National Institute for Health and Care Excellence

Final

Suspected sepsis: recognition, diagnosis and early management

(A) Evidence reviews for stratifying risk of severe illness or death from sepsis

NICE guideline NG51

Evidence reviews underpinning recommendations 1.5.1 to 1.5.5, 1.6.3, 1.6.4, 1.7.2 and 1.10.1 and recommendation for research 2 in the NICE guideline

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Final

These evidence reviews were developed by NICE

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1.1 Review question

In adults and young people (16 and over) with suspected sepsis in acute hospital settings, ambulance trusts and acute mental health facilities, what is the association between NEWS2 bands (0, 1 to 4, 5 to 6, 7 or above) and risk of severe illness or death?

1.1.1 Introduction

Sepsis is defined as a life-threatening organ dysfunction due to a dysregulated host response to infection. It requires early recognition and immediate management to prevent the progression of the condition towards a septic shock (a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities and substantially increased mortality). However, identification of the septic patient is not always straightforward as the signs of sepsis are often subtle, nonspecific, and frequently missed in an emergency triage or prehospital setting.

The recommendations on managing people with sepsis in acute hospital settings are organised around stratification of risk. The review focused on the risk stratification of patients with suspected sepsis triggered by the Academy of Medical Royal Colleges (AoMRC) report. This report was produced by the AoMRC in collaboration with the UK Faculty of Intensive Care Medicine, using a multi-professional working group, comprised of 28 individuals, including patient representatives. To help stratify the risk of deterioration in adults and young people (16 and over) with suspected sepsis this report recommends the use of the UK's National Early Warning Score 2 (NEWS2) scale to identify and respond to people at risk of acute deterioration. The NEWS2 tool which is the updated version of the NEWS (published after the current version of NG51 guideline was developed) is formally endorsed by NHS England and NHS Improvement to become the early warning system for identifying acutely ill patients including those with sepsis. NEWS2 has seen widespread uptake across the NHS in England – at present 100% of ambulance trusts and 76% of acute trusts are using NEWS2, with other early warning scores in place in other areas. However, confusion caused by the current variation in practice can compromise patient safety, something that would be eliminated by use of a common tool. Through standardisation of NEWS2, NHS England can reduce the number of patients whose conditions deteriorate while in hospital, and potentially save thousands of lives a year.

This review is a partial update of the NICE guideline on Sepsis: recognition, diagnosis and early management (NG51). The sepsis risk stratification tool under consideration in this guideline update is the NEWS2 tool used in young people and adults of 16 years and over with suspected sepsis presenting to ambulance trusts, acute mental health facilities and acute hospital settings in which NHS care is received.

The aim of this review is therefore to assess the association between NEWS2 bands (0, 1 to 4, 5 to 6, greater than 7) and risk of mortality and severe illness in adults and young people (16 and over) with suspected sepsis.

1.1.2 Summary of the protocol

The review aimed to identify studies assessing the association between different NEWS2 bands and risk of severe illness or death from sepsis in adults and young people (16 and over) that fulfilled the conditions listed in Table 1. The criteria were specified during protocol developed in agreement with the committee members. For full details of the review protocol see Appendix A.

Table 1: PICO table summary

Population	**Inclusion criteria:** Adults and young people (16 and over) with suspected sepsis presenting to: • Acute hospital settings • Ambulance trusts • Acute mental health facilities **Exclusion criteria:** • Children (15 and under) • Pregnant and recently pregnant women • People undergoing anticancer treatment with suspected or confirmed neutropenic sepsis • Primary care setting
Intervention / Test	NEWS/NEWS2 risk brackets on the initial antimicrobial treatment of sepsis (0, 1 to 4, 5 to 6, 7 or above)
Outcomes	• Mortality (e.g. in-hospital mortality, mortality due to sepsis, all-cause mortality measured at 28 days or nearest time point, or as reported in individual studies • Escalation of care (e.g. increase in NEWS2 score/band, involvement of senior consultant, intensive care unit (ICU) admission, rehospitalisation or as reported in individual studies) • Hospital readmission rates • Unplanned critical care admission • Health related quality of life (measured by EQ5D or SF-36 or other validated questionnaires)
Measures of association	For each outcome, accuracy measures will be reported where available: • Adjusted relative risk (RRr) or odds ratios (ORr) for patient outcomes in the higher risk groups relative to the lowest risk group measured at a specific time point • Adjusted hazard ratios (HRs) if outcomes are measured over time for those in higher risk groups relative to the lowest risk group
Study type	• Prospective cohort studies • Systematic reviews of these studies If sufficient evidence not found: • Retrospective cohort studies

