Cochrane Library

Cochrane Database of Systematic Reviews

Automated monitoring for the early detection of sepsis in critically ill patients (Protocol)

Evans DJW, Lewis SR, Kourbeti IS, Alderson P, Smith AF

Evans DJW, Lewis SR, Kourbeti IS, Alderson P, Smith AF.
Automated monitoring for the early detection of sepsis in critically ill patients.
Cochrane Database of Systematic Reviews 2016, Issue 10. Art. No.: CD012404.
DOI: 10.1002/14651858.CD012404.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
BACKGROUND 1
OBJECTIVES 2
METHODS 2
ACKNOWLEDGEMENTS 6
REFERENCES 6
APPENDICES 7
CONTRIBUTIONS OF AUTHORS 8
DECLARATIONS OF INTEREST 8
SOURCES OF SUPPORT 9

[Intervention Protocol]

Automated monitoring for the early detection of sepsis in critically ill patients

David JW Evans[1], Sharon R Lewis[2], Irene S Kourbeti[3], Phil Alderson[4], Andrew F Smith[5]

[1]Lancaster Health Hub, Lancaster University, Lancaster, UK. [2]Patient Safety Research Department, Royal Lancaster Infirmary, Lancaster, UK. [3]Department of Acute and Emergency Medicine, Furness General Hospital, Barrow-in-Furness, UK. [4]National Institute for Health and Care Excellence, Manchester, UK. [5]Department of Anaesthesia, Royal Lancaster Infirmary, Lancaster, UK

Contact address: David JW Evans, Lancaster Health Hub, Lancaster University, Lancaster, UK. d.evans1@lancaster.ac.uk.

Editorial group: Cochrane Anaesthesia, Critical and Emergency Care Group.
Publication status and date: New, published in Issue 10, 2016.

Citation: Evans DJW, Lewis SR, Kourbeti IS, Alderson P, Smith AF. Automated monitoring for the early detection of sepsis in critically ill patients. *Cochrane Database of Systematic Reviews* 2016, Issue 10. Art. No.: CD012404. DOI: 10.1002/14651858.CD012404.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate whether automated systems for the early detection of sepsis can reduce the time to appropriate treatment and improve clinical outcomes in critically ill patients in the ICU.

BACKGROUND

Description of the condition

Sepsis is a clinical syndrome defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection" (Gotts 2016; Singer 2016). The criteria for the diagnosis of sepsis have evolved over time and are generally defined by international consensus groups (ACCP/SCCM 1992; Levy 2003; Singer 2016). If left untreated, sepsis can lead to septic shock (defined as "vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate level greater than 2 mmol/L (> 18 mg/dL) in the absence of hypovolaemia" (Singer 2016); and previously defined as severe sepsis and hypotension that is not reversed by fluid resuscitation (Dellinger 2013)), when mortality can exceed 50% (Gotts 2016). Patients with sepsis often require admission to the intensive care unit (ICU) and the incidence of sepsis in ICU patients initially admitted for other critical illnesses is also high (20% to 70% of ICU patients in Europe, with considerable variance by country) (Vincent 2006). The diagnosis of sepsis is challenging and time consuming, and often requires the combination of information from several sources (e.g. patient history, laboratory data, and physiological data) at regular intervals (Cohen 2015). The complexity of diagnosis combined with the degree of illness results in a significant cost for treating sepsis in the ICU. For example, the cost of treating each patient with sepsis in the ICU was recently estimated as approximately EUR 29,000 in the Netherlands (Koster-Brouwer 2014), or GBP 20,000 in the UK (UK Sepsis Trust 2013).

