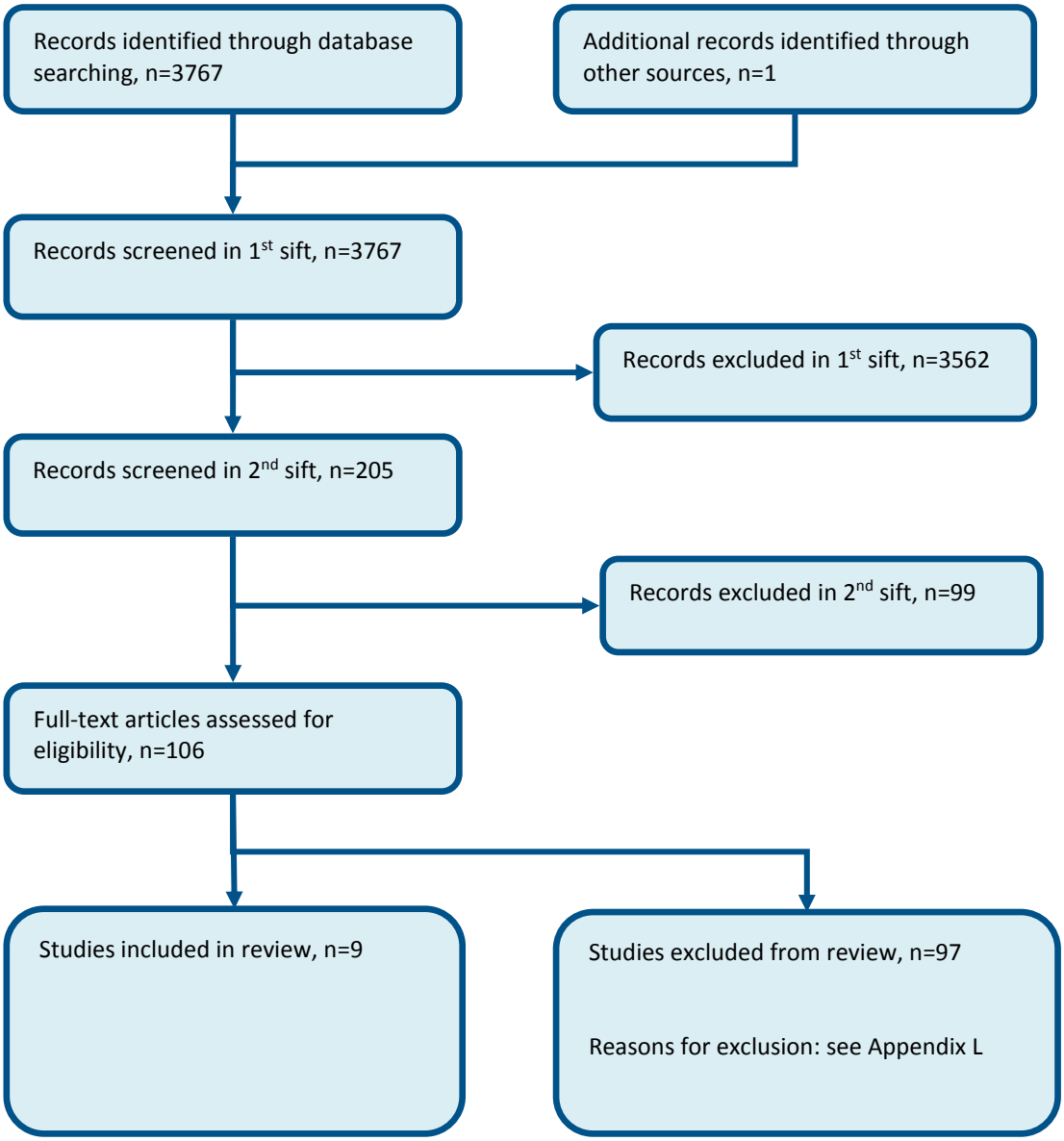
E.7 Empiric antimicrobial treatment

Figure 7: Flow chart of clinical article selection for the review of timing of antimicrobials



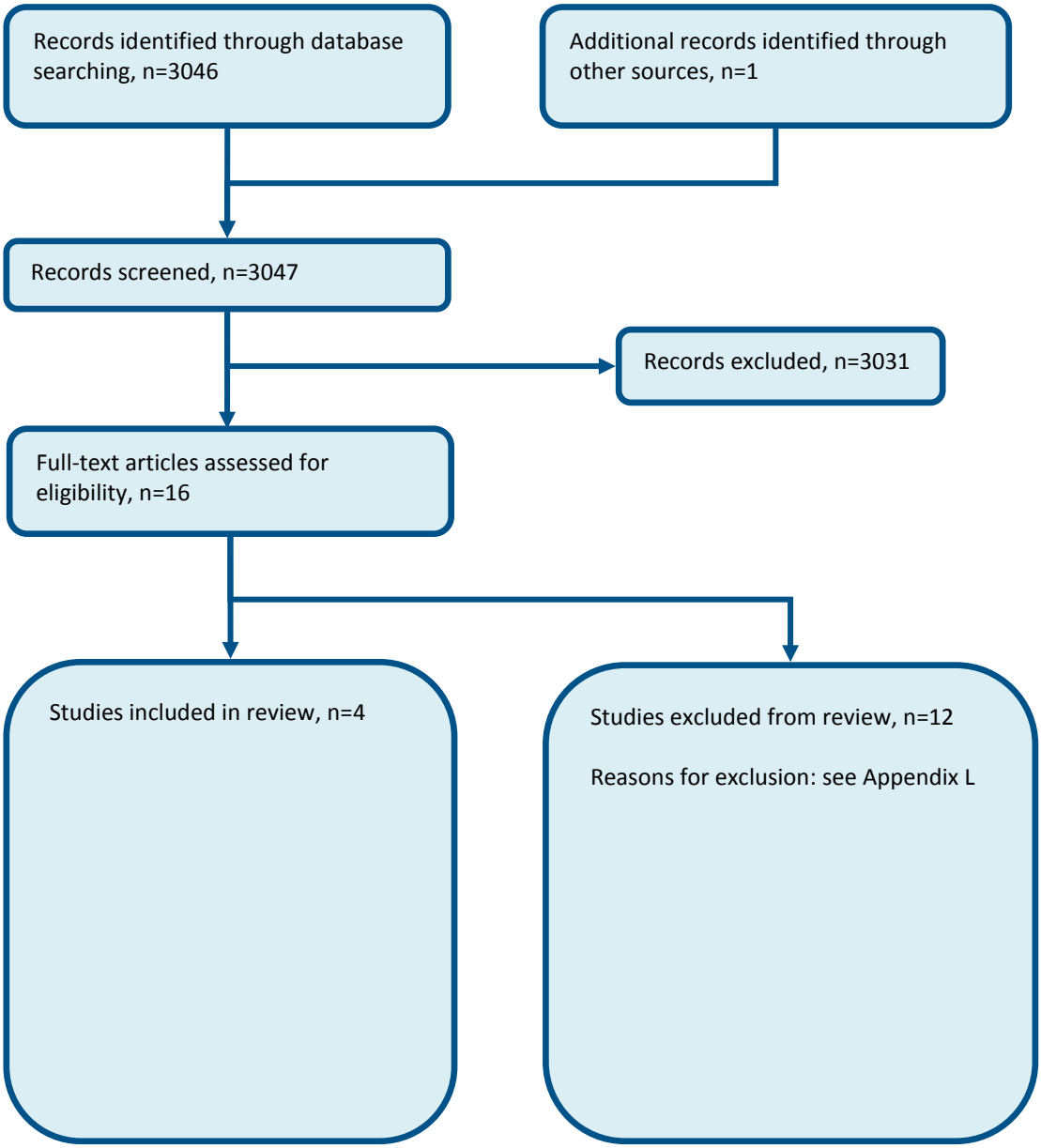
E.8 IV fluid administration

Figure 8: Flow chart of clinical article selection for the review of IV fluid administration



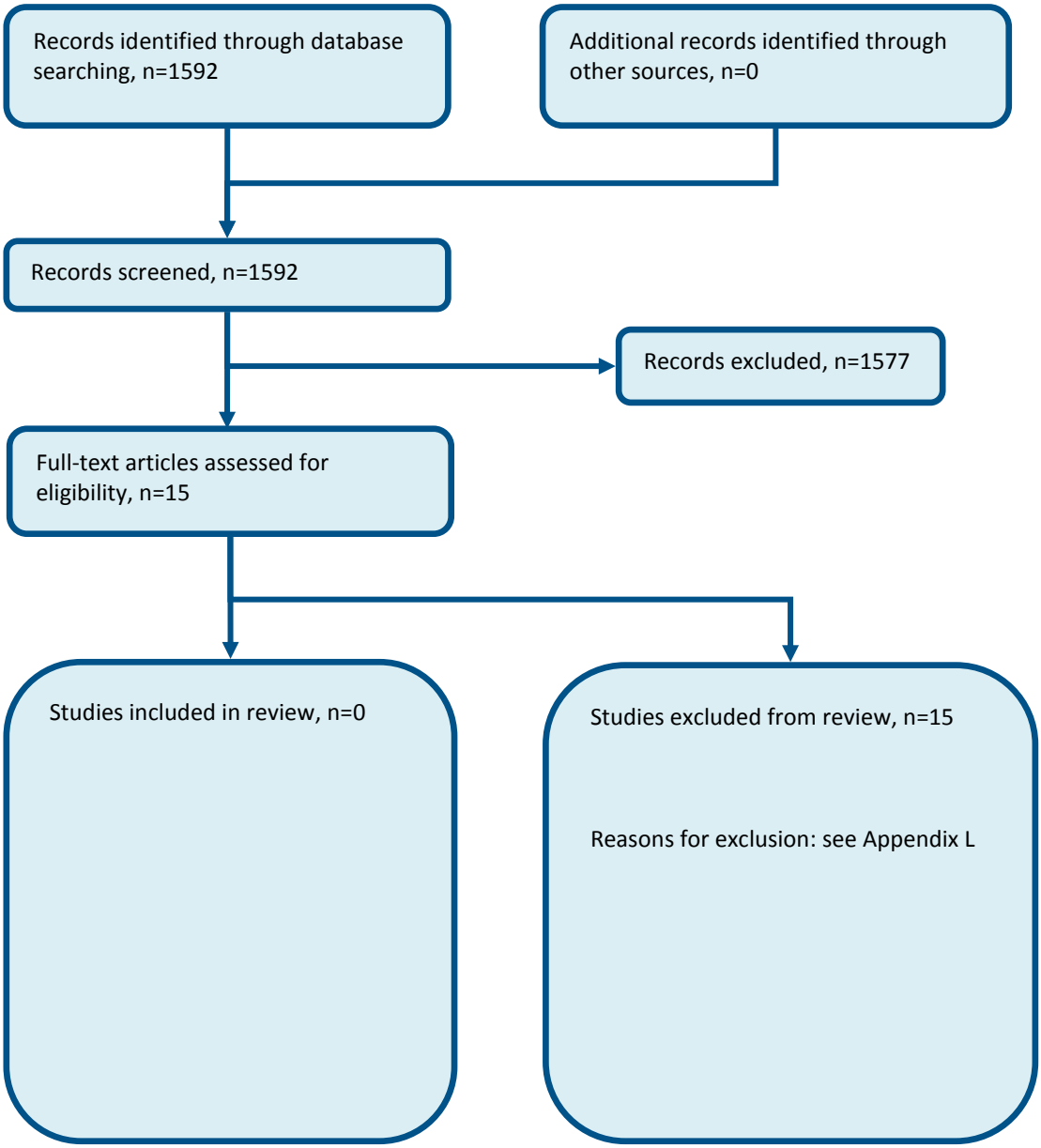
E.9 Escalation of care

Figure 9: Flow chart of clinical article selection for the review of escalation of care



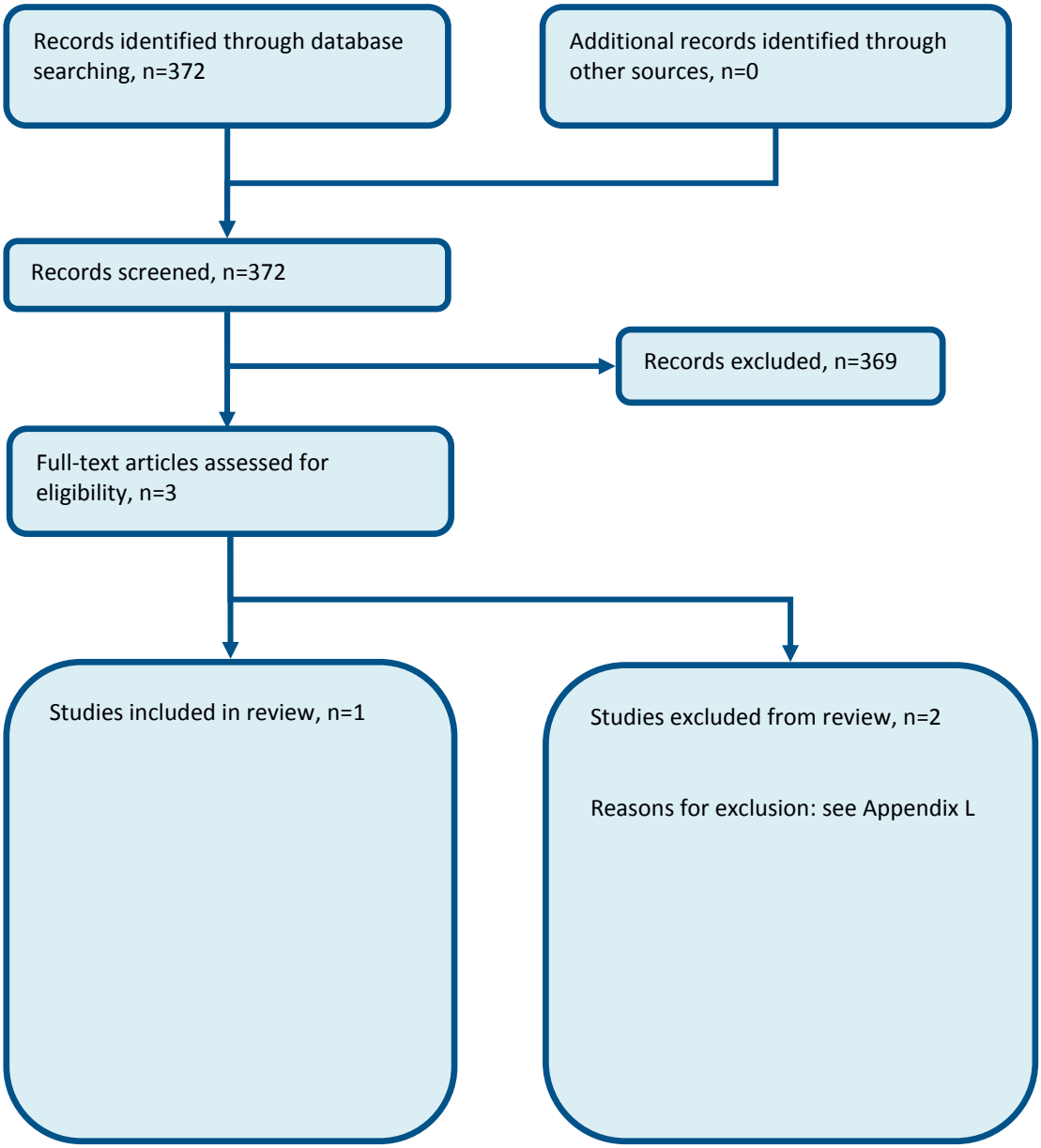
E.10 Supplemental oxygen

Figure 10: Flow chart of clinical article selection for the review of use of supplemental oxygen



E.11 Use of bicarbonate

Figure 11: Flow chart of clinical article selection for the review of bicarbonate