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods section in Appendix B.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

As the NEWS 2 tool was introduced in 2017, the evidence-base was expected to be small. Therefore, the committee members agreed to also include studies that assess the NEWS tool (the first version of the tool introduced in 2012) and the associated risk of severe illness or death from sepsis in adults and young people (16+). In this case, the studies assessing the NEWS tool were downgraded for indirectness in the GRADE analysis.

Prospective and retrospective observational cohort studies were considered in addition to systematic reviews of these study types.

The review protocol specified that where statistically possible, a meta-analytic approach will be used to give an overall summary effect. However, this was not statistically possible due to differences in the NEWS bands and cut off points used in the included studies. Where data allowed, forest plots were used to visualise the odds ratios (ORs) and the associated risk per outcome for different NEWS risk categories as reported in each included study.

The review protocol also specified that, where possible, subgroup analyses would be conducted for age (young people, adults, and older adults), people who are approaching the end of their life, people with COVID-19 and suspected sepsis and the type of tool used (NEWS and NEWS2). However, these subgroups could not be analysed due to insufficient data.

As no published guidance on applying GRADE to reviews on prognosis exists, a modified approach using the GRADE framework was applied. The committee did not define a clinical decision threshold prospectively, therefore the line of no effect was used at the clinical decision threshold for the purpose of rating imprecision in GRADE.

1.1.3.1 Search methods – prognostic evidence

A NICE information specialist conducted the searches on 30th June 2022. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley); Cochrane Database of Systematic Reviews (CDSR) (Wiley); Embase (OVID); Medline (OVID) and MEDLINE Epub Ahead-of-Print (OVID).

Evidence from the original guideline (NG51) was also reviewed.

Detailed search strategies for each database and method are provided in Appendix C.

1.1.3.2 Search methods – cost-effectiveness evidence

A NICE information specialist conducted the searches on 30th June 2022. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley); Cochrane Database of Systematic Reviews (CDSR) (Wiley); Embase (OVID); Medline (OVID) and MEDLINE Epub Ahead-of-Print (OVID).

Detailed search strategies for each database and method are provided in Appendix C.

1.1.3.3 Protocol deviations

Several sources were added during the search as the numbers of articles being obtained were relatively low and it was feasible within the time and resources available to expand the list of sources beyond those specified in the protocol. Websites covering government, charities and sepsis related organisations such as the NHS England, the Department of Health and Social Care, the Royal College of Physicians, the Royal College of Emergency Medicine, Sepsis Trust, Surviving Sepsis Campaign, the Sepsis Alliance, the Sepsis Research, First Response, TRIP (Turning Research into Practice), FERN (Find Evidence, Retrieve Now) were searched on 4th and 5th July 2022. This was to ensure comprehensive coverage of the potential literature.

1.1.4 Prognostic evidence

1.1.4.1 Included studies

A systematic search, limited to 2012 onwards (since the endorsement of the first version of the NEWS tool) which was carried out to identify studies specified for this evidence review identified 509 records through database searching and 17 records identified through other searches. After deduplication, 377 records were screened at title and abstract stage. 348 records were discarded as they did not fulfil the review inclusion criteria. 29 records were sourced for full text screening. Of these, 27 full-text articles were further excluded with reasons. After the full text screening, 2 studies fulfilled the eligibility criteria and were included for narrative synthesis. All studies were retrospective cohort studies.