Description of the intervention

Automated monitoring systems provide a means of monitoring patient data continuously, and can facilitate the assembly of data from unconnected information systems (Hooper 2012). These tools are variously referred to as alert systems, detection systems

and monitoring systems (Makam 2015). In essence, the systems process clinical data - that are routinely collected - to identify sepsis according to predetermined diagnostic thresholds, and include an electronic means of alerting staff. Although the algorithms (i.e. criteria) used to identify sepsis vary between the different automated systems (Buck 2014; Nachimuthu 2012), their key feature is an ability to monitor one or more electronic systems (e.g. patient electronic health records) for potential indicators of sepsis. For example, a system may 'listen' for modified systematic inflammatory response syndrome (SIRS) criteria (Hooper 2012), although SIRS criteria have recently been deemed to have inadequate specificity and sensitivity for the detection of sepsis (Singer 2016). Following detection of potential sepsis, the system should provide an automated notification (e.g. via email, phone message or pager) to the relevant physician or nurse, flagging the requirement for clinical evaluation and potential initiation of therapy (Hooper 2012; Koenig 2011). The use of electronic early-recognition tools has previously been validated in the critical care setting for detection of acute respiratory distress syndrome (ARDS) (Koenig 2011). Potential adverse effects of automated systems might include the failure to detect sepsis and alarm fatigue (i.e. where frequent false alarms cause staff to ignore notification of potential sepsis).

How the intervention might work

Automated detection systems monitor patient data continuously to facilitate the early detection of sepsis in the ICU. The diagnosis of sepsis or septic shock is particularly time-sensitive, as the length of time until initiation of appropriate antimicrobial therapy or fluid resuscitation is a critical determinant of survival in these patients (Dellinger 2013; Kumar 2006; Rivers 2001; Yealy 2014). Therefore, guidelines recommend early fluid resuscitation of the septic patient within six hours of recognition of sepsis, and administration of broad-spectrum antibiotics within one hour of the recognition of septic shock or severe sepsis without septic shock (Dellinger 2013). Automated detection systems offer the possibility of monitoring patients in 'real-time' (Meurer 2009), and can alert the relevant physicians or nurses (e.g. by email or pager) to the need for timely clinical evaluation and potential initiation of treatment.

Why it is important to do this review

Although the rate of mortality from sepsis has improved (Kaukonen 2014; McPherson 2013), national audits indicate that clinical standards relevant to the management of patients with sepsis are not being met, despite ongoing education programmes (CEM 2012). The UK Parliamentary Ombudsman recently published a detailed report that identified common themes in 10 case studies of patients that died following sepsis (Parliamentary Ombudsman 2013). Failings were identified throughout the care pathway, from carrying out a timely initial assessment and identifying the source of infection, to adequate monitoring and timely initiation of treatment (Parliamentary Ombudsman 2013). Automated monitoring systems for the detection of sepsis may facilitate earlier detection and treatment of sepsis in the ICU, potentially increasing adherence to clinical standards and improving patient outcomes.

Additionally, sepsis is the most expensive condition treated in hospitals, accounting for approximately 5% of total hospitalization costs and an overall annual cost of USD 20.3 billion in the USA (Torio 2011), and more than GBP 2.5 billion in the UK (UK Sepsis Trust 2013). Early detection of sepsis via automated systems and subsequent timely intervention may reduce treatment costs and overall resource use (Rivers 2001; Yealy 2014). The UK Sepsis Trust estimates that there are more than 100,000 hospitalizations per year for sepsis, and that achieving 80% delivery of basic standards of care could result in a potential cost saving of GBP 170 million per year, even after allowing for increased survival-related costs (UK Sepsis Trust 2013).

Finally, it is now recognized that sepsis is associated with a significant long-term mortality, morbidity and a reduction in health-related quality of life (Winters 2010), thus reinforcing the importance of early effective treatment from both a patient and resource utilization perspective. In summary, there is clear rationale to synthesize the evidence relating to the use of automated systems for the detection of sepsis.

OBJECTIVES

To evaluate whether automated systems for the early detection of sepsis can reduce the time to appropriate treatment and improve clinical outcomes in critically ill patients in the ICU.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs) reported as full text, or published as abstract only, and unpublished data. We will not exclude unblinded studies. We will exclude cross-over studies as it would not be feasible to evaluate automated monitoring followed by standard care (or vice-versa) in the same patient as the detection of sepsis requires treatment. We will exclude quasi-RCTs (studies using inadequate methods for randomization such as date of birth of participant or date of ICU admission).