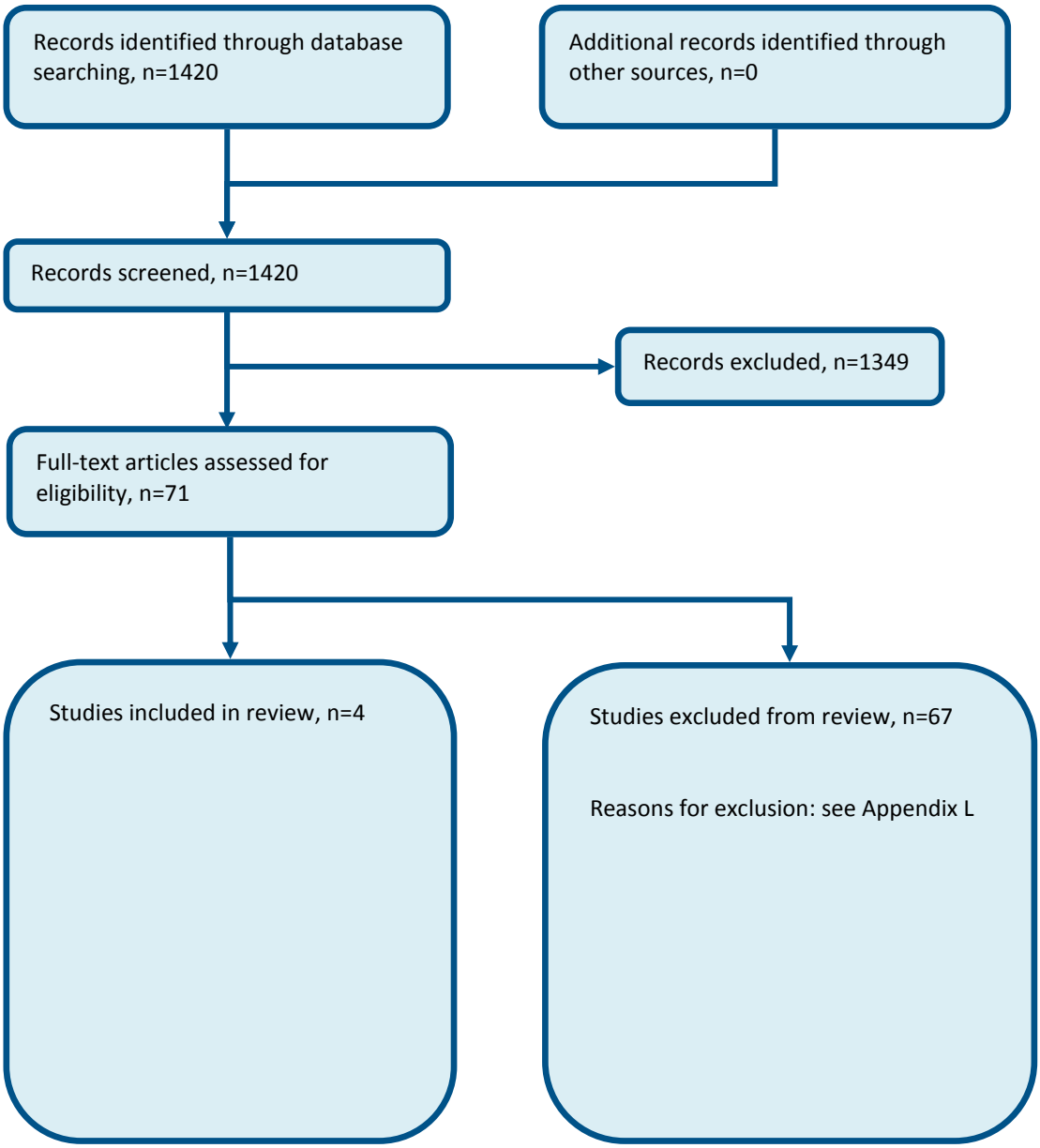


E.12 Early goal-directed therapy

None.

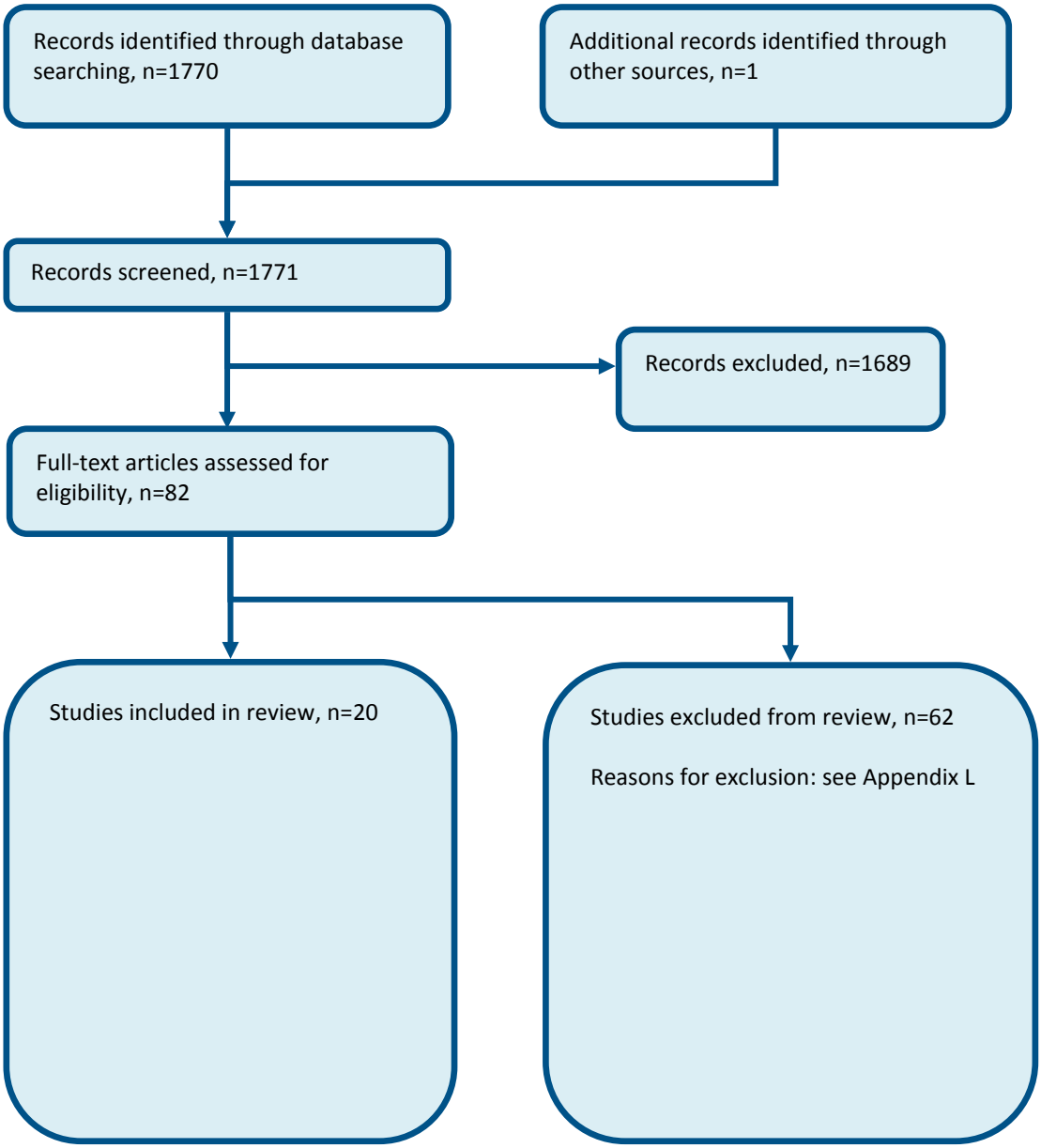
E.13 Monitoring

Figure 12: Flow chart of clinical article selection for the review of monitoring (use of scoring systems)



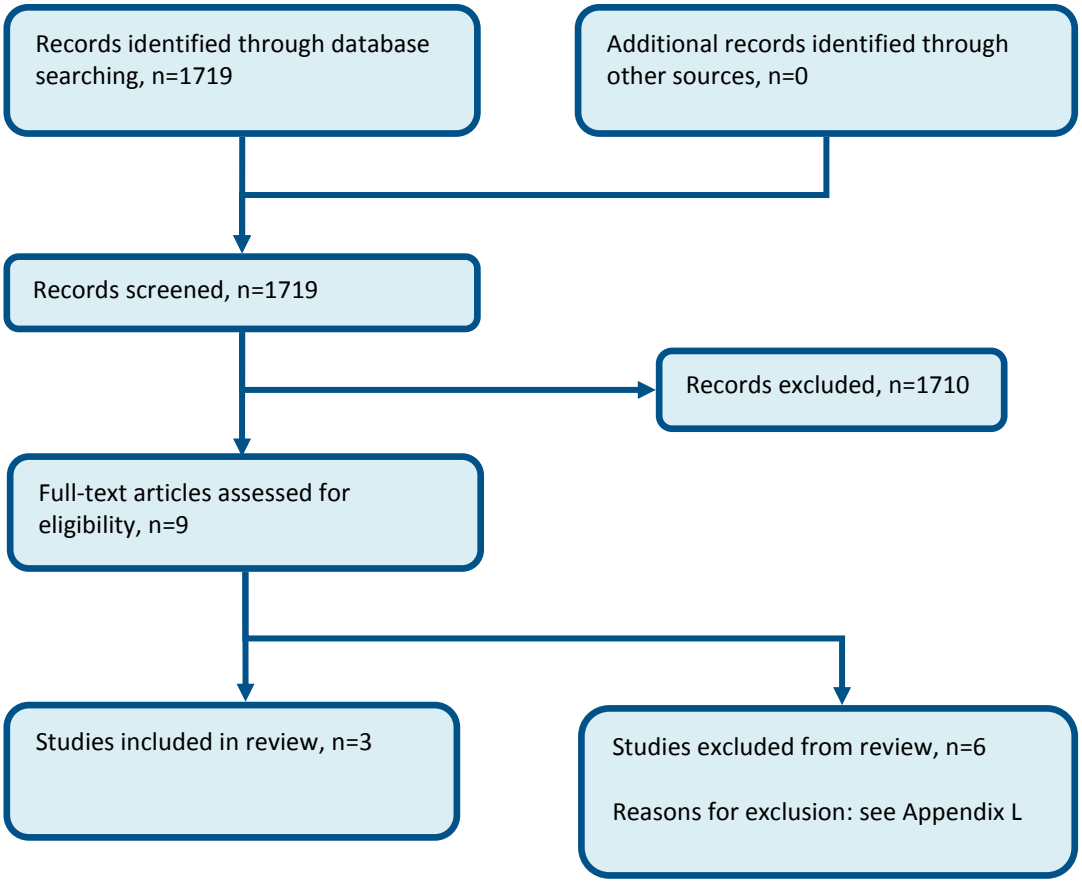
E.14 Inotropic agents and vasopressors

Figure 13: Flow chart of clinical article selection for the review of inotropic agents



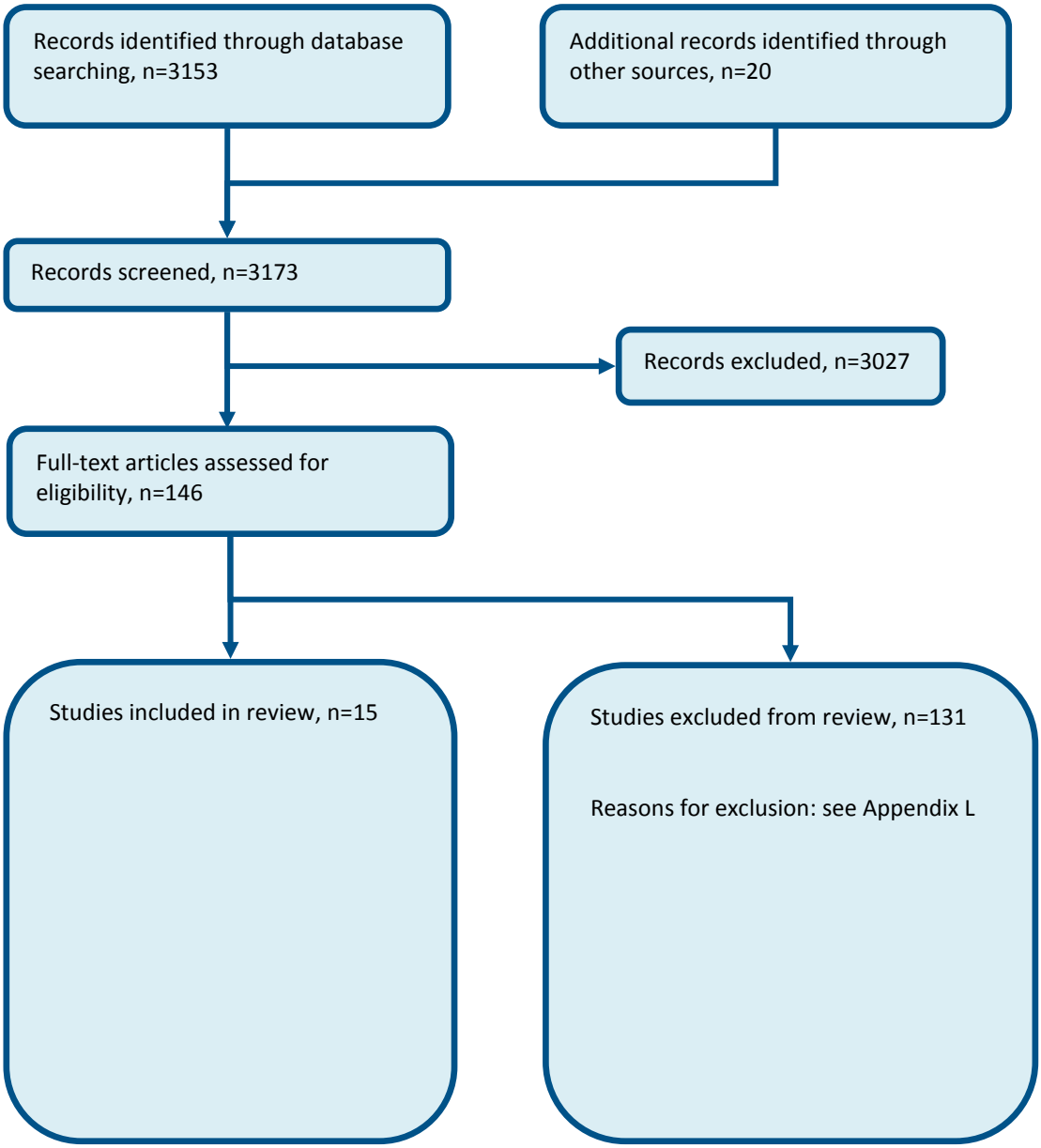
E.15 Patient education, information and support

Figure 14: Flow chart of clinical article selection for the review of patient education, information and support



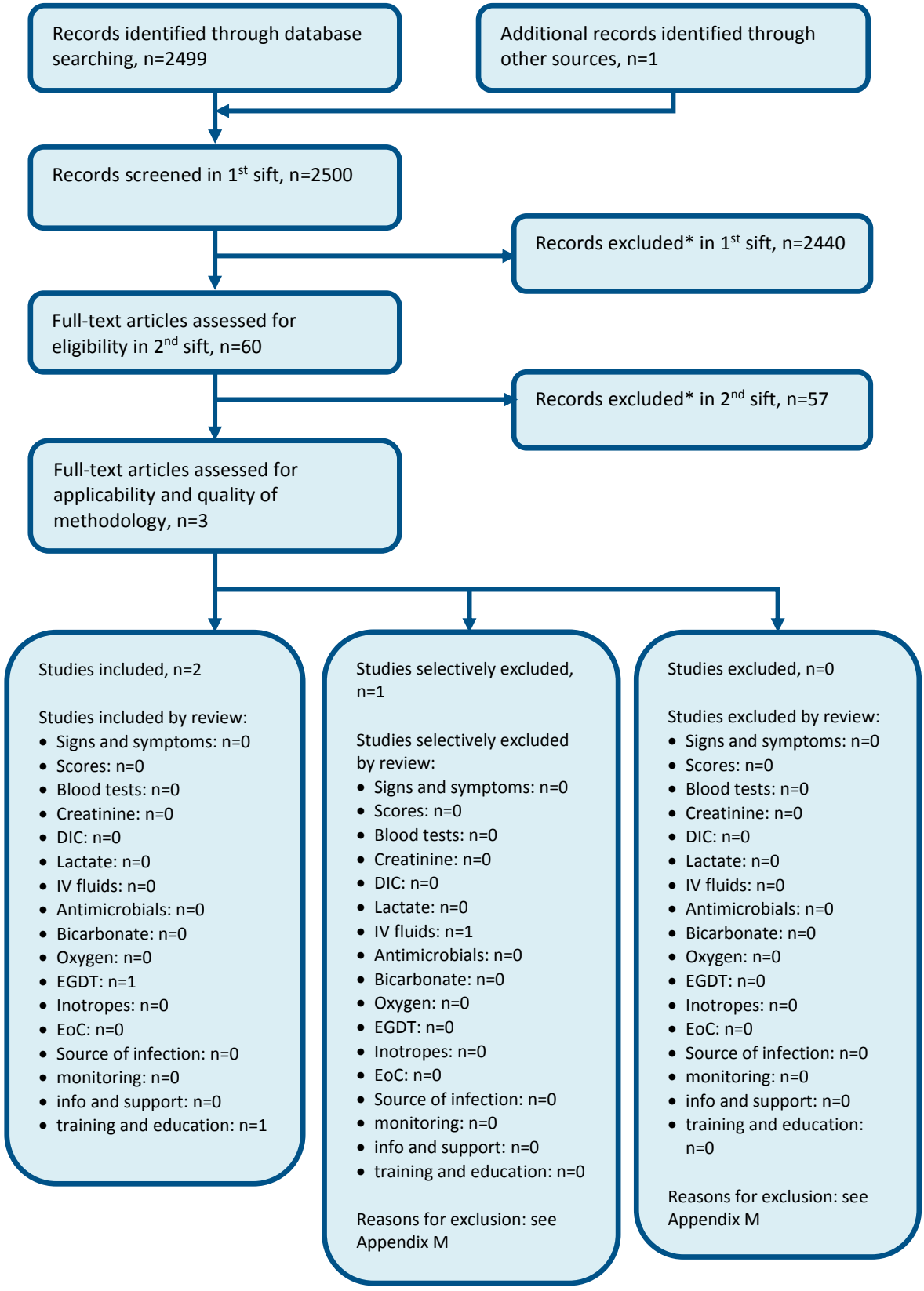
E.16 Education and training

Figure 15: Flow chart of clinical article selection for the review of education and training



Appendix F: Health economic article selection

Figure 16: Flow chart of economic article selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix G: Literature search strategies

G.1 Contents

Search strategies used for the Sepsis guideline are outlined below and were run in accordance with the methodology in the NICE guidelines manual.[1] All searches were run up to 9 October 2015 unless otherwise stated. Any studies added to the databases after this date (even those published prior to this date) were not included unless specifically stated in the text. We do not routinely search for

electronic, ahead of print or 'online early' publications. Where possible searches were limited to retrieve material published in English.