One of the studies identified through the database search (Corfield et al, 2014) was also included in the previous guideline NG51.

The full search strategy is presented in Appendix C. The PRISMA diagram for the study selection process is included in Appendix D.

1.1.4.2 Excluded studies

All excluded references with reasons for exclusion are given in Appendix J.

1.1.5 Summary of studies included in the prognostic evidence

Studies that used the NEWS2 tool to stratify the risk of severe illness or death in young people and adults (16 and over) with suspected sepsis were not identified.

The indirect evidence presented in this review comes from two UK retrospective cohort studies with suspected or confirmed sepsis using the NEWS as a stratification tool. Sepsis was defined as a systemic inflammatory response syndrome provoked by an infection (Sepsis 2) in Corfield et al, 2014 and as a life-threatening organ dysfunction due to a dysregulated host response to infection (Sepsis 3) in Hargreaves et al, 2020.

The total number of participants was 3236 with a median age of 72 (Corfield 2014) and 79 (Hargreaves et al, 2020). One study (Corfield et al, 2014) included participants with suspected or confirmed sepsis presenting to emergency departments (ED) and one study (Hargreaves et al, 2020) included people with suspected sepsis presenting to ambulance services (prehospital setting), ED and hospital wards.

The summary of these studies is presented below:

Table 2: Summary of included studies

Study and type	Location, setting	Population characteristics	Prognostic risk factor	Outcomes, measures and follow up	Risk of bias, applicability
Corfield et al, 2014 Retrospective cohort study	- UK, Scotland - 20 district general and teaching hospital EDs	People (≥16) with suspected or confirmed sepsis in ED Def: Sepsis 2 N=2003 Median age: 72 (59-81)	NEWS categories: 0–4 5–6 7–8 9–20	- ICU admission within 2 days of attendance - 30-day mortality (in hospital). - Age adjusted ORs for higher NEWS category relative to the lowest band (0-4) Follow up to discharge or death	- Moderate - Indirectly applicable
Hargreaves et al, 2020 Retrospective cohort study Sepsis definition: Sepsis 3	- UK, southeast - two non specialist hospitals and ambulance services	Adults (≥18) with suspected sepsis in prehospital, ED and ward setting Def: Sepsis 3 N=1233 Median age: 79 (68-86)	NEWS category: NEWS ≥5 vs NEWS<5	- 30-day mortality (prehospital, ED and hospital ward) in people with persistent NEWS≥5 - ICU admission Adjusted ORs Follow up 30 days	- Low - Indirectly applicable
ED-Emergency Department; ICU-Intensive Care Unit; NEWS-National Early Warning Score					

Baseline characteristics were partially reported in one study (Corfield et al, 2014) and detailed in the second study (Hargreaves et al, 2020). The study of Corfield et al, 2014 reported age adjusted ORs and no other confounding factors were accounted for. In the study of Hargreaves et al, 2020, logistic regression was performed using backward stepwise selection starting with 11 variables including age, change in NEWS, ED lactate, past medical history and acute kidney injury. As a result, Corfield et al, 2014 was judged to be of a moderate risk of bias.

Studies assessed the associations of the NEWS categories with intensive care unit (ICU) admission and 30-day mortality. The follow up was to hospital discharge or death within 30 days.

Although both studies used the NEWS tool, the risk stratification used to assess the associated risk in the studies differed. Corfield et al, 2014 used the NEWS categories 0 to 4 (low); 5 to 6 (medium); 7 to 8 (high) and 9 to 20 (very high), while in Hargreaves et al, 2020 the cut-off point of NEWS score 5 and above was utilised. As a result, it was not possible to meaningfully meta-analyse the outcome data. To visualise the associated risk for each category as reported in the included studies, forest plots we generated (Appendix F).

Other outcomes of interest e.g., health related quality of life, hospital readmission rates, unplanned critical care admission or mortality other than 30 days were not reported. Also, no studies conducted in acute mental health facilities were found.

The detailed evidence tables, risk of bias and assessment of study applicability are presented in Appendix