Types of participants

We will include participants of any age who are admitted to intensive or critical care units for critical illness (including, but not limited to postsurgery, trauma, stroke, myocardial infarction, arrhythmia, burns, and hypovolaemic or haemorrhagic shock). We will exclude participants who are admitted with confirmed sepsis.

Types of interventions

We will include studies that randomize participants to receive monitoring for sepsis using an automated system versus standard care (i.e. systems where paper-based or other formats of observation charts are reviewed by staff directly). We define an automated system as any process capable of screening patient records or data (one or more systems) automatically at intervals for markers or characteristics that are indicative of sepsis. The parameters/algorithm used by the system (for example, the thresholds of blood pressure indicative of hypotension or the nature of the biomarkers employed) may vary. However, if the system identifies a potential case of sepsis, it should flag the patient's record and alert the relevant healthcare professional (via email, pager or phone message).

Types of outcome measures

Primary outcomes

1. Time to initiation of antimicrobial therapy*
2. Time to initiation of fluid resuscitation*
3. 30-day mortality

*Time to initiation starts at the time of admission.

Note: studies are not required to distinguish between sepsis that is detected via standard care pathways and sepsis detected via the automated system in the intervention group; if studies employ adequate control groups and sample sizes, and if automated monitoring confers a benefit, a difference between groups should be detectable.

Secondary outcomes

1. Length of stay in ICU
2. Failed detection of sepsis during ICU stay
3. Quality of life measured at the latest available time point post-discharge from ICU (preferred measure SF-36 then EQ-5D)

Search methods for identification of studies

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE (OvidSP); Embase (OvidSP); CINAHL (EBSCO host); ISI Web of Science; and LILACS (BIREME interface). We will adopt the MEDLINE search strategy for all of the other databases (see Appendices for details of search terms). We will also conduct a search of Clinicaltrials.gov (www.clinicaltrials.gov), and the World Health Organization trials portal (www.who.int/ictrp/en/). We will search all databases from their date of inception to present, with no restriction on country or language of publication.

Searching other resources

We will check the bibliography of all relevant primary studies and review articles to identify additional studies that may be relevant to the review. We will consult grey literature as appropriate.

Data collection and analysis

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Selection of studies

Using Covidence (Covidence 2015), two review authors (DE, SL) will independently screen titles and abstracts arising from the searches, for possible inclusion in the review; we will retrieve and assess the full-text articles of these potentially relevant studies and two review authors (DE, SL) will independently identify: a) studies for inclusion in the review; and b) ineligible studies; recording the reasons for exclusion in the 'Characteristics of excluded studies' table. We will resolve disagreements by discussion or, if required, through consultation with a third author (PA or AS). We will identify and exclude duplicate records, and multiple reports of the same study will be collated so that the study is the unit of interest. We will summarize the results of the selection process using a PRISMA flow diagram (Moher 2009).

Data extraction and management

We will use a data collection form to collect study characteristics and outcome data from the included studies; the form will be piloted on at least one study. One review author will extract the following information:

1. methods: study design; total duration of study; number of study centres and location; study setting; date of study;
2. participants: number of participants that were: a) randomly assigned, b) discontinued the study, and c) excluded from the analyses after randomization; condition and severity of condition; inclusion and exclusion criteria;
3. intervention: intervention, comparator, algorithm/criteria used by the automated system;

4. outcomes: primary and secondary outcomes including details of time points;

5. other information: trial funding and potential conflicts of interest of authors.

Two review authors (DE, SL) will independently extract outcome data from the included studies. We will resolve disagreements by discussion or involvement of a third author (PA or AS). One review author (DE) will transfer the data into Review Manager 5 (RevMan 2014), and the accuracy of the data will be confirmed by comparison with individual studies. A second review author (SL) will perform a spot check of study characteristics for accuracy against the original trial reports.