Table 17: Database date parameters

Database	Dates searched
Medline	1946 – 9 October 2015
Embase	1974 – 9 October 2015
The Cochrane Library	Cochrane Reviews to 2015 Issue 10 of 12 CENTRAL to 2015 Issue 9 of 12 DARE to 2013 Issue 2 of 4
	HTA to 2013 Issue 3 of 4
	NHSEED to 2013 Issue 2 of 4
PsycINFO (Ovid) PsycINFO (ProQuest)	1806 - March Week 1 2015 1806 – 6 October 2015
CINAHL	1981 – 6 October 2015

Searches for the **clinical reviews** were run in Medline (OVID), Embase (OVID) and the Cochrane Library (Wiley). Additional searches were run in CINAHL and PsycINFO for some questions see Table 18.

Table 18: Databases searched

	Question	Databases
G.4.7	Acid-base pH	Medline/Embase/Cochrane Library
G.4.6	Antimicrobials	Medline/Embase/Cochrane Library
G.4.3	Blood tests	Medline/Embase/Cochrane Library
G.4.13	Educational programmes/Identification protocols	Medline/Embase/Cochrane Library
G.4.10	Escalation of care	Medline/Embase/Cochrane Library
G.5.1	Health economic reviews	Medline/Embase/CRD/HEED
G.4.12	Information support	Medline/Embase/Cochrane Library /CINAHL/PsycINFO
G.4.9	Inotropes	Medline/Embase/Cochrane Library
G.4.5	IV Fluids	Medline/Embase/Cochrane Library
G.4.11	Monitoring	Medline/Embase/Cochrane Library
G.4.8	Oxygen	Medline/Embase/Cochrane Library
G.5.2	Quality of life reviews	Medline/Embase
G.4.2	Scoring systems/Prognostic tools	Medline/Embase/Cochrane Library
G.4.1	Signs and symptoms	Medline/Embase/Cochrane Library
G.4.4	Supplementary blood tests	Medline/Embase/Cochrane Library

Searches for **intervention and diagnostic studies** were usually constructed using a PICO format where population (P) terms were combined with Intervention (I) and sometimes Comparison (C) terms. An intervention can be a drug, a procedure or a diagnostic test. Outcomes (O) are rarely used in search strategies for interventions. Search filters were also added to the search where appropriate.

Searches for **prognostic studies** were usually constructed combining population terms with prognostic variable terms and sometimes outcomes. Search filters were added to the search where appropriate.

Searches for the **health economic reviews** were run in Medline, Embase, the NHS Economic Evaluations Database (NHS EED), the Health Technology Assessment (HTA) database and the Health Economic Evaluation Database (HEED). The Health Economic Evaluation Database (HEED) ceased production in 2014 with access ceasing in January 2015. For the final dates of HEED searches, please see individual economic questions.

For Medline and Embase an economic filter (instead of a study type filter) was added to the same clinical search strategy. Searches in CRD and HEED were constructed using population terms only.

G.2 Population search strategies

G.2.1 Standard sepsis population

The standard sepsis population was used in all questions except question 11 [G.4.11]

Medline search terms

1.	exp sepsis/
2.	sepsis.ti,ab.
3.	blood-borne pathogens/
4.	(blood adj2 (pathogen* or poison*)).ti,ab.
5.	exp systemic inflammatory response syndrome/
6.	'systemic inflammatory response syndrome'.ti,ab.
7.	sirs.ti,ab.
8.	(septicaemi* or septicemi*).ti,ab.
9.	(septic adj2 shock).ti,ab.
10.	(pyaemi* or pyemi* or pyohemi*).ti,ab.
11.	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab.
12.	or/1-11

Embase search terms

1.	exp *sepsis/
2.	sepsis.ti,ab.
3.	*bloodborne bacterium/
4.	(blood adj2 (pathogen* or poison*)).ti,ab.
5.	exp *systemic inflammatory response syndrome/
6.	sirs.ti,ab.
7.	'systemic inflammatory response syndrome'.ti,ab.
8.	*septicemia/
9.	(septicaemi* or septicemi*).ti,ab.
10.	*septic shock/
11.	(septic adj2 shock).ti,ab.
12.	(pyaemi* or pyemi* or pyohemi*).ti,ab.
13.	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab.

14.	or/1-13

Cochrane search terms

#1.	MeSH descriptor: [sepsis] explode all trees
#2.	MeSH descriptor: [blood-borne pathogens] explode all trees
#3.	MeSH descriptor: [systemic inflammatory response syndrome] explode all trees
#4.	((systemic inflammatory response syndrome) or (sirs) or (sepsis)):ti,ab
#5.	(septicaemi* or septicemi* or pyaemi* or pyemi* or pyohemi* or bacteremi* or fungemi* or parasitemi* or viremi* or bacteraemi* or fungaemi* or parasitaemi* or viraemi*):ti,ab
#6.	(septic near/2 shock):ti,ab
#7.	(blood near/2 (pathogen* or poison*)):ti,ab
#8.	{or #1-#7}

CINAHL search terms

S1.	(MH "sepsis+")
S2.	(MH "systemic inflammatory response syndrome+")
S3.	(MH "bloodborne pathogens")
S4.	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*)
S5.	(pyaemi* or pyemi* or pyohemi*)
S6.	(septic n2 shock)
S7.	(septicaemi* or septicemi*)
S8.	sirs or sepsis
S9.	(blood n2 (pathogen* or poison*))
S10.	S1 orS2 orS3 orS4 orS5 orS6 orS7 orS8 or S9

PsycINFO (Ovid) search terms

1.	sepsis.ti,ab.
2.	(blood adj2 (pathogen* or poison*)).ti,ab.
3.	systemic inflammatory response syndrome'.ti,ab.
4.	sirs.ti,ab.
5.	(septicaemi* or septicemi*).ti,ab.
6.	(septic adj2 shock).ti,ab.
7.	(pyaemi* or pyemi* or pyohemi*).ti,ab.
8.	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab.
9.	or/1-8

PsycINFO (ProQUEST) search terms

1.	(ti,ab(sepsis) or ti,ab(blood near/2 (pathogen* or poison*)) or ti,ab(systemic inflammatory response syndrome) or ti,ab(sirs) or ti,ab(septicaemi* or septicemi*) or ti,ab(septic near/2 shock) or ti,ab(bacter*emi* or fung*emi* or parasite*emi* or vir*emi*)

CRD search terms

1.	(MeSH descriptor sepsis explode all trees)
2.	(MeSH descriptor blood-borne pathogens explode all trees)
3.	(MeSH descriptor systemic inflammatory response syndrome explode all trees)
4.	((systemic inflammatory response syndrome) or (sirs) or (sepsis))
5.	((septicaemi* or septicemi* or pyaemi* or pyemi* or pyohemi* or bacteremi* or fungemi* or

	parasitemi* or viremi* or bacteraemi* or fungaemi* or parasitaemi* or viraemi*))
6.	((septic adj2 shock))
7.	((blood adj2 (pathogen* or poison*)))
8.	(#1 or #2 or #3 or #4 or #5 or #6 or #7)

HEED search terms

1.	ax=sepsis or septicaemi* or septicemi* or systemic inflammatory response syndrome or sirs or pyaemi* or pyemi* or pyohemi* or bacteremi* or fungemi* or parasitemi* or viremi* or bacteraemi* or fungaemi* or parasitaemi* or viraemi*
2.	ax=septic shock
3.	ax=blood pathogen or blood pathogens or blood borne pathogen or blood borne pathogens
4.	ax=blood poisoning
5.	cs=1 or 2 or 3 or 4

G.2.2 Standard bacterial meningitis population

The standard bacterial meningitis population was used in questions G.4.4, G.4.10, G.4.13 and G.5.1 only.

Medline search terms

1.	exp bacterial meningitis/
2.	((bacterial* or infect*) adj3 (meningitis or meningitides)).ti,ab.
3.	((bacterial* or infect*) adj3 meninges).ti,ab.
4.	(infect* adj3 (leptomeninges or subarachnoid space?)).ti,ab.
5.	((meningitis or meningitides) adj3 (e coli or escherichia coli)).ti,ab.
6.	((meningitis or meningitides) adj3 (haemophilus or hemophilus)).ti,ab.
7.	((meningitis or meningitides) adj3 listeria).ti,ab.
8.	((meningitis or meningitides or meningeal or pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.
9.	meningoencephalitis.ti,ab.
10.	meningoencephalitis/
11.	meningitis/
12.	exp pneumococcal infections/
13.	pneumococc*.ti,ab.
14.	exp neisseria meningitidis/
15.	(neisseria adj1 meningitidis).ti,ab.
16.	exp meningococcal infections/
17.	(meningococcosis or meningococc* or meningococcemia).ti,ab.
18.	exp streptococcal infections/
19.	streptococc*.ti,ab.
20.	or/1-19

Embase search terms

1.	exp bacterial meningitis/
2.	((bacterial* or infect*) adj3 (meningitis or meningitides)).ti,ab.
3.	((bacterial* or infect*) adj3 meninges).ti,ab.
4.	(infect* adj3 (leptomeninges or subarachnoid space?)).ti,ab.

5.	((meningitis or meningitides) adj3 (e coli or escherichia coli)).ti,ab.
6.	((meningitis or meningitides) adj3 (haemophilus or hemophilus)).ti,ab.
7.	((meningitis or meningitides) adj3 listeria).ti,ab.
8.	((meningitis or meningitides or meningeal or pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.
9.	meningoencephalitis.ti,ab.
10.	meningoencephalitis/
11.	meningitis/
12.	exp pneumococcal infections/
13.	pneumococc*.ti,ab.
14.	exp neisseria meningitidis/
15.	(neisseria adj1 meningitidis).ti,ab.
16.	exp meningococcal infections/
17.	(meningococcosis or meningococc* or meningococcemia).ti,ab.
18.	exp streptococcal infections/
19.	streptococc*.ti,ab.
20.	or/1-19

Cochrane search terms

#1.	MeSH descriptor: [meningitis, bacterial] explode all trees
#2.	((bacterial* or infect*) near/3 (meningitis or meningitides)):ti,ab
#3.	((bacterial* or infect*) near/3 meninges):ti,ab
#4.	(infect* near/3 (leptomeninges or subarachnoid space?)):ti,ab
#5.	((meningitis or meningitides) near/3 (e coli or escherichia coli)):ti,ab
#6.	((meningitis or meningitides) near/3 (haemophilus or hemophilus)):ti,ab
#7.	((meningitis or meningitides) near/3 listeria):ti,ab
#8.	((meningitis or meningitides or meningeal or Pachymeningitis) near/3 (tuberculosis or tuberculous or tubercular)):ti,ab
#9.	meningoencephalitis:ti,ab
#10.	MeSH descriptor: [meningoencephalitis] this term only
#11.	MeSH descriptor: [meningitis] this term only
#12.	MeSH descriptor: [pneumococcal infections] explode all trees
#13.	pneumococc*:ti,ab
#14.	MeSH descriptor: [neisseria meningitidis] explode all trees
#15.	(neisseria near/1 meningitidis):ti,ab
#16.	MeSH descriptor: [meningococcal infections] explode all trees
#17.	(meningococcosis or meningococc* or meningococcemia):ti,ab
#18.	MeSH descriptor: [streptococcal infections] explode all trees
#19.	streptococc*:ti,ab
#20.	{or #1-#19}

CRD search terms

1.	(MeSH descriptor meningitis, bacterial explode all trees)
2.	((mening*))
3.	(MeSH descriptor meningoencephalitis explode all trees)

4.	(MeSH descriptor meningitis explode all trees)
5.	(MeSH descriptor meningitis explode all trees)
6.	((pneumococc*))
7.	(MeSH descriptor neisseria meningitidis explode all trees)
8.	(MeSH descriptor meningococcal infections explode all trees)
9.	(MeSH descriptor streptococcal infections explode all trees)
10.	((streptococc*))
11.	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)

HEED search terms

6.	ax=mening* or pneumococc* or streptococc*

G.3 Study filter search terms

G.3.1 Excluded study designs and publication types

The following study designs and publication types were removed from retrieved results using the NOT operator.

Medline search terms

1.	letter/
2.	editorial/
3.	news/
4.	exp historical article/
5.	anecdotes as topic/
6.	comment/
7.	case report/
8.	(letter or comment*).ti.
9.	or/1-8
10.	randomized controlled trial/ or random*.ti,ab.
11.	9 not 10
12.	animals/ not humans/
13.	exp animals, laboratory/
14.	exp animal experimentation/
15.	exp models, animal/
16.	exp rodentia/
17.	(rat or rats or mouse or mice).ti.
18.	or/11-17

Embase search terms

1.	letter.pt. or letter/
2.	note.pt.
3.	editorial.pt.
4.	case report/ or case study/
5.	(letter or comment*).ti.
6.	or/1-5

7.	randomized controlled trial/ or random*.ti,ab.
8.	6 not 7
9.	animal/ not human/
10.	nonhuman/
11.	exp animal experiment/
12.	exp experimental animal/
13.	animal model/
14.	exp rodent/
15.	(rat or rats or mouse or mice).ti.
16.	or/8-15

CINAHL search terms

S11.	pt anecdote or pt audiovisual or pt bibliography or pt biography or pt book or pt book review or pt brief item or pt cartoon or pt commentary or pt computer program or pt editorial or pt games or pt glossary or pt historical material or pt interview or pt letter or pt listservs or pt masters thesis or pt obituary or pt pamphlet or pt pamphlet chapter or pt pictorial or pt poetry or pt proceedings or pt "questions and answers" or pt response or pt software or pt teaching materials or pt website

G.3.2 Randomised controlled trials (RCT) search terms

Medline search terms

1.	randomized controlled trial.pt.
2.	controlled clinical trial.pt.
3.	randomi#ed.ab.
4.	placebo.ab.
5.	drug therapy.fs.
6.	randomly.ab.
7.	trial.ab.
8.	groups.ab.
9.	or/1-8

Embase search terms

1.	random*.ti,ab.
2.	factorial*.ti,ab.
3.	(crossover* or cross over*).ti,ab.
4.	((doubl* or singl*) adj blind*).ti,ab.
5.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
6.	crossover procedure/
7.	double blind procedure/
8.	single blind procedure/
9.	randomized controlled trial/
10.	or/1-9

G.3.3 Systematic review (SR) search terms

Medline search terms

1.	meta-analysis/
2.	meta-analysis as topic/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

Embase search terms

1.	systematic review/
2.	meta-analysis/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

G.3.4 Health economics (HE) search terms

Medline search terms

1.	economics/
2.	value of life/
3.	exp "costs and cost analysis"/
4.	exp economics, hospital/
5.	exp economics, medical/
6.	economics, nursing/
7.	economics, pharmaceutical/
8.	exp "fees and charges"/
9.	exp budgets/
10.	budget*.ti,ab.
11.	cost*.ti.
12.	(economic* or pharmaco?economic*).ti.
13.	(price* or pricing*).ti,ab.
14.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15.	(financ* or fee or fees).ti,ab.