Assessment of risk of bias in included studies

Two review authors (DE and SL) will independently assess the risk of bias for each study according to criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another author (PA or AS). We will assess the risk of bias for the following domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting;
7. other bias.

For each domain, we will grade the risk of bias as high, low or unclear, and provide justification for our judgement in the 'risk of bias' table. We will summarize the risk of bias judgements across the included studies for each of the domains listed; we will present a summary 'Risk of bias' figure. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for a patient-reported outcome such as quality of life may be very different from that for mortality). If information relating to risk of bias is based on unpublished data or correspondence with a study investigator, we will note this in the 'Risk of bias' table. When considering treatment effects, we will take into account the risk of bias for the studies that contributed to each outcome.

Measures of treatment effect

We will analyse dichotomous data (e.g. mortality, failed detection of sepsis) as risk ratios or Mantel-Haenszel odds ratios when the outcome is an infrequent event (i.e. less than 10%), or Peto odds ratios when the outcome is very rare (i.e. less than 1%), and use 95% confidence intervals. We will analyse*c*ontinuous data (e.g. quality of life, length of ICU stay) as mean difference or standardized mean difference, depending on whether the same scale is used to measure an outcome, again with 95% confidence intervals. We will enter data presented as a scale with a consistent direction of effect across studies. We will extract hazard ratios and standard error for time-to-event data (e.g. time to initiation of antibiotics/fluid resuscitation) and we will perform meta-analysis using generic inverse variance methodology (Higgins 2011).

Unit of analysis issues

If multiple trial arms are reported in a single trial, we will only include the relevant arms. With the exception of time-to-event data, if two comparisons are combined in the same meta-analysis (e.g. intervention A versus standard care and intervention B versus standard care), we will halve the control group to avoid double-counting (Higgins 2011). We will deal with studies with a cluster design according to the advice in section 16.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

Where possible, we will contact study investigators or sponsors to obtain missing outcome data or verify important study characteristics. If this is not possible, and missing data are considered likely to introduce serious bias, we will use available case data if necessary, rather than imputed values. We will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis. Any assumptions and imputations to handle missing data will be clearly described and the effect of imputation will be explored by sensitivity analyses.

Where possible, missing standard deviations will be computed from other statistics such as standard errors, confidence intervals or P values, according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If standard deviations cannot be calculated, they will be imputed (e.g. from other studies in the meta-analysis).

Where studies report mortality at a time point other than 30 days, we will contact the authors to see if 30-day data are available, or incorporate the additional time point in our analysis, recording this in the 'Differences between protocol and review' section.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the trials included in each analysis. Where moderate or significant heterogeneity is found to be present (i.e. I^2 statistic $\geq$ 40%), we will report it and explore possible causes by analysis of prespecified subgroups. The Chi² test will be interpreted as indicating evidence of statistical heterogeneity when the P value is equal to or less than 0.10.

Assessment of reporting biases

If we are able to pool data from more than 10 trials, we will explore possible small study and publication biases by creating and examining a funnel plot.

To assess within-study reporting bias of outcomes, we will check trial protocols against published reports. For studies published after 1 July 2005, we will screen the Clinical Trial Register at the International Clinical Trials Registry Platform of the World Health Organization (http://apps.who.int/trialssearch) and Clinicaltrials.gov (https://clinicaltrials.gov/) for the trial protocol. We will evaluate whether selective reporting of outcomes is present.

Data synthesis

We will undertake meta-analyses only where this is meaningful (i.e. if the treatments, participants, criteria for the diagnosis of sepsis, and the underlying clinical question are similar enough for pooling to make sense) and where measures of heterogeneity indicate that pooling of results is appropriate. For example, the criteria for the diagnosis of sepsis have evolved (ACCP/SCCM 1992; Levy 2003; Singer 2016), and will likely influence the populations of participants examined by relevant studies from different periods. It may not be meaningful to incorporate RCTs with different definitions of sepsis in the same meta-analysis. We will use a random-effects statistical model.

'Summary of findings' table

We will use the principles of the GRADE system (Guyatt 2008), to assess the quality of the body of evidence associated with the following outcomes in our review: time to initiation of antimicrobial therapy, time to initiation of fluid resuscitation, 30-day mortality, failed detection of sepsis, length of stay in ICU, failure to detect sepsis, and quality of life (postdischarge).

Two authors (DE, SL) will independently assess the quality of the evidence. We will use the five GRADE considerations (study limitations, inconsistency, imprecision, indirectness and publication bias) to assess the quality of the body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes. The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence takes into consideration within-study risk of bias (methodologic quality) (Guyatt 2011b), the directness of the evidence (Guyatt 2011c), heterogeneity of the data (Guyatt 2011d), precision of effect estimates (Guyatt 2011e), and risk of publication bias (Guyatt 2011f). We will use methods and recommendations described in Chapter 8 (section 8.5 and 8.7), Chapter 11 and Chapter 13 (section 13.5) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011; Schünemann 2011), using GRADEpro software. We will justify all decisions to downgrade the quality of studies using footnotes and we will make comments to aid readers' understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses:

1. **Severity of sepsis:** e.g. sepsis versus septic shock (defined as either: a) vasopressor requirement to maintain a minimum mean arterial pressure of 65 mmHg or greater and a serum lactate level greater than 2 mmol/L (> 18 mg/dL) in the absence of hypovolaemia (Singer 2016); or b) severe sepsis plus hypotension not reversed by fluid resuscitation (Dellinger 2013)). We note that more recently, it has been determined that sepsis does not follow a continuum through severe sepsis to septic shock (Singer 2016). Therefore, participants who are considered as having 'severe sepsis' (previously defined as acute organ dysfunction secondary to infection (Dellinger 2013)), will be considered as having 'sepsis' for the purpose of this review.
2. **Algorithms:** (i.e. criteria) for detection. It is possible that the algorithms employed by different automated detection systems could vary substantially, and could represent a source of heterogeneity. We will explore potential algorithm-derived heterogeneity by subgroup analysis if common features can be identified.

We will perform subgroup analyses for each of the primary outcomes (where relevant). We will use the formal test for subgroup interactions in Review Manager 5 (RevMan 2014). The magnitude of the effects will be compared between the subgroups by means of assessing the overlap of the confidence intervals of the summary estimate. Non-overlap of the confidence intervals indicates statistical significance.

Sensitivity analysis

We plan to carry out the following sensitivity analyses.

1. Unpublished data (i.e. no peer-reviewed full-text paper available).
2. Trials with inadequate or unclear methods of random sequence generation or allocation concealment (i.e. high risk or unclear risk of selection bias).
3. Trials with inadequate or unclear methods of blinding of outcome assessor (i.e. high risk or unclear risk of performance bias); this subanalysis may be particularly relevant to trials reporting quality of life (i.e. a subjective outcome).
4. Studies with missing data (e.g. to examine the effect of imputed data or data based on assumptions).
5. Trials that use outdated criteria for the diagnosis/severity of sepsis (i.e. definitions used prior to those reported by Singer 2016)

The category of bias (e.g. high/unclear/low risk) will be determined during the 'Risk of bias' assessment, the criteria for this are described in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Sensitivity analyses will be performed using a fixed-effect model.

ACKNOWLEDGEMENTS

Thank you to the Cochrane Anaesthesia, Critical and Emergency Care editorial team for reviewing the protocol critically; in particular we would like to thank Rodrigo Cavallazzi (content editor), Jing Xie (statistical editor), Mazen Bader, Djillali Annane, Jean-Louis Vincent, Peter Kruger (peer reviewers).

REFERENCES

Additional references

ACCP/SCCM 1992
American College of Chest Physicians/Society of Critical Care Medicine. American College of Chest Physicians/ Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Critical Care Medicine* 1992;**20**(6):864–74.