16.	(value adj2 (money or monetary)).ti,ab.
17.	or/1-16

Embase search terms

1.	health economics/
2.	exp economic evaluation/
3.	exp health care cost/
4.	exp fee/
5.	budget/
6.	funding/
7.	budget*.ti,ab.
8.	cost*.ti.
9.	(economic* or pharmaco?economic*).ti.
10.	(price* or pricing*).ti,ab.
11.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
12.	(financ* or fee or fees).ti,ab.
13.	(value adj2 (money or monetary)).ti,ab.
14.	or/1-13

G.3.5 Quality of life (QOL) search terms

Medline search terms

1.	quality-adjusted life years/
2.	sickness impact profile/
3.	(quality adj2 (wellbeing or well-being)).ti,ab.
4.	sickness impact profile.ti,ab.
5.	disability adjusted life.ti,ab.
6.	(qal* or qtime* or qwb* or daly*).ti,ab.
7.	(euroqol* or eq5d* or eq 5d*).ti,ab.
8.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
9.	(health utility* or utility score* or disutilit*).ti,ab.
10.	(hui or hui1 or hui2 or hui3).ti,ab.
11.	health* year* equivalent*.ti,ab.
12.	(hye or hyes).ti,ab.
13.	rosser.ti,ab.
14.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
15.	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.
16.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
17.	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.
18.	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.
19.	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.
20.	or/1-19

Embase search terms

1.	quality adjusted life year/

2.	"quality of life index"/
3.	short form 12/ or short form 20/ or short form 36/ or short form 8/
4.	sickness impact profile/
5.	(quality adj2 (wellbeing or well-being)).ti,ab.
6.	sickness impact profile.ti,ab.
7.	disability adjusted life.ti,ab.
8.	(qal* or qtime* or qwb* or daly*).ti,ab.
9.	(euroqol* or eq5d* or eq 5d*).ti,ab.
10.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
11.	(health utility* or utility score* or disutilit*).ti,ab.
12.	(hui or hui1 or hui2 or hui3).ti,ab.
13.	health* year* equivalent*.ti,ab.
14.	(hye or hyes).ti,ab.
15.	rosser.ti,ab.
16.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
17.	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.
18.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
19.	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.
20.	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.
21.	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.
22.	or/1-21

G.3.6 Diagnostic test accuracy (DIAG) search terms

Medline search terms

1.	exp "sensitivity and specificity"/
2.	(sensitivity or specificity).ti,ab.
3.	((pre test or pretest or post test) adj probability).ti,ab.
4.	(predictive value* or ppv or npv).ti,ab.
5.	likelihood ratio*.ti,ab.
6.	likelihood function/
7.	(roc curve* or auc).ti,ab.
8.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
9.	gold standard.ab.
10.	or/1-9

Embase search terms

1.	exp "sensitivity and specificity"/
2.	(sensitivity or specificity).ti,ab.
3.	((pre test or pretest or post test) adj probability).ti,ab.
4.	(predictive value* or ppv or npv).ti,ab.
5.	likelihood ratio*.ti,ab.
6.	(roc curve* or auc).ti,ab.
7.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or

	effectiveness)).ti,ab.
8.	diagnostic accuracy/
9.	diagnostic test accuracy study/
10.	gold standard.ab.
11.	or/1-10

G.3.7 Observational studies (OBS) search terms

Medline search terms

1.	epidemiologic studies/
2.	exp case control studies/
3.	exp cohort studies/
4.	cross-sectional studies/
5.	case control.ti,ab.
6.	(cohort adj (study or studies or analys*)).ti,ab.
7.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
8.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
9.	or/1-8

Embase search terms

1.	clinical study/
2.	exp case control study/
3.	family study/
4.	longitudinal study/
5.	retrospective study/
6.	prospective study/
7.	cross-sectional study/
8.	cohort analysis/
9.	follow-up/
10.	cohort*.ti,ab.
11.	9 and 10
12.	case control.ti,ab.
13.	(cohort adj (study or studies or analys*)).ti,ab.
14.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
15.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
16.	or/1-8,11-15

G.3.8 Prognostic/prediction rule (PROG) search terms

Medline search terms

1.	predict.ti.
2.	(validat* or rule*).ti,ab.

3.	(predict* and (outcome* or risk* or model*)).ti,ab.
4.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
5.	decision*.ti,ab. and Logistic models/
6.	(decision* and (model* or clinical*)).ti,ab.
7.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
8.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
9.	ROC curve/
10.	or/1-9

Embase search terms

1.	predict*.ti.
2.	(validat* or rule*).ti,ab.
3.	(predict* and (outcome* or risk* or model*)).ti,ab.
4.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
5.	decision*.ti,ab. and Statistical model/
6.	(decision* and (model* or clinical*)).ti,ab.
7.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
8.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
9.	receiver operating characteristic/
10.	or/1-9

G.4 Searches for specific questions

G.4.1 Signs and symptoms

- What is the predictive value/utility of different signs and symptoms, alone or in combination, for the diagnosis of sepsis?

Medline search terms

1.	Standard sepsis population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	*heart rate/
6.	*respiratory rate/
7.	((heart or pulse or respirat* or breath*) adj2 rate).ti,ab.
8.	*blood pressure/
9.	((systolic or blood) adj2 pressure).ti,ab.
10.	exp *consciousness disorders/
11.	(consciousness or unconsciousness or semiconsciousness).ti,ab.
12.	*delirium/

13.	((alter* or chang*) adj2 mental state*).ti,ab.
14.	(oxygen saturation or blood oxygen or sats).ti,ab.
15.	*anoxia/
16.	(anoxia or anoxemia or anoxaemia or hypoxia or hypoxaemia or hypoxemia or "oxygen deficien*").ti,ab.
17.	*body temperature/
18.	exp *body temperature changes/
19.	(fever* or hypothermi* or hyperthermi* or pyrex* or febri* or hyper-therm* or hyper-pyrex* or hypo-therm* or body temperature?).ti,ab.
20.	or/5-19
21.	*accidental falls/
22.	(fall or falls or falling).ti,ab.
23.	*dysuria/
24.	*oliguria/
25.	(oliguria or hypouresis or dysuria).ti,ab.
26.	*pallor/
27.	*exanthema/
28.	(pallor or cyanosis or exanthem* or rash*).ti,ab.
29.	*cyanosis/
30.	((pale or mottled or pallid or wan or ashen or blue) adj2 (skin or lips or tongue or lip)).ti,ab.
31.	((ill* or sick* or unwell) adj3 (look* or appear*)).ti,ab.
32.	((reduc* or low*) adj2 urin* adj2 (volume? or output? or level?)).ti,ab.
33.	*chills/
34.	*shivering/
35.	(chill? or rigor? or shiver*).ti,ab.
36.	exp *pain/
37.	pain?.ti,ab.
38.	exp *vaginal discharge/
39.	(vagina* adj2 (discharge* or secret*)).ti,ab.
40.	(capill?ary refill time? or crt).ti,ab.
41.	*capillary resistance/
42.	*microcirculation/
43.	((cold or chill*) adj3 (hand? or feet or foot)).ti,ab.
44.	*respiratory sounds/
45.	(rales or crackles or rhonchi or grunt*).ti,ab.
46.	((chest or sternal or sternum or intercostal) adj3 (in drawing or in?drawing or recess* or retract*)).ti,ab.
47.	((respirat* or breath*) adj3 (distress* or disorder? or alter*)).ti,ab.
48.	((nose or nasal or nostril? or alar) adj3 flar*).ti,ab.
49.	*Cranial fontanelles/
50.	(fontanel* adj3 (bulg* or tens*)).ti,ab.
51.	(pulse adj2 pressure).ti,ab.
52.	*arterial pressure/
53.	(mean arterial adj2 pressure).ti,ab.

54.	(confus* adj2 mental state*).ti,ab.
55.	*confusion/
56.	exp *diarrhea/
57.	diarrh*.ti,ab.
58.	(water* adj3 (bowel movement* or stool* or feces or faeces or fecal or foecal)).ti,ab.
59.	*vomiting/
60.	(vomit* or emesis or emeses).ti,ab.
61.	*crying/
62.	((weak* or continu* or high-pitch* or high pitch*) adj2 (cry* or voice* or sound* or articulat*)).ti,ab.
63.	*postpartum period/
64.	*pregnant women/
65.	(pregnant or pregnancy).ti,ab.
66.	or/21-65
67.	exp "signs and symptoms"/
68.	symptom assessment/
69.	diagnosis/ or prognosis/
70.	(clinical adj3 (manifestation? or feature? or finding? or aspect? or marker?)).ti,ab.
71.	(presenting adj3 (feature? or finding? or factor?)).ti,ab.
72.	presentation?.ti,ab.
73.	(physical adj3 (manifestaion? or characteristic? or feature? or finding?)).ti,ab.
74.	(sign or signs or symptom* or recogni* or identif* or complain*).ti,ab.
75.	(diagnos* or prognos* or assess* or criteria* or predict*).ti,ab.
76.	or/67-75
77.	(20 or 66) and 76
78.	Study filters RCT [G.3.2] or SR [G.3.3] or OBS [G.3.7]
79.	4 and 77 and 78
80.	limit 80 to yr="1990 -Current"

Embase search terms

1.	Standard sepsis population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	*heart rate/
6.	*breathing rate/
7.	((heart or pulse or respirat* or breath*) adj2 rate).ti,ab.
8.	*systolic blood pressure/
9.	((systolic or blood) adj2 pressure).ti,ab.
10.	*consciousness level/
11.	exp *consciousness disorder/
12.	(consciousness or unconsciousness or semiconsciousness).ti,ab.
13.	((alter* or chang*) adj2 mental state*).ti,ab.
14.	*delirium/

15.	(oxygen saturation or blood oxygen or sats).ti,ab.
16.	*oxygen saturation/
17.	*anoxia/
18.	(anoxia or anoxemia or anoxaemia or hypoxia or hypoxaemia or hypoxemia or "oxygen deficien*").ti,ab.
19.	*body temperature/
20.	exp *body temperature disorder/
21.	(fever* or hypothermi* or hyperthermi* or pyrex* or febri* or hyper-therm* or hyper-pyrex* or hypo-therm* or body temperature?).ti,ab.
22.	or/5-21
23.	*falling/
24.	(fall or falls or falling).ti,ab.
25.	*dysuria/
26.	*oliguria/
27.	(oliguria or hypouresis or dysuria).ti,ab.
28.	*pallor/
29.	*rash/
30.	(pallor or cyanosis or exanthem* or rash*).ti,ab.
31.	*cyanosis/
32.	((pale or mottled or pallid or wan or ashen or blue) adj2 (skin or lips or tongue or lip)).ti,ab.
33.	((ill* or sick* or unwell) adj3 (look* or appear*)).ti,ab.
34.	((reduc* or low*) adj2 urin* adj2 (volume? or output? or level?)).ti,ab.
35.	*chill/
36.	*shivering/
37.	(chill? or rigor? or shiver*).ti,ab.
38.	exp *pain/
39.	pain?.ti,ab.
40.	*vagina discharge/
41.	(vagina* adj2 (discharge* or secret*)).ti,ab.
42.	(capill?ary refill time? or crt).ti,ab.
43.	*capillary resistance/
44.	*microcirculation/
45.	((cold or chill*) adj3 (hand? or feet or foot)).ti,ab.
46.	*abnormal respiratory sound/
47.	(rales or crackles or rhonchi or grunt*).ti,ab.
48.	((chest or sternal or sternum or intercostal) adj3 (in drawing or in?drawing or recess* or retract*)).ti,ab.
49.	((respirat* or breath*) adj3 (distress* or disorder? or alter*)).ti,ab.
50.	((nose or nasal or nostril? or alar) adj3 flar*).ti,ab.
51.	*fontanel/
52.	(fontanel* adj3 (bulg* or tens*)).ti,ab.
53.	*pathological crying/ or *crying/
54.	((weak* or continu* or high-pitch* or high pitch*) adj2 (cry* or voice* or sound* or articulat*)).ti,ab.

55.	(pulse adj2 pressure).ti,ab.
56.	*arterial pressure/
57.	(mean arterial adj2 pressure).ti,ab.
58.	(confus* adj2 mental state*).ti,ab.
59.	*confusion/ or *acute confusion/ or *"confusion (uncertainty)"/
60.	exp *diarrhea/
61.	diarrh*.ti,ab.
62.	(water* adj3 (bowel movement* or stool* or feces or faeces or fecal or foecal)).ti,ab.
63.	*vomiting/
64.	(vomit* or emesis or emeses).ti,ab.
65.	*puerperium/
66.	*pregnant woman/
67.	(pregnant or pregnancy).ti,ab.
68.	or/23-67
69.	symptom assessment/
70.	diagnosis/
71.	prognosis/
72.	(clinical adj3 (manifestation? or feature? or finding? or aspect? or marker?)).ti,ab.
73.	(presenting adj3 (feature? or finding? or factor?)).ti,ab.
74.	presentation?.ti,ab.
75.	(physical adj3 (manifestaion? or characteristic? or feature? or finding?)).ti,ab.
76.	(sign or signs or symptom* or recogni* or identif* or complain*).ti,ab.
77.	(diagnos* or prognos* or assess* or criteria* or predict*).ti,ab.
78.	exp symptomatology/
79.	or/69-78
80.	(22 or 68) and 79
81.	Study filters RCT [G.3.2] or SR [G.3.3] or OBS [G.3.7]
82.	4 and 80 and 81
83.	limit 82 to yr="1990 -Current"

Cochrane search terms

#1.	Standard sepsis population [G.2.1]
#2.	[mh "heart rate"]
#3.	[mh "respiratory rate"]
#4.	[mh "body temperature changes"]
#5.	[mh "body temperature"]
#6.	[mh anoxia]
#7.	[mh delirium]
#8.	[mh "blood pressure"]
#9.	[mh "consciousness disorders"]
#10.	((heart or pulse or respirat* or breath*) near/2 rate):ti,ab
#11.	((systolic or blood) near/2 pressure):ti,ab
#12.	(consciousness or unconsciousness or semiconsciousness):ti,ab
#13.	((alter* or chang*) near/2 mental state*):ti,ab

#14.	(oxygen saturation or blood oxygen or sats):ti,ab
#15.	(anoxia or anoxemia or anoxaemia or hypoxia or hypoxaemia or hypoxemia or "oxygen deficien*"):ti,ab
#16.	(fever* or hypothermi* or hyperthermi* or pyrex* or febri* or hyper-therm* or hyper-pyrex* or hypo-therm* or body temperature*):ti,ab
#17.	{or #2-#16}
#18.	MeSH descriptor: [accidental falls] explode all trees
#19.	(fall or falls or falling):ti,ab
#20.	MeSH descriptor: [dysuria] explode all trees
#21.	MeSH descriptor: [oliguria] explode all trees
#22.	(oliguria or hypouresis or dysuria):ti,ab
#23.	MeSH descriptor: [pallor] explode all trees
#24.	MeSH descriptor: [exanthema] explode all trees
#25.	(pallor or cyanosis or exanthem* or rash*):ti,ab
#26.	MeSH descriptor: [cyanosis] explode all trees
#27.	((pale or mottled or pallid or wan or ashen or blue) near/2 (skin or lips or tongue or lip)):ti,ab
#28.	((ill* or sick* or unwell) adj3 (look* or appear*)):ti,ab
#29.	((reduc* or low*) near/2 urin* near/2 (volume? or output? or level?)):ti,ab
#30.	MeSH descriptor: [chills] explode all trees
#31.	MeSH descriptor: [shivering] explode all trees
#32.	(chill? or rigor? or shiver*):ti,ab
#33.	MeSH descriptor: [pain] explode all trees
#34.	pain?.ti,ab
#35.	MeSH descriptor: [vaginal discharge] explode all trees
#36.	(vagina* near/2 (discharge* or secret*)):ti,ab
#37.	(capill?ary refill time? or crt):ti,ab
#38.	MeSH descriptor: [capillary resistance] explode all trees
#39.	MeSH descriptor: [microcirculation] explode all trees
#40.	((cold or chill*) near/3 (hand? or feet or foot)):ti,ab
#41.	MeSH descriptor: [respiratory sounds] explode all trees
#42.	(rales or crackles or rhonchi or grunt*):ti,ab
#43.	((chest or sternal or sternum or intercostal) adj3 (in drawing or in?drawing or recess* or retract*)):ti,ab
#44.	((respirat* or breath*) near/3 (distress* or disorder? or alter*)):ti,ab
#45.	((nose or nasal or nostril? or alar) near/3 flar*):ti,ab
#46.	MeSH descriptor: [cranial fontanelles] explode all trees
#47.	(fontanel* near/3 (bulg* or tens*)):ti,ab
#48.	MeSH descriptor: [crying] explode all trees
#49.	((weak* or continu* or high-pitch* or high pitch*) near/2 (cry* or voice* or sound* or articulat*)):ti,ab
#50.	(pulse adj2 pressure):ti,ab
#51.	MeSH descriptor: [arterial pressure] explode all trees
#52.	(mean arterial adj2 pressure):ti,ab
#53.	(confus* adj2 mental state*):ti,ab

#54.	MeSH descriptor: [confusion] explode all trees
#55.	MeSH descriptor: [diarrhea] explode all trees
#56.	diarrh*:ti,ab
#57.	(water* near/3 (bowel movement* or stool* or feces or faeces or fecal or foecal)):ti,ab
#58.	MeSH descriptor: [vomiting] explode all trees
#59.	(vomit* or emesis or emeses):ti,ab
#60.	MeSH descriptor: [postpartum period] explode all trees
#61.	MeSH descriptor: [pregnant women] explode all trees
#62.	(pregnant or pregnancy):ti,ab
#63.	{or #18-#62}
#64.	[mh "signs and symptoms"]
#65.	[mh "symptom assessment"]
#66.	[mh ^diagnosis]
#67.	[mh ^prognosis]
#68.	(clinical near/3 (manifestation* or feature* or finding* or aspect* or marker*)):ti,ab
#69.	(presenting near/3 (feature* or finding* or factor*)):ti,ab
#70.	presentation*:ti,ab
#71.	(physical near/3 (manifestaion* or characteristic* or feature* or finding*)):ti,ab
#72.	(sign or signs or symptom* or recogni* or identif* or complain*):ti,ab
#73.	(diagnos* or prognos* or assess* or criteria* or predict*):ti,ab
#74.	{or #64-#73}
#75.	#1 and (#17 or #63) and #74 Publication Year from 1990 to 2015

G.4.2 Scoring systems/Prognostic tools

- What is the most accurate and cost effective assessment tool to identify patients with sepsis?

Medline search terms

1.	Standard sepsis population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	*"predictive value of tests"/
6.	*"severity of illness index"/
7.	*decision support techniques/
8.	*triage/mt [methods]
9.	scor* system*.ti,ab.
10.	(risk adj2 calculation*).ti,ab.
11.	((risk or warn* or triage* or observation* or observ*) adj2 (system* or scor*)).ti,ab.
12.	(severity adj2 index).ti,ab.
13.	(curb65 or crb65).ti,ab.
14.	exp *health status indicators/
15.	"track and trigger".ti,ab.
16.	((trigger or calling or alert) adj5 criteria).ti,ab.

17.	or/5-16
18.	((paediatric or pediatric or child*) adj4 (observation* or observ* or scor*)).ti,ab.
19.	(tool kit or toolkit).ti,ab.
20.	"sequential organ failure assessment".ti,ab.
21.	"acute physiology and chronic health evaluation".ti,ab.
22.	"mortality probability model*".ti,ab.
23.	"predisposition infection response and organ dysfunction".ti,ab.
24.	"mortality in emergency department sepsis".ti,ab.
25.	"rapid emergency medicine score".ti,ab.
26.	"emergency severity index".ti,ab.
27.	"simplified acute physiology score".ti,ab.
28.	"pediatric logistic organ dysfunction".ti,ab.
29.	"pediatric risk of mortality score".ti,ab.
30.	"glasgow meningococcal sepsis prognostic score".ti,ab.
31.	"pediatric index of mortality ".ti,ab.
32.	(pews or mews or mts or pops or sofa or apache or mpm or piro or meds or rems or esi or saps or saps ii or pelod or prism or gmsps or pim).ti,ab.
33.	or/18-32
34.	intensive care units/
35.	33 not 34
36.	4 and (17 or 35)

Embase search terms

1.	Standard sepsis population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	*"predictive value"/
6.	*"severity of illness index"/
7.	*decision support system/
8.	scor* system*.ti,ab.
9.	(risk adj2 calculation*).ti,ab.
10.	((risk or warn* or triage* or observation* or observ*) adj2 (system* or scor*)).ti,ab.
11.	(severity adj2 index).ti,ab.
12.	(curb65 or crb65).ti,ab.
13.	exp *health status indicators/
14.	"track and trigger".ti,ab.
15.	((trigger or calling or alert) adj5 criteria).ti,ab.
16.	or/5-15
17.	((paediatric or pediatric or child*) adj4 (observation* or observ* or scor*)).ti,ab.
18.	(tool kit or toolkit).ti,ab.
19.	"sequential organ failure assessment".ti,ab.
20.	"acute physiology and chronic health evaluation".ti,ab.
21.	"mortality probability model*".ti,ab.

22.	"predisposition infection response and organ dysfunction".ti,ab.
23.	"mortality in emergency department sepsis".ti,ab.
24.	"rapid emergency medicine score".ti,ab.
25.	"emergency severity index".ti,ab.
26.	"simplified acute physiology score".ti,ab.
27.	"pediatric logistic organ dysfunction".ti,ab.
28.	"pediatric risk of mortality score".ti,ab.
29.	"glasgow meningococcal sepsis prognostic score".ti,ab.
30.	"pediatric index of mortality ".ti,ab.
31.	(pews or mews or mts or pops or sofa or apache or mpm or piro or meds or rems or esi or saps or saps ii or pelod or prism or gmsps or pim).ti,ab.
32.	apache/
33.	*"named inventories, questionnaires and rating scales"/
34.	sequential organ failure assessment score/ or simplified acute physiology score/
35.	*scoring system/
36.	or/17-35
37.	intensive care unit/
38.	36 not 37
39.	4 and (16 or 38)

Cochrane search terms

#1.	Standard sepsis population [G.2.1]
#2.	MeSH descriptor: [predictive value of tests] this term only
#3.	MeSH descriptor: [severity of illness index] this term only
#4.	MeSH descriptor: [decision support techniques] this term only
#5.	MeSH descriptor: [triage] explode all trees and with qualifier(s): [Methods - MT]
#6.	scor* system*:ti,ab
#7.	(risk near/2 calculation*):ti,ab
#8.	((risk or warn* or triage* or observation* or observ*) near/2 (system* or scor*)):ti,ab
#9.	(severity near/2 index):ti,ab
#10.	(curb65 or crb65):ti,ab
#11.	MeSH descriptor: [health status indicators] this term only
#12.	track and trigger:ti,ab
#13.	((trigger or calling or alert) near/5 criteria):ti,ab
#14.	{or #2-#13}
#15.	((paediatric or pediatric or child*) near/4 (observation* or observ* or scor*)):ti,ab
#16.	(tool kit or toolkit):ti,ab
#17.	sequential organ failure assessment:ti,ab
#18.	acute physiology and chronic health evaluation:ti,ab
#19.	mortality probability model*:ti,ab
#20.	predisposition infection response and organ dysfunction:ti,ab
#21.	mortality in emergency department sepsis:ti,ab
#22.	rapid emergency medicine score:ti,ab
#23.	emergency severity index:ti,ab

#24.	simplified acute physiology score:ti,ab
#25.	pediatric logistic organ dysfunction:ti,ab
#26.	pediatric risk of mortality score:ti,ab
#27.	(pews or mews or mts or pops or sofa or apache or mpm or piro or meds or rems or esi or saps or saps ii or pelod or prism or gmsps or pim):ti,ab
#28.	{or #15-#27}
#29.	MeSH descriptor: [intensive Care] explode all trees
#30.	#28 not #29
#31.	#1 and (#14 or #30)

G.4.3 Blood tests

- What is the predictive value/usefulness of blood tests for the recognition and early assessment of sepsis?

Medline search terms

1.	Standard sepsis population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	biological markers/
6.	(blood adj6 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
7.	blood gas analysis/
8.	(abg or vbg or cbg).ti,ab.
9.	blood glucose/an, bl, du [analysis, blood, diagnostic use]
10.	lactic acid/an, bl, du [analysis, blood, diagnostic use]
11.	((lactate or lactic) adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
12.	exp blood cell count/
13.	((blood or leukocyte* or leucocyte* or erythrocyte* or thrombocyte* or platelet or wbc* or rbc*) adj2 (differential or count*)).ti,ab.
14.	(fbc or cbc or fbe).ti,ab.
15.	(polymorph* or polymorphonucleocyte* or neutrophil*).ti,ab.
16.	((polymorph* or polymorphonucleocyte* or neutrophil*) adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
17.	leukocytes/an, bl, di, du [analysis, blood, diagnosis, diagnostic use]
18.	neutrophils/an, bl, bs, di [analysis, blood, blood supply, diagnosis]
19.	blood platelets/an [analysis]
20.	urea/an, bl, du [analysis, blood, diagnostic use]
21.	(urea adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
22.	electrolytes/bl, du [blood, diagnostic use]
23.	(electrolyte* adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
24.	u&e.ti,ab.

25.	(blood urea nitrogen adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
26.	bun.ti,ab.
27.	((kidney or renal) adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
28.	creatinine/bl, du [blood, diagnostic use]
29.	(creatinine adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
30.	((liver or hepatic) adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
31.	limax.ti,ab.
32.	((coagul* or anticoagul* or act) adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
33.	(partial thromboplastin time or ptt or aptt or pt or aptr).ti,ab.
34.	((prothrombin or bleed* or clot* or thrombin or blood) adj2 time*).ti,ab.
35.	fibrinogen/bl, di, du [blood, diagnosis, diagnostic use]
36.	(fibrinogen* adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
37.	c-reactive protein/bl, du [blood, diagnostic use]
38.	(c-reactive protein* adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
39.	or/5-38
40.	Study filters RCT [G.3.2] or SR [G.3.3] or DIAG [G.3.6]
41.	4 and 39 and 40

Embase search terms

1.	Standard sepsis population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	*biological marker/
6.	(blood adj6 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
7.	*blood gas analysis/
8.	(abg or vbg or cbg).ti,ab.
9.	*glucose blood level/
10.	*lactic acid/
11.	((lactate or lactic) adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
12.	exp *blood cell count/
13.	((blood or leukocyte* or leucocyte* or erythrocyte* or thrombocyte* or platelet or wbc* or rbc*) adj2 (differential or count*)).ti,ab.
14.	(fbc or cbc or fbe).ti,ab.
15.	(polymorph* or polymorphonucleocyte* or neutrophil*).ti,ab.
16.	((polymorph* or polymorphonucleocyte* or neutrophil*) adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.

17.	*leukocyte/
18.	*neutrophil/
19.	*thrombocyte/an [drug analysis]
20.	*urea/
21.	(urea adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
22.	*electrolyte/
23.	(electrolyte* adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
24.	u&e.ti,ab.
25.	(blood urea nitrogen adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
26.	bun.ti,ab.
27.	((kidney or renal) adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
28.	*creatinine/
29.	(creatinine adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
30.	((liver or hepatic) adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
31.	limax.ti,ab.
32.	((coagul* or anticoagul* or act) adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
33.	(partial thromboplastin time or ptt or aptt or pt or aptr).ti,ab.
34.	((prothrombin or bleed* or clot* or thrombin or blood) adj2 time*).ti,ab.
35.	*fibrinogen/
36.	(fibrinogen* adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
37.	*c reactive protein/
38.	(c-reactive protein* adj3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)).ti,ab.
39.	or/5-38
40.	Study filters RCT [G.3.2] or SR [G.3.3] or DIAG [G.3.6]
41.	4 and 39 and 40

Cochrane search terms

#1.	Standard sepsis population [G.2.1]
#2.	MeSH descriptor: [biological markers] explode all trees
#3.	(blood near/6 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)):ti,ab
#4.	MeSH descriptor: [blood gas analysis] explode all trees
#5.	(abg or vbg or cbg):ti,ab
#6.	MeSH descriptor: [blood glucose] explode all trees
#7.	MeSH descriptor: [lactic acid] explode all trees and with qualifier(s): [analysis - an, blood - bl, diagnostic use - du]
#8.	((lactate or lactic) near/3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)):ti,ab

#9.	MeSH descriptor: [blood cell count] explode all trees
#10.	((blood or leukocyte* or leucocyte* or erythrocyte* or thrombocyte* or platelet or wbc* or rbc*) near/2 (differential or count*)):ti,ab
#11.	(fbc or cbc or fbe):ti,ab
#12.	(polymorph* or polymorphonucleocyte* or neutrophil*):ti,ab
#13.	((polymorph* or polymorphonucleocyte* or neutrophil*) near/3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)):ti,ab
#14.	MeSH descriptor: [leukocytes] explode all trees
#15.	MeSH descriptor: [neutrophils] explode all trees
#16.	MeSH descriptor: [blood platelets] explode all trees
#17.	MeSH descriptor: [urea] explode all trees and with qualifier(s): [analysis - an, blood - bl, diagnostic use - du]
#18.	(urea near/3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)) ;ti,ab
#19.	MeSH descriptor: [electrolytes] explode all trees and with qualifier(s): [blood - bl, diagnostic use - du]
#20.	(electrolyte* near/3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)):ti,ab
#21.	u&e:ti,ab
#22.	(blood urea nitrogen near/3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)):ti,ab
#23.	bun:ti,ab
#24.	((kidney or renal) near/3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)):ti,ab
#25.	MeSH descriptor: [creatinine] explode all trees and with qualifier(s): [blood - bl, diagnostic use - du]
#26.	(creatinine near/3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)):ti,ab
#27.	((liver or hepatic) near/3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)):ti,ab
#28.	limax:ti,ab
#29.	((coagul* or anticoagul* or act) near/3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)):ti,ab
#30.	(partial thromboplastin time or ptt or aptt or pt or aptr):ti,ab
#31.	((prothrombin or bleed* or clot* or thrombin or blood) near/2 time*):ti,ab
#32.	MeSH descriptor: [fibrinogen] explode all trees
#33.	(fibrinogen* near/3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)):ti,ab
#34.	MeSH descriptor: [c-reactive protein] explode all trees
#35.	(c-reactive protein* near/3 (analys* or analyze* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay)):ti,ab
#36.	{or #2-#35}
#37.	#1 and #36

G.4.4 Supplementary blood tests

Searches for the following three questions were were run as one search:

- What is the predictive value of lactate in people with sepsis for the recognition and early assessment of worsening sepsis?
- What is the predictive value of serum creatinine in people with sepsis for the recognition and early assessment of worsening sepsis?
- What is the predictive value of disseminated intravascular coagulation in people with sepsis for the recognition and early assessment of worsening sepsis?