Buck 2014
Buck KM. Developing an early sepsis alert program. *Journal of Nursing Care Quality* 2014;**29**(2):124–32.

CEM 2012
College of Emergency Medicine. CEM Clinical Audits 2011-12: Severe Sepsis & Septic Shock. http:// secure.rcem.ac.uk/code/document.asp?ID=6408 2012; accessed: 19 January 2016.

Cohen 2015
Cohen J, Vincent JL, Adhikari NK, Machado FR, Angus DC, Calandra T, et al. Sepsis: a roadmap for future research. *Lancet Infectious Diseases* 2015;**15**(5):581–614.

Covidence 2015 [Computer program]
Vertitas Health Innovation Ltd. Covidence. http:// www.covidence.com/. Vertitas Health Innovation Ltd, 2015; accessed: 19 January 2016.

Dellinger 2013
Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Critical Care Medicine* 2013;**41**(2):580–637.

Gotts 2016
Gottes JE, Matthay MA. Sepsis: pathophysiology and clinical management. *BMJ* 2016;**353**:i1585. [PUBMED: 27217054]

Guyatt 2008
Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians. *BMJ* 2008;**336**:995–8. [MEDLINE: 18456631]

Guyatt 2011b
Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *Journal of Clinical Epidemiology* 2011;**64**(4):407–15.

Guyatt 2011c
Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *Journal of Clinical Epidemiology* 2011;**64**(12):1303–10.

Guyatt 2011d
Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. *Journal of Clinical Epidemiology* 2011;**64**(12):1294–302.

Guyatt 2011e
Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. *Journal of Clinical Epidemiology* 2011;**64**(12):1283–93.

Guyatt 2011f
Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. *Journal of Clinical Epidemiology* 2011;**64**(12):1277–82.

Higgins 2011
Higgins JP, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hooper 2012
Hooper MH, Weavind L, Wheeler AP, Martin JB, Gowda SS, Semler MW, et al. Randomized trial of automated, electronic monitoring to facilitate early detection of sepsis in the intensive care unit. *Critical Care Medicine* 2012;**40** (7):2096–101.

Kaukonen 2014
Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. *JAMA* 2014;**311**(13):1308–16.

Koenig 2011
Koenig HC, Finkel BB, Khalsa SS, Lanken PN, Prasad M, Urbani R, et al. Performance of an automated electronic acute lung injury screening system in intensive care unit patients. *Critical Care Medicine* 2011;**39**(1):98–104.

Koster-Brouwer 2014
Koster-Brouwer ME, Klein Klouwenberg PM, Pasma W, van der Poll T, Bonten MJ, Cremer OL. Criticial care

management of sepsis: a cost-analysis from a health care perspective. *European Society for Intensive Care Medicine* 2014;**40**(1):S1–S308.

Kumar 2006
Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Critical Care Medicine* 2006;**34**(6):1589–96.

Levy 2003
Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Critical Care Medicine* 2003;**31**(4):1250–6.

Makam 2015
Makam AN, Nguyen OK, Auerbach AD. Diagnostic accuracy and effectiveness of automated electronic sepsis alert systems: a systematic review. *Journal of Hospital Medicine* 2015;**10**(6):396–402.

McPherson 2013
McPherson D, Griffiths C, Williams M, Baker A, Klodawski E, Jacobson B, et al. Sepsis-associated mortality in England: an analysis of multiple cause of death data from 2001 to 2010. *BMJ Open* 2013;**3**(8):pii: e002586.

Meurer 2009
Meurer WJ, Smith BL, Losman ED, Sherman D, Yaksich JD, Jared JD, et al. Real-time identification of serious infection in geriatric patients using clinical information system surveillance. *Journal of the American Geriatric Society* 2009;**57**(1):40–5.

Moher 2009
Moher D, Liberati A, Tetzlaff J, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.. *PLOS Medicine* 2009;**6**(7): e1000097. [DOI: 10.1371/journal.pmed.1000097]

Nachimuthu 2012
Nachimuthu SK, Haug PJ. Early detection of sepsis in the emergency department using Dynamic Bayesian Networks. *AMIA Annual Symposium Proceedings* 2012;**2012**:653–62.

Parliamentary Ombudsman 2013
Time to Act: Severe sepsis: rapid diagnosis and treatment saves lives. http://www.ombudsman.org.uk/__data/assets/pdf_file/0004/22666/FINAL_Sepsis_R eport_web.pdf accessed 19 January 2016.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rivers 2001
Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New England Journal of Medicine* 2001;**345**:1368-77.

Schünemann 2011
Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JP, Green S editor(s), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The CochraneCollaboration, 2011. Available from handbook.cochrane.org.

Singer 2016
Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;**315**(8):801–10.

Torio 2011
Torio CM, Andrews RM. National inpatient hospital costs: the most expensive conditions by payer, 2011. HCUP Statistical Brief #160. Agency for Healthcare Research and Quality, Rockville, MD August 2013; Vol. http: //www.hcup–us.ahrq.gov/reports/statbriefs/sb160.pdf: accessed19 Janaury 2016.

UK Sepsis Trust 2013
UK Sepsis Trust. Briefing document. UK Sepsis Trust: http: //sepsistrust.org/wp-content/uploads/2013/10/briefing.pdf 2013; accessed 19 January 2016.

Vincent 2006
Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al. Sepsis in European intensive care units: results of the SOAP study. *Critical Care Medicine* 2006;**34** (2):344–53.

Winters 2010
Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, Sevransky JE. Long-term mortality and quality of life in sepsis: a systematic review. *Criticial Care Medicine* 2010;**38**:1276-83.

Yealy 2014
Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, et al. A randomized trial of protocol-based care for early septic shock. *New England Journal of Medicine* 2014;**370**(18):1683-93.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE (Ovid SP) search strategy

1 (((automated or electronic) adj3 (monitoring or detect*)) or (early adj3 (monitoring or detect* or treat* or recogn* or initiat*)) or (pre?defined adj3 criteria) or (system* adj3 (paper or computer or monitoring or detection or automated))).mp. (189259)
2 Sepsis/ or Shock, Septic/ or (septic* or sepsis).mp. (127937)
3 1 and 2 (2867)
4 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh. (2852749)
5 3 and 4

CONTRIBUTIONS OF AUTHORS

David JW Evans (DE), Sharon R Lewis (SL), Andrew F Smith (AS), Phil Alderson (PA) and Irene Kourbeti (IK)

Conceiving the review: DE

Co-ordinating the review: DE

Undertaking manual searches: DE, SL

Screening search results: DE, SL, IK

Organizing retrieval of papers: DE, SL

Screening retrieved papers against inclusion criteria: DE, SL, IK

Appraising quality of papers: DE, SL, IK

Abstracting data from papers: DE, SL, IK

Writing to authors of papers for additional information: DE, SL

Providing additional data about papers: DE, SL, IK

Obtaining and screening data on unpublished studies: DE, SL

Data management for the review:DE, SL

Entering data into Review Manager (RevMan 2014): DE, SL

RevMan statistical data: DE, SL, PA

Other statistical analysis not using RevMan: DE, SL, PA

Interpretation of data: DE, SL, IK, PA, AS

Statistical inferences: PA

Writing the review: DE

Securing funding for the review: AS, PA, SL

Performing previous work that was the foundation of the present study: not applicable

Guarantor for the review (one author): AS

Person responsible for reading and checking review before submission: DE

DECLARATIONS OF INTEREST

David JW Evans: provides freelance writing services to medical communication agencies.

Sharon R Lewis: none known.

Andrew F Smith: none known.

Phil Alderson: none known.

Irene Kourbeti: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- This project was supported by the National Institute for Health Research, via Cochrane Programme Grant to the Anaesthesia, Critical and Emergency Care Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health, UK.