Medline search terms

1.	Standard sepsis population [G.2.1]
2.	Standard bacterial meningitis population [G.2.2]
3.	exp arthritis, infectious/ or exp bone diseases, infectious/ or exp community-acquired infections/ or exp respiratory tract infections/ or exp skin diseases, infectious/ or exp soft tissue infections/ or exp urinary tract infections/ or "meningitis".mp. or "serious infections".mp. or exp gastroenteritis/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4.	or/1-3
5.	Excluded study designs and publication types [G.3.1]
6.	4 not 5
7.	Limit 6 to English language
8.	exp lactic acid/
9.	(lactate* or lactic acid).ti,ab.
10.	8 or 9
11.	exp disseminated intravascular coagulation/
12.	(disseminated adj2 intravascular adj2 (coagulat* or coagulopath* or clot*)).ti,ab.
13.	((consumption or consumptive) adj1 coagulopath*).ti,ab.
14.	dic.ti,ab.
15.	or/11-14
16.	creatinine/
17.	(creatinine or cystatin c or acr or kreatinine).ti,ab.
18.	16 or 17
19.	acute kidney injury/
20.	kidney tubular necrosis, acute/
21.	(aki or acute kidney necrosis or acute kidney tubul* necrosis or acute kidney injury).ti,ab.
22.	((acute or early) adj (kidney or renal) adj (failure* or injur* or insufficien* or dysfunction* or impair*)).ti,ab.
23.	or/19-22
24.	15 or (18 and 23)
25.	Study filters PROG [G.3.8]
26.	7 and 24 and 25
27.	7 and 10
28.	26 or 27

Embase search terms

1.	Standard sepsis population [G.2.1]
2.	Standard bacterial meningitis population [G.2.2]
3.	exp infectious arthritis/ or exp hematogenous osteomyelitis/ or exp communicable disease/ or

	exp respiratory tract infection/ or exp skin infection/ or exp soft tissue infection/ or exp urinary tract infection/ or exp gastroenteritis/ or (serious and infections).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
4.	or/1-3
5.	Excluded study designs and publication types [G.3.1]
6.	4 not 5
7.	Limit 6 to English language
8.	exp lactic acid/
9.	(lactate* or lactic acid).ti,ab.
10.	8 or 9
11.	exp disseminated intravascular clotting/
12.	(disseminated adj2 intravascular adj2 (coagulat* or coagulopath* or clot*)).ti,ab.
13.	((consumption or consumptive) adj1 coagulopath*).ti,ab.
14.	DIC.ti,ab.
15.	or/11-14
16.	creatinine/
17.	(creatinine or cystatin c or acr or kreatinine).ti,ab.
18.	16 or 17
19.	acute kidney failure/ or acute kidney tubule necrosis/
20.	(aki or acute kidney necrosis or acute kidney tubul* necrosis or acute kidney injury).ti,ab.
21.	((acute or early) adj (kidney or renal) adj (failure* or injur* or insufficien* or dysfunction* or impair*)).ti,ab.
22.	or/19-21
23.	15 or (18 and 22)
24.	Study filters PROG [G.3.8]
25.	7 and 23 and 24
26.	7 and 10
27.	25 or 26

Cochrane search terms

#1.	Standard sepsis population [G.2.1]
#2.	Standard bacterial meningitis population [G.2.2]
#3.	MeSH descriptor: [arthritis, infectious] explode all trees
#4.	MeSH descriptor: [bone diseases, infectious] explode all trees
#5.	MeSH descriptor: [community-acquired infections] explode all trees
#6.	MeSH descriptor: [respiratory tract infections] explode all trees
#7.	MeSH descriptor: [skin diseases, infectious] explode all trees
#8.	MeSH descriptor: [soft tissue infections] explode all trees
#9.	MeSH descriptor: [urinary tract infections] explode all trees
#10.	MeSH descriptor: [gastroenteritis] explode all trees
#11.	serious infections
#12.	or/1-11
#13.	MeSH descriptor: [lactic acid] explode all trees
#14.	(lactate* or lactic acid):ti,ab

#15.	#13 or #14
#16.	MeSH descriptor: [disseminated intravascular coagulation] explode all trees
#17.	(disseminated near/2 intravascular near/2 (coagulat* or coagulopath* or clot*)):ti,ab
#18.	((consumption or consumptive) next coagulopath*):ti,ab
#19.	dic:ti,ab
#20.	{or #16-#19}
#21.	MeSH descriptor: [creatinine] this term only
#22.	(creatinine or cystatin c or acr or kreatinine):ti,ab
#23.	#21 or #22
#24.	MeSH descriptor: [acute kidney injury] this term only
#25.	MeSH descriptor: [kidney tubular necrosis, acute] this term only
#26.	(aki or acute kidney necrosis or acute kidney tubul* necrosis or acute kidney injury):ti,ab
#27.	((acute or early) adj (kidney or renal) adj (failure* or injur* or insufficien* or dysfunction* or impair*)):ti,ab
#28.	{or #24-#27}
#29.	#23 and #28
#30.	#15 or #20 or #29
#31.	#12 or #30

G.4.5 IV Fluids

Searches for the following three questions were run as one search:

- What is the most clinical and cost effective immediate/bolus IV fluid for resuscitation of patients with sepsis?
- What is the clinical and cost effectiveness of different volumes/dosages of immediate/bolus IV fluid resuscitation in patients with sepsis?
- What is the most clinically and cost effective rate of administration of immediate/bolus IV fluids in patients with sepsis?

Medline search terms

1.	Standard sepsis population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	fluid therapy/
6.	exp water-electrolyte balance/
7.	exp water-electrolyte imbalance/
8.	((fluid* or electrolyte*) adj3 (document* or chart* or strateg* or regimen* or load*)).ti,ab.
9.	((fluid* or electrolye* or water) adj3 (requir* or need* or prescri* or intravenous or iv or infusion* or drip or drips or maint* or volume* or therap* or administrat* or manag* or balance* or imbalance* or overload* or loss* or status or monit* or assess* or reassess* or evaluat* or re-evaluat* or reevaluat*)).ti,ab.
10.	((fluid* or volum*) adj3 (restor* or resus* or replac* or deplet* or deficien* or replenish* or therap* or substitut* or rehydrat*)).ti,ab.
11.	(fluid* adj3 (challenge or bolus)).ti,ab.
12.	(volume adj2 (expand* or expansion* or substitut*)).ti,ab.

13.	((perioperativ* or intraoperativ* or postoperativ*) adj3 fluid*).ti,ab.
14.	(euvol?emi* or normovol?emi*).ti,ab.
15.	insensible loss*.ti,ab.
16.	hyponatr?emi*.ti,ab.
17.	exp hemoglobins/
18.	h?emoglobin*.ti,ab.
19.	((red blood cell* or rbc or prbc or red cell* or blood or packed cell* or erythrocyte*or fluid* or volum* or plasma*) adj5 (therap* or transfus* or replac* or resuscita* or substitut* or restor* or deficien* or replenish*)).ti,ab.
20.	exp plasma/
21.	(ffp or ((frozen or thawed or tp or fresh) adj3 plasma)).ti,ab.
22.	((lyophili?ed or freeze-dried or liquid or "not frozen" or "never frozen") adj3 plasma).ti,ab.
23.	(fdsp or fdp or lqp or lhp).ti,ab.
24.	exp freeze drying/ and plasma.ti,ab,sh.
25.	((platelet* or thrombocyte*) adj3 (transfus* or prophyla* or therap* or infus* or administ*)).ti,ab.
26.	blood platelets/
27.	or/5-26
28.	Study filters RCT [G.3.2] or SR [G.3.3] or OBS [G.3.7]
29.	4 and 27 and 28

Embase search terms

1.	Standard sepsis population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	*fluid therapy/
6.	exp *electrolyte balance/
7.	exp *electrolyte disturbance/
8.	fluid resuscitation/
9.	((fluid* or electrolyte*) adj3 (document* or chart* or strateg* or regimen* or load*)).ti,ab.
10.	((fluid* or electrolye* or water) adj3 (requir* or need* or prescri* or intravenous or iv or infusion* or drip or drips or maint* or volume* or therap* or administrat* or manag* or balance* or imbalance* or overload* or loss* or status or monit* or assess* or reassess* or evaluat* or re-evaluat* or reevaluat*)).ti,ab.
11.	((fluid* or volum*) adj3 (restor* or resus* or replac* or deplet* or deficien* or replenish* or therap* or substitut* or rehydrat*)).ti,ab.
12.	(fluid* adj3 (challenge or bolus)).ti,ab.
13.	(volume adj2 (expand* or expansion* or substitut*)).ti,ab.
14.	((perioperativ* or intraoperativ* or postoperativ*) adj3 fluid*).ti,ab.
15.	(euvol?emi* or normovol?emi*).ti,ab.
16.	insensible loss*.ti,ab.
17.	hyponatr?emi*.ti,ab.
18.	exp *hemoglobin/
19.	h?emoglobin*.ti,ab.
20.	((red blood cell* or rbc or prbc or red cell* or blood or packed cell* or erythrocyte* or fluid* or

	volum*) adj3 (therap* or transfus* replac* or resuscita* or substitut* or restor* or deficien* or replenish*)).ti,ab.
21.	exp *plasma/
22.	((ffp or frozen or fresh or thawed or tp) adj3 plasma).ti,ab.
23.	((lyophili?ed or freeze-dried or liquid or "not frozen" or "never frozen") adj3 plasma).ti,ab.
24.	(fdsp or fdp or lqp or lhp).ti,ab.
25.	exp *freeze drying/ and plasma.ti,ab,sh.
26.	((platelet* or thrombocyte*) adj3 (transfus* or prophyla* or therap* or infus* or administ*)).ti,ab.
27.	*thrombocyte/
28.	or/5-28
29.	Study filters RCT [G.3.2] or SR [G.3.3] or OBS [G.3.7]
30.	4 and 28 and 29

Cochrane search terms

#1.	Standard sepsis population [G.2.1]
#2.	MeSH descriptor: [fluid therapy] explode all trees
#3.	MeSH descriptor: [water-electrolyte balance] explode all trees
#4.	MeSH descriptor: [water-electrolyte imbalance] explode all trees
#5.	((fluid* or electrolyte*) near/3 (document* or chart* or strateg* or regimen* or load*)):ti,ab
#6.	((fluid* or electrolye* or water) near/3 (requir* or need* or prescri* or intravenous or iv or infusion* or drip or drips or maint* or volume* or therap* or administrat* or manag* or balance* or imbalance* or overload* or loss* or status or monit* or assess* or reassess* or evaluat* or re-evaluat* or reevaluat*)):ti,ab
#7.	((fluid* or volum*) near/3 (restor* or resus* or replac* or deplet* or deficien* or replenish* or therap* or substitut* or rehydrat*)):ti,ab
#8.	(fluid* near/3 (challenge or bolus)):ti,ab
#9.	(volume near/2 (expand* or expansion* or substitut*)):ti,ab
#10.	((perioperativ* or intraoperativ* or postoperativ*) near/3 fluid*):ti,ab
#11.	(euvol*emi* or normovol*emi*):ti,ab
#12.	insensible loss*:ti,ab
#13.	hyponatr*emi*:ti,ab
#14.	mesh descriptor: [hemoglobins] explode all trees
#15.	h*emoglobin*:ti,ab
#16.	((red blood cell* or rbc or prbc or red cell* or blood or packed cell* or erythrocyte*or fluid* or volum* or plasma*) near/5 (therap* or transfus* or replac* or resuscita* or substitut* or restor* or deficien* or replenish*)):ti,ab
#17.	mesh descriptor: [plasma] explode all trees
#18.	((ffp or frozen or thawed or tp or fresh) near/3 plasma):ti,ab
#19.	((lyophili?ed or freeze-dried or liquid or "not frozen" or "never frozen") near/3 plasma):ti,ab
#20.	(fdsp or fdp or lqp or lhp):ti,ab
#21.	MeSH descriptor: [freeze drying] explode all trees
#22.	((platelet* or thrombocyte*) near/3 (transfus* or prophyla* or therap* or infus* or administ*)):ti,ab
#23.	MeSH descriptor: [blood platelets] explode all trees
#24.	{or #2-#23}

#25.	#1 and #24

G.4.6 Antimicrobials

Searches for the following two questions were run as one search:

- What are the most clinically and cost effective timings of IV or IM empiric antimicrobial treatments in patients with (a) septic shock, (b) severe sepsis without shock or (c) sepsis?
- What is the most clinically and cost effective IV or IM empiric antimicrobial treatment in patients with sepsis?

Medline search terms

1.	Standard sepsis population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	*anti-infective agents/
6.	exp anti-bacterial agents/
7.	((antiinfect* or anti infect* or anti-infect*) adj3 (agent* or therap* or treatment*)).ti,ab.
8.	((anti-mycobacterial* or antimycobacterial* or anti-mycobacterial*) adj3 (agent* or therap* or treatment*)).ti,ab.
9.	(microbicid* or bacteriocid* or bactericid*).ti,ab.
10.	((antibacterial* or anti bacterial* or anti-bacterial* or bacteriocidal or anti-microbial* or antimicrobial*) adj3 (agent* or therap* or treatment*)).ti,ab.
11.	(antibiotic* or anti-biotic* or anti biotic*).ti,ab.
12.	exp *beta-lactams/
13.	(co-amoxiclav or amoxicillin-clavulanic or piperacillin or tazobactam or tazocin or piptazobatam or ampicillin or sulbactam).ti,ab.
14.	(benzylpenicillin or flucloxacillin or amoxicillin).ti,ab.
15.	(cephalosporin* or cefuroxime or cefotaxime or ceftriaxone or ceftazidime or ceftaroline or ceftobiprole or cefipime).ti,ab.
16.	aztreonam.ti,ab.
17.	(carbapenem* or imipenem or meropenem or ertapenem).ti,ab.
18.	aminoglycosides/ or gentamicins/
19.	amikacin/
20.	tobramycin/
21.	(gentamicin or amikacin or tobramycin).ti,ab.
22.	ciprofloxacin/ or levofloxacin/
23.	(ciprofloxacin or levofloxacin).ti,ab.
24.	teicoplanin/ or vancomycin/
25.	(vancomycin or teicoplanin).ti,ab.
26.	daptomycin/
27.	daptomycin.ti,ab.
28.	clindamycin/
29.	tigecycline.ti,ab.
30.	rifampin/
31.	rifampicin.ti,ab.

32.	chloramphenicol/
33.	chloramphenicol.ti,ab.
34.	co-trimoxazole.ti,ab.
35.	colistin/
36.	colistin.ti,ab.
37.	metronidazole/
38.	metronidazole.ti,ab.
39.	exp erythromycin/
40.	(clar#thromycin or clindamycin or linezolid).ti,ab.
41.	(azithromycin or erythromycin).ti,ab.
42.	doxycycline/
43.	doxycycline.ti,ab.
44.	or/5-43
45.	time factors/
46.	((early or earlier or time or timing or late or later or delay*) adj4 (initiat* or start* or treat* or therap* or administ* or prescri* or antibiotic*)).ti,ab.
47.	45 or 46
48.	Study filters RCT [G.3.2] or SR [G.3.3] or OBS [G.3.7]
49.	4 and 44 and 47 and 48

Embase search terms

1.	Standard sepsis population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	*antiinfective agent/
6.	((antiinfect* or anti infect* or anti-infect*) adj3 (agent* or therap* or treatment*)).ti,ab.
7.	((anti-mycobacterial* or antimycobacterial* or anti-mycobacterial*) adj3 (agent* or therap* or treatment*)).ti,ab.
8.	(microbicid* or bacteriocid* or bactericid*).ti,ab.
9.	((antibacterial* or anti bacterial* or anti-bacterial* or bacteriocidal or anti-microbial* or antimicrobial*) adj3 (agent* or therap* or treatment*)).ti,ab.
10.	(antibiotic* or anti-biotic* or anti biotic*).ti,ab.
11.	exp *beta lactam antibiotic/
12.	exp *beta lactamase inhibitor/
13.	exp *penicillin derivative/
14.	exp *cephalosporin derivative/
15.	*aztreonam/
16.	exp *aminoglycoside antibiotic agent/
17.	exp *quinoline derived antiinfective agent/
18.	exp *polypeptide antibiotic agent/
19.	*rifampicin/
20.	*chloramphenicol/
21.	*cotrimoxazole/
22.	*linezolid/

23.	exp *macrolide/
24.	exp *tetracycline derivative/
25.	(co-amoxiclav or amoxicillin-clavulanic or piperacillin or tazobactam or tazocin or piptazobatam or ampicillin or sulbactam).ti,ab.
26.	(benzylpenicillin or flucloxacillin or amoxicillin).ti,ab.
27.	(cephalosporin* or cefuroxime or cefotaxime or ceftriaxone or ceftazidime or ceftaroline or ceftobiprole or cefipime).ti,ab.
28.	aztreonam.ti,ab.
29.	(carbapenem* or imipenem or meropenem or ertapenem).ti,ab.
30.	(gentamicin or amikacin or tobramycin).ti,ab.
31.	(ciprofloxacin or levofloxacin).ti,ab.
32.	(vancomycin or teicoplanin).ti,ab.
33.	daptomycin.ti,ab.
34.	tigecycline.ti,ab.
35.	rifampicin.ti,ab.
36.	chloramphenicol.ti,ab.
37.	co-trimoxazole.ti,ab.
38.	colistin.ti,ab.
39.	metronidazole.ti,ab.
40.	(clar#thromycin or clindamycin or linezolid).ti,ab.
41.	(azithromycin or erythromycin).ti,ab.
42.	doxycycline.ti,ab.
43.	or/5-42
44.	*time/
45.	therapy delay/
46.	((prompt or hour* or rapid or within or early or earlier or late* or time* or late or later or delay*) adj8 (initiat* or start* or treat* or therap* or administ* or prescri* or antibiotic*)).ti,ab.
47.	or/44-46
48.	Study filters RCT [G.3.2] or SR [G.3.3] or OBS [G.3.7]
49.	4 and 43 and 47 and 48

Cochrane search terms

#1.	Standard sepsis population [G.2.1]
#2.	MeSH descriptor: [anti-infective agents] explode all trees
#3.	((antiinfect* or anti infect* or anti-infect*) near/3 (agent* or therap* or treatment*)):ti,ab
#4.	((anti-mycobacterial* or antimycobacterial* or anti-mycobacterial*) near/3 (agent* or therap* or treatment*)):ti,ab
#5.	(microbicid* or bacteriocid* or bactericid*):ti,ab
#6.	((antibacterial* or anti bacterial* or anti-bacterial* or bacteriocidal or anti-microbial* or antimicrobial*) near/3 (agent* or therap* or treatment*)):ti,ab
#7.	(antibiotic* or anti-biotic* or anti biotic*):ti,ab
#8.	MeSH descriptor: [beta-lactams] explode all trees
#9.	(co-amoxiclav or amoxicillin-clavulanic or piperacillin or tazobactam or tazocin or piptazobatam or ampicillin or sulbactam):ti,ab
#10.	(benzylpenicillin or flucloxacillin or amoxicillin):ti,ab

#11.	(cephalosporin* or cefuroxime or cefotaxime or ceftriaxone or ceftazidime or ceftaroline or ceftobiprole or cefipime):ti,ab
#12.	aztreonam:ti,ab
#13.	(carbapenem* or imipenem or meropenem or ertapenem):ti,ab
#14.	MeSH descriptor: [aminoglycosides] explode all trees
#15.	(gentamicin or amikacin or tobramycin):ti,ab
#16.	MeSH descriptor: [fluoroquinolones] explode all trees
#17.	(ciprofloxacin or levofloxacin):ti,ab
#18.	MeSH descriptor: [glycopeptides] explode all trees
#19.	(vancomycin or teicoplanin):ti,ab
#20.	MeSH descriptor: [daptomycin] explode all trees
#21.	daptomycin:ti,ab
#22.	MeSH descriptor: [clindamycin] explode all trees
#23.	tigecycline:ti,ab
#24.	MeSH descriptor: [rifampin] explode all trees
#25.	rifampicin:ti,ab
#26.	MeSH descriptor: [chloramphenicol] explode all trees
#27.	chloramphenicol:ti,ab
#28.	MeSH descriptor: [trimethoprim-sulfamethoxazole combination] explode all trees
#29.	co-trimoxazole:ti,ab
#30.	MeSH descriptor: [colistin] explode all trees
#31.	colistin:ti,ab
#32.	MeSH descriptor: [metronidazole] explode all trees
#33.	metronidazole:ti,ab
#34.	MeSH descriptor: [erythromycin] explode all trees
#35.	MeSH descriptor: [doxycycline] explode all trees
#36.	(clar?thromycin or clindamycin or linezolid):ti,ab
#37.	(azithromycin or erythromycin):ti,ab
#38.	doxycycline:ti,ab
#39.	{or #2-#38}
#40.	[mh "time factors"]
#41.	((prompt or hour* or rapid or within or early or earlier or late* or time* or late or later or delay*) near/8 (initiat* or start* or treat* or therap* or administ* or prescri* or antibiotic*)):ti,ab
#42.	#40 and #41
#43.	#1 and #39 and #42

G.4.7 Acid-base pH

- Is acid-base balance (that is, the use of bicarbonate) clinically and cost effective in people with sepsis?

Medline search terms

1.	Standard sepsis population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2

4.	Limit 3 to English language
5.	acid-base equilibrium/ or acid-base imbalance/
6.	(acid base or acid-base or ph).ti,ab.
7.	exp bicarbonates/
8.	bicarbonate*.ti,ab.
9.	anion gap*.ti,ab.
10.	or/5-9
11.	Study filters RCT [G.3.2] or SR [G.3.3] or OBS [G.3.7]
12.	4 and 10 and 11

Embase search terms

1.	Standard sepsis population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	*ph/
6.	*bicarbonate blood level/ or exp *bicarbonate/
7.	(acid base or acid-base or ph).ti,ab.
8.	bicarbonate*.ti,ab.
9.	anion gap*.ti,ab.
10.	or/5-9
11.	Study filters RCT [G.3.2] or SR [G.3.3] or OBS [G.3.7]
12.	4 and 10 and 11

Cochrane search terms

#1.	Standard sepsis population [G.2.1]
#2.	MeSH descriptor: [acid-base equilibrium] explode all trees
#3.	MeSH descriptor: [acid-base imbalance] explode all trees
#4.	MeSH descriptor: [bicarbonates] explode all trees
#5.	(acid base or acid-base or ph):ti,ab
#6.	anion gap*:ti,ab
#7.	bicarbonate*:ti,ab
#8.	{or #2-#7}
#9.	#1 and #8

G.4.8 Oxygen

- Is the use of supplemental oxygen clinically and cost effective in patients with sepsis?

Medline search terms

1.	Standard sepsis population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	oxygen inhalation therapy/
6.	oxygen/

7.	oxygen.ti,ab.
8.	noninvasive ventilation/
9.	oximetry/
10.	hyperoxia/
11.	exp oxygen consumption/
12.	((non invasive or noninvasive) adj ventilat*).ti,ab.
13.	(oximetry or hyperoxia).ti,ab.
14.	or/5-13
15.	Study filters RCT [G.3.2] or SR [G.3.3] or OBS [G.3.7]
16.	4 and 14 and 15

Embase search terms

1.	Standard sepsis population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	*oxygen therapy/
6.	*oxygen/
7.	oxygen.ti,ab.
8.	noninvasive ventilation/
9.	oximetry/
10.	hyperoxia/
11.	exp oxygen consumption/
12.	((non invasive or noninvasive) adj ventilat*).ti,ab.
13.	(oximetry or hyperoxia).ti,ab.
14.	or/5-13
15.	Study filters RCT [G.3.2] or SR [G.3.3] or OBS [G.3.7]
16.	4 and 14 and 15

Cochrane search terms

#1.	Standard sepsis population [G.2.1]
#2.	MeSH descriptor: [oxygen inhalation therapy] explode all trees
#3.	MeSH descriptor: [oxygen] explode all trees
#4.	oxygen:ti,ab
#5.	MeSH descriptor: [noninvasive ventilation] explode all trees
#6.	MeSH descriptor: [oximetry] explode all trees
#7.	MeSH descriptor: [hyperoxia] explode all trees
#8.	MeSH descriptor: [oxygen consumption] explode all trees
#9.	(non invasive or noninvasive) near/1 ventilat*:ti,ab
#10.	(oximetry or hyperoxia):ti,ab
#11.	{or #2-#10}
#12.	#1 and #11

G.4.9 Inotropes

Searches for the following two questions were run as one search:

- What is the most clinical and cost effective inotropic agent and vasopressor for early management of people with severe sepsis?
- What are the most clinically and cost effective timings of inotropic agents and vasopressors in patients with sepsis?

Medline search terms

1.	Standard sepsis population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	inotrope*.ti,ab.
6.	inotropic*.ti,ab.
7.	milrinone/
8.	enoximone/
9.	dobutamine/
10.	exp dopamine/
11.	soproterenol/
12.	(milrinone or primacor).ti,ab.
13.	(enoximone or perfan).ti,ab.
14.	(dobutamine or dopamine).ti,ab.
15.	(dopexamine or isoprenaline or dopacard or dobutrex or isuprel).ti,ab.
16.	(vasoactive agent* or vasopressor* or vasopressin*).ti,ab.
17.	(adrenalin or epinephrine).ti,ab.
18.	epinephrine/
19.	metaraminol/
20.	metaraminol.ti,ab.
21.	norepinephrine/
22.	(noradrenalin* or norepinrphrine).ti,ab.
23.	or/5-22
24.	Study filters RCT [G.3.2] or SR [G.3.3] or OBS [G.3.7]
25.	4 and 23 and 24

Embase search terms

1.	Standard sepsis population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	inotrope*.ti,ab.
6.	inotropic*.ti,ab.
7.	milrinone/
8.	enoximone/
9.	dobutamine/

10.	exp dopamine/
11.	(milrinone or primacor).ti,ab.
12.	(enoximone or perfan).ti,ab.
13.	(dobutamine or dopamine).ti,ab.
14.	(dopexamine or isoprenaline or dopacard or dobutrex or isuprel).ti,ab.
15.	(vasoactive agent* or vasopressor* or vasopressin*).ti,ab.
16.	(adrenalin or epinephrine).ti,ab.
17.	adrenalin/
18.	isoprenaline/
19.	noradrenalin/
20.	metaraminol/
21.	metaraminol.ti,ab.
22.	(noradrenalin* or norepinephrine).ti,ab.
23.	or/5-22
24.	Study filters RCT [G.3.2] or SR [G.3.3] or OBS [G.3.7]
25.	4 and 23 and 24

Cochrane search terms

#1.	Standard sepsis population [G.2.1]
#2.	inotrope*:ti,ab
#3.	inotropic*:ti,ab
#4.	MeSH descriptor: [milrinone] this term only
#5.	MeSH descriptor: [enoximone] this term only
#6.	MeSH descriptor: [dobutamine] this term only
#7.	MeSH descriptor: [dopamine] explode all trees
#8.	(milrinone or primacor):ti,ab
#9.	(enoximone or perfan):ti,ab
#10.	(dobutamine or dopamine):ti,ab
#11.	(dopexamine or isoprenaline or dopacard or dobutrex or isuprel):ti,ab
#12.	(vasoactive agent* or vasopressor* or vasopressin*):ti,ab
#13.	(adrenalin or epinephrine):ti,ab
#14.	MeSH descriptor: [epinephrine] this term only
#15.	MeSH descriptor: [isoproterenol] this term only
#16.	MeSH descriptor: [metaraminol] this term only
#17.	metaraminol:ti,ab
#18.	MeSH descriptor: [norepinephrine] this term only
#19.	(noradrenalin* or norepinrphrine):ti,ab
#20.	{or #2-#19}
#21.	#1 and #20

G.4.10 Escalation of care

Searches for the following two questions were run as one search:

- When is the most appropriate time for care of people with sepsis to be directed to (a) a senior healthcare professional, and (b) critical care providers?

Medline search terms

1.	Standard sepsis population [G.2.1]
2.	Standard bacterial meningitis population [G.2.2]
3.	1 or 2
4.	Excluded study designs and publication types [G.3.1]
5.	3 not 4
6.	Limit 5 to English language
7.	"delivery of health care"/
8.	exp critical care/
9.	((intensive or critical) adj2 care).ti,ab.
10.	(intensivist* or consultant* or specialist* or senior*1 or junior*1 or sho or registrar* or spr or house officer* or houseofficer* or housestaff* or physician* or intern*1 or internship or resident*1 or fellow*1 or foundation doctor or nurs*).ti,ab.
11.	or/7-10
12.	*time factors/
13.	(time or times or timing or referral or refer or refers or referring).ti,ab.
14.	((early or earlie* or late or later or schedul* or hour* or rapid* or fast* or slow* or delay* or immediate* or escalat* or manage* or managing or hospital) adj2 care).ti,ab.
15.	or/12-14
16.	Study filters RCT [G.3.2] or SR [G.3.3] or OBS [G.3.7]
17.	6 and 11 and 15 and 16
18.	limit 17 to yr="1999 -Current"

Embase search terms

1.	Standard sepsis population [G.2.1]
2.	Standard bacterial meningitis population [G.2.2]
3.	1 or 2
4.	Excluded study designs and publication types [G.3.1]
5.	3 not 4
6.	Limit 5 to English language
7.	*health care delivery/
8.	*exp intensive care/
9.	((intensive or critical) adj2 care).ti,ab.
10.	(intensivist* or consultant* or specialist* or senior*1 or junior*1 or sho or registrar* or spr or house officer* or houseofficer* or housestaff* or physician* or intern*1 or internship or resident*1 or fellow*1 or foundation doctor or nurs*).ti,ab.
11.	or/7-10
12.	*time factors/
13.	(time or times or timing or referral or refer or refers or referring).ti,ab.
14.	((early or earlie* or late or later or schedul* or hour* or rapid* or fast* or slow* or delay* or immediate* or escalat* or manage* or managing or hospital) adj2 care).ti,ab.
15.	or/12-14
16.	Study filters RCT [G.3.2] or SR [G.3.3] or OBS [G.3.7]
17.	6 and 11 and 15 and 16

18.	limit 17 to yr="1999 -Current"

Cochrane search terms

#1.	Standard sepsis population [G.2.1]
#2.	Standard bacterial meningitis population [G.2.2]
#3.	#1 or #2
#4.	MeSH descriptor: [delivery of health care] this term only
#5.	MeSH descriptor: [critical care] explode all trees
#6.	((intensive or critical) near/2 care):ti,ab
#7.	(intensivist* or consultant* or specialist* or senior*1 or junior*1 or SHO or registrar* or SPR or house officer* or houseofficer* or housestaff* or physician* or intern*1 or internship or resident*1 or fellow*1 or foundation doctor or nurs*):ti,ab
#8.	{or #4-#7}
#9.	MeSH descriptor: [time factors] explode all trees
#10.	(time or times or timing or referral or refer or refers or referring):ti,ab
#11.	((early or earlie* or late or later or schedul* or hour* or rapid* or fast* or slow* or delay* or immediate* or escalat* or manage* or managing or hospital) near/2 care):ti,ab
#12.	{or #9-#11}
#13.	#3 and #8 and #12 Publication Year from 1999 to 2015

G.4.11 Monitoring

- In people with sepsis or severe sepsis, what is the clinical and cost effectiveness of scoring systems, and specified blood markers in monitoring response to treatment?

Medline search terms

1.	(early warn* adj4 (system* or scor* or criteri* or tool*)).ti,ab.
2.	(pews or mews).ti,ab.
3.	1 or 2
4.	Excluded study designs and publication types [G.3.1]
5.	3 not 4
6.	Limit 5 to English language

Embase search terms

1.	(early warn* adj4 (system* or scor* or criteri* or tool*)).ti,ab.
2.	(pews or mews).ti,ab.
3.	1 or 2
4.	Excluded study designs and publication types [G.3.1]
5.	3 not 4
6.	Limit 5 to English language

Cochrane search terms

#1.	(early warn* near/4 (system* or scor* or criteri* or tool*)):ti,ab
#2.	(pews or mews):ti,ab
#3.	#1 or #2

G.4.12 Information support

Searches for the following four questions were run as one search:

- What information, education and support would be useful for people assessed for possible sepsis, but discharged from medical care
- What information, education and support would be useful for people at high risk of sepsis
- What information, education and support would be useful for people who have sepsis or severe sepsis, families and carers
- What information, education and support would be useful for people who survived episodes of severe sepsis

Medline search terms

1.	Standard sepsis population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	patient education as topic/
6.	patient acceptance of health care/
7.	patient satisfaction/
8.	patient education handout/
9.	consumer health information/
10.	(information adj (need* or requirement* or support*)).ti,ab.
11.	(discharg* adj2 (information* or advice)).ti,ab.
12.	((patient* or carer* or famil* or parent*1 or father*1 or mother*1 or caregiver* or next of kin) adj3 (inform* or educat* or support* or advice* or advise*)).ti,ab.
13.	((patient* or carer* or famil* or parent*1 or father*1 or mother*1 or caregiver* or next of kin) adj2 (pamphlet* or leaflet* or booklet* or manual* or brochure* or publication* or handout* or website* or web site* or web page* or webpage* or video* or dvd* or education or educate or educating or literature or information or internet or computer* or program* or interactive or email* or e-mail* or wireless or bluetooth or telephone or phone or sms or text*)).ti,ab.
14.	or/5-13
15.	4 and 14
16.	limit 15 to yr="1990 -Current"

Embase search terms

1.	Standard sepsis population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	patient education/
6.	patient attitude/
7.	patient satisfaction/
8.	consumer health information/
9.	(information adj (need* or requirement* or support*)).ti,ab.
10.	(discharg* adj2 (information* or advice)).ti,ab.
11.	((patient* or carer* or famil* or parent*1 or father*1 or mother*1 or caregiver* or next of kin) adj3 (inform* or educat* or support* or advice* or advise*)).ti,ab.

12.	((patient* or carer* or famil* or parent*1 or father*1 or mother*1 or caregiver* or next of kin) adj2 (pamphlet* or leaflet* or booklet* or manual* or brochure* or publication* or handout* or website* or web site* or web page* or webpage* or video* or dvd* or education or educate or educating or literature or information or internet or computer* or program* or interactive or email* or e-mail* or wireless or bluetooth or telephone or phone or sms or text*)).ti,ab.
13.	or/5-12
14.	4 and 13
15.	limit 14 to yr="1990 -Current"

Cochrane search terms

#1.	Standard sepsis population [G.2.1]
#2.	[mh "patient education as topic"]
#3.	[mh "patient acceptance of health care"]
#4.	[mh "patient satisfaction"]
#5.	[mh "patient education handout"]
#6.	[mh "consumer health information"]
#7.	(information near/1 (need* or requirement* or support*)):ti,ab
#8.	(discharg* near/2 (information* or advice)):ti,ab
#9.	((patient* or carer* or famil* or parent or parents or father* or mother* or caregiver* or "next of kin") near/3 (inform* or educat* or support* or advice* or advise*)):ti,ab
#10.	((patient* or carer* or famil* or parent or parents or father* or mother* or caregiver* or "next of kin") near/2 (pamphlet* or leaflet* or booklet* or manual* or brochure* or publication* or handout* or website* or web site* or web page* or webpage* or video* or dvd* or education or educate or educating or literature or information or internet or computer* or program* or interactive or email* or e-mail* or wireless or bluetooth or telephone or phone or sms or text*)):ti,ab
#11.	{or #2-#10}
#12.	#1 and #11 Publication Year from 1990 to 2015

CINAHL search terms

S1.	Standard sepsis population [G.2.1]
S2.	Excluded study designs and publication types [G.3.1]
S3.	1 not 2
S4.	Limit 3 to English language
S5.	(MH "patient satisfaction")
S6.	(MH "consumer health information")
S7.	(MH "patient discharge education")
S8.	(MH "patient education")
S9.	(discharg* n2 (information* or advice))
S10.	(information n1 (need* or requirement* or support*))
S11.	((patient* or carer* or famil* or parent or parents or father* or mother* or caregiver* or next of kin) n3 (inform* or educat* or support* or advice* or advise*))
S12.	((patient* or carer* or famil* or parent or parents or father* or mother* or caregiver* or next of kin) n2 (pamphlet* or leaflet* or booklet* or manual* or brochure* or publication* or handout* or website* or web site* or web page* or webpage* or video* or dvd* or education or educate or educating or literature or information or internet or computer* or program* or interactive or email* or e-mail* or wireless or bluetooth or telephone or phone or sms or text*))

S13.	S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12
S14.	S4 and S13 Limiters - Published Date: 19900101-20151231; Exclude MEDLINE records

PsycINFO (Ovid) search terms

1.	Standard sepsis population [G.2.1]
2.	limit 1 to (English language)
3.	client education/
4.	client attitudes/
5.	client satisfaction/
6.	(information adj (need* or requirement* or support*)).ti,ab.
7.	(discharg* adj2 (information* or advice)).ti,ab.
8.	((patient* or carer* or famil* or parent*1 or father*1 or mother*1 or caregiver* or next of kin) adj3 (inform* or educat* or support* or advice* or advise*)).ti,ab.
9.	((patient* or carer* or famil* or parent*1 or father*1 or mother*1 or caregiver* or next of kin) adj2 (pamphlet* or leaflet* or booklet* or manual* or brochure* or publication* or handout* or website* or web site* or web page* or webpage* or video* or dvd* or education or educate or educating or literature or information or internet or computer* or program* or interactive or email* or e-mail* or wireless or bluetooth or telephone or phone or SMS or text*)).ti,ab.
10.	or/3-9
11.	2 and 10
12.	limit 11 to yr="1990 -Current"

PsycINFO (ProQUEST) search terms

1.	Standard sepsis population [G.2.1]
2.	((su.exact("client education") or su.exact("client attitudes") or su.exact("client satisfaction") or (ti,ab(information near (need* or requirement* or support*)) or ti,ab(discharg* near/2 (information* or advice)))) or ti,ab((patient* or carer* or famil* or parent* or father* or mother* or caregiver* or "next of kin") near/3 (inform* or educat* or support* or advice* or advise*)) or ti,ab((patient* or carer* or famil* or parent* or father* or mother* or caregiver* or "next of kin") near/2 (pamphlet* or leaflet* or booklet* or manual* or brochure* or publication* or handout* or website* or "web site*" or "web page*" or webpage* or video* or dvd* or education or educate or educating or literature or information or internet or computer* or program* or interactive or email* or e-mail* or wireless or bluetooth or telephone or phone or sms or text*))
3.	1 and 2 additional limits - Date: From 1990 to 2015; Language: English

G.4.13 Educational programmes/Identification protocols

- What education and training programmes are available, effective and cost effective for the early recognition, diagnosis and management of sepsis and severe sepsis?

Medline search terms

1.	Standard sepsis population [G.2.1]
2.	Standard bacterial meningitis population [G.2.2]
3.	1 or 2
4.	Excluded study designs and publication types [G.3.1]
5.	3 not 4
6.	Limit 5 to English language

7.	exp health personnel/
8.	(clinician* or doctor* or physician* or nurse or nurses* or specialist* or registrar* or gp or gps or general practitioner* or hca or hcas or health care assistant* or consultant* or trainee* or team or teams or personnel or staff or professional* or healthcare).ti,ab.
9.	exp primary health care/
10.	exp physician's practice patterns/
11.	exp family practice/
12.	exp physicians, primary care/
13.	exp general practice/
14.	exp physicians, family/
15.	exp general practitioners/
16.	((primary or communit*) adj5 care).ti,ab.
17.	(family practi* or family doctor* or family physician* or gp* or general practi*).ti,ab.
18.	exp community health services/ or exp community health centers/
19.	exp ambulatory care/
20.	casualty*.tw.
21.	paramedic*.ti,ab.
22.	((ambulance or ambulatory) adj2 (care or caring)).ti,ab.
23.	emergency medical services/
24.	"pre hospital*".ti,ab.
25.	or/7-24
26.	early diagnosis/
27.	education/
28.	exp education, professional/
29.	exp inservice training/
30.	((program* or system or systems) adj4 (sepsis or septic* or (blood adj2 (pathogen* or poison*)) or systemic inflammatory response syndrome' or sirs or pyaemi* or pyemi* or pyohemi* or bacter?emi* or fung?emi* or parasit?emi* or vir?emi*)).ti,ab.
31.	(manag* and (sepsis or septic* or (blood adj2 (pathogen* or poison*)) or systemic inflammatory response syndrome' or sirs or pyaemi* or pyemi* or pyohemi* or bacter?emi* or fung?emi* or parasit?emi* or vir?emi*)).ti.
32.	(manag* adj3 (sepsis or septic* or (blood adj2 (pathogen* or poison*)) or systemic inflammatory response syndrome' or sirs or pyaemi* or pyemi* or pyohemi* or bacter?emi* or fung?emi* or parasit?emi* or vir?emi*)).ti,ab.
33.	(awareness or identif* or recogni* or detect* or alert* or warn*).ti.
34.	((awareness or identif* or recogni* or detect* or alert* or warn*) adj3 (sepsis or septic* or (blood adj2 (pathogen* or poison*)) or systemic inflammatory response syndrome' or sirs or pyaemi* or pyemi* or pyohemi* or bacter?emi* or fung?emi* or parasit?emi* or vir?emi*)).ab.
35.	(education* or train* or program* or learn*).ti.
36.	((program* or system or systems) adj4 (meningitis or meningitides or meningococc* or meningococcemia or pneumoccoc* or streptococc*)).ti,ab.
37.	manage*.ti.
38.	(meningitis or meningitides or meningococc* or meningococcemia or pneumoccoc* or streptococc*).ti.
39.	37 and 38
40.	(manag* adj3 (meningitis or meningitides or meningococc* or meningococcemia or pneumoccoc* or streptococc*)).ti,ab.
41.	((awareness or identif* or recogni* or detect* or alert* or warn*) adj3 (meningitis or

	meningitides or meningococc* or meningococcemia or pneumoccoc* or streptococc*)).ab.
42.	or/26-36,39-41
43.	6 and 25 and 42

Embase search terms

1.	Standard sepsis population [G.2.1]
2.	Standard bacterial meningitis population [G.2.2]
3.	1 or 2
4.	Excluded study designs and publication types [G.3.1]
5.	3 not 4
6.	Limit 5 to English language
7.	exp health personnel/
8.	(clinician* or doctor* or physician* or nurse or nurses* or specialist* or registrar* or gp or gps or general practitioner* or hca or hcas or health care assistant* or consultant* or trainee* or team or teams or personnel or staff or professional* or healthcare).ti,ab.
9.	exp primary health care/
10.	exp professional practice/
11.	exp clinical practice/
12.	exp general practice/
13.	general practitioner/
14.	((primary or communit*) adj5 care).ti,ab.
15.	exp ambulatory care/
16.	exp community care/
17.	health center/
18.	paramedic*.ti,ab.
19.	((ambulance or ambulatory) adj2 (care or caring)).ti,ab.
20.	emergency health service/
21.	"pre hospital*".ti,ab.
22.	or/7-21
23.	early diagnosis/
24.	education/
25.	exp education, professional/
26.	exp inservice training/
27.	((program* or system or systems) adj4 (sepsis or septic* or (blood adj2 (pathogen* or poison*)) or systemic inflammatory response syndrome' or sirs or pyaemi* or pyemi* or pyohemi* or bacter?emi* or fung?emi* or parasit?emi* or vir?emi*)).ti,ab.
28.	(manag* and (sepsis or septic* or (blood adj2 (pathogen* or poison*)) or systemic inflammatory response syndrome' or sirs or pyaemi* or pyemi* or pyohemi* or bacter?emi* or fung?emi* or parasit?emi* or vir?emi*)).ti.
29.	(manag* adj3 (sepsis or septic* or (blood adj2 (pathogen* or poison*)) or systemic inflammatory response syndrome' or sirs or pyaemi* or pyemi* or pyohemi* or bacter?emi* or fung?emi* or parasit?emi* or vir?emi*)).ti,ab.
30.	(awareness or identif* or recogni* or detect* or alert* or warn*).ti.
31.	((awareness or identif* or recogni* or detect* or alert* or warn*) adj3 (sepsis or septic* or (blood adj2 (pathogen* or poison*)) or systemic inflammatory response syndrome' or sirs or pyaemi* or pyemi* or pyohemi* or bacter?emi* or fung?emi* or parasit?emi* or vir?emi*)).ab.

32.	(education* or train* or program* or learn*).ti.
33.	((program* or system or systems) adj4 (meningitis or meningitides or meningococc* or meningococcemia or pneumoccoc* or streptococc*)).ti,ab.
34.	manage*.ti.
35.	(meningitis or meningitides or meningococc* or meningococcemia or pneumoccoc* or streptococc*).ti.
36.	34 and 35
37.	(manag* adj3 (meningitis or meningitides or meningococc* or meningococcemia or pneumoccoc* or streptococc*)).ti,ab.
38.	((awareness or identif* or recogni* or detect* or alert* or warn*) adj3 (meningitis or meningitides or meningococc* or meningococcemia or pneumoccoc* or streptococc*)).ab.
39.	or/23-33,36-38
40.	6 and 22 and 39

Cochrane search terms

#1.	Standard sepsis population [G.2.1]
#2.	Standard bacterial meningitis population [G.2.2]
#3.	#1 or #2
#4.	MeSH descriptor: [health personnel] explode all trees
#5.	(clinician* or doctor* or physician* or nurse or nurses* or specialist* or registrar* or gp or gps or general practitioner* or hca or hcas or health care assistant* or consultant* or trainee* or team or teams or personnel or staff or professional* or healthcare):ti,ab
#6.	MeSH descriptor: [primary health care] explode all trees
#7.	MeSH descriptor: [physician's practice patterns] explode all trees
#8.	MeSH descriptor: [family practice] explode all trees
#9.	MeSH descriptor: [physicians, primary care] explode all trees
#10.	MeSH descriptor: [general practice] explode all trees
#11.	MeSH descriptor: [general practitioners] explode all trees
#12.	((primary or communit*) near/5 care):ti,ab
#13.	(family practi* or family doctor* or family physician* or gp* or general practi*):ti,ab
#14.	MeSH descriptor: [community health services] explode all trees
#15.	MeSH descriptor: [community health centers] explode all trees
#16.	MeSH descriptor: [ambulatory care] explode all trees
#17.	casualty*:ti,ab,kw
#18.	paramedic*:ti,ab
#19.	((ambulance or ambulatory) near/2 (care or caring)):ti,ab
#20.	MeSH descriptor: [emergency medical services] this term only
#21.	pre hospital*:ti,ab
#22.	{or #4-#21}
#23.	MeSH descriptor: [early diagnosis] this term only
#24.	MeSH descriptor: [education] this term only
#25.	MeSH descriptor: [education, professional] explode all trees
#26.	MeSH descriptor: [inservice training] explode all trees
#27.	((program* or system or systems) near/4 (sepsis or septic* or (blood near/2 (pathogen* or poison*)) or systemic inflammatory response syndrome' or sirs or pyaemi* or pyemi* or pyohemi* or bacter?emi* or fung?emi* or parasit?emi* or vir?emi*)):ti,ab

#28.	(manag* and (sepsis or septic* or (blood near/2 (pathogen* or poison*)) or systemic inflammatory response syndrome' or sirs or pyaemi* or pyemi* or pyohemi* or bacter?emi* or fung?emi* or parasit?emi* or vir?emi*)):ti
#29.	(manag* near/j3 (sepsis or septic* or (blood near/2 (pathogen* or poison*)) or systemic inflammatory response syndrome' or sirs or pyaemi* or pyemi* or pyohemi* or bacter?emi* or fung?emi* or parasit?emi* or vir?emi*)):ti,ab
#30.	(awareness or identif* or recogni* or detect* or alert* or warn*):ti
#31.	((awareness or identif* or recogni* or detect* or alert* or warn*) near/3 (sepsis or septic* or (blood near/2 (pathogen* or poison*)) or systemic inflammatory response syndrome' or sirs or pyaemi* or pyemi* or pyohemi* or bacter?emi* or fung?emi* or parasit?emi* or vir?emi*)):ab
#32.	(education* or train* or program* or learn*):ti
#33.	((program* or system or systems) near/4 (meningitis or meningitides or meningococc* or meningococcemia or pneumoccoc* or streptococc*)) .ti,ab
#34.	manage*:ti
#35.	(meningitis or meningitides or meningococc* or meningococcemia or pneumoccoc* or streptococc*):ti
#36.	#34 and #35
#37.	(manag* near/3 (meningitis or meningitides or meningococc* or meningococcemia or pneumoccoc* or streptococc*)):ti,ab
#38.	((awareness or identif* or recogni* or detect* or alert* or warn*) near/3 (meningitis or meningitides or meningococc* or meningococcemia or pneumoccoc* or streptococc*)):ab
#39.	{or #23-#33,#36-#38}
#40.	#3 and #22 and #39

G.5 Health economics search

G.5.1 Health economic (HE) reviews

Economic searches were conducted in Medline, Embase, CRD and HEED.

Medline & Embase search terms

1.	1. Standard sepsis population [G.2.1]
2.	2. Standard bacterial meningitis population [G.2.2]
3.	3. 1 or 2
4.	4. Excluded study designs and publication types [G.3.1]
5.	5. 3 not 4
6.	6. Limit 5 to English language
7.	7. Study filter HE [G.3.4]
8.	8. 6 and 7
9.	9. limit 8 to yr="2012 -Current"

CRD search terms

#1.	Standard sepsis population [G.2.1]
#2.	Standard bacterial meningitis population [G.2.2]
#3.	(#1 or #2)
#4.	((#3) from 1999 to 2015) in NHSEED
#5.	((#3) from 1999 to 2015) in HTA

HEED search terms

1.	Standard sepsis population [G.2.1]
2.	Standard bacterial meningitis population [G.2.2]
3.	cs=1 or 2 jd=2012-2014

G.5.2 Quality of life (QOL) reviews

Quality of life searches were conducted in Medline and Embase only

Medline & Embase search terms

1.	10.	Standard sepsis population [G.2.1]
2.	11.	Excluded study designs and publication types [G.3.1]
3.	12.	1 not 2
4.	13.	Limit 3 to English language
5.	14.	exp child/ not (exp child/ and (exp adult/ or adolescent/))
6.	15.	exp infant/ not (exp infant/ and (exp adult/ or adolescent/))
7.	16.	5 or 6
8.	17.	4 not 7
9.	18.	Study filter QOL [G.3.5]
10.	19.	8 and 9

G.6 References: Appendix A-G

1 National Institute for Health and Clinical Excellence. The guidelines manual. London: National Institute for Health and Clinical Excellence; 2012. Available from: http://publications.nice.org.uk/the-guidelines-manual-pmg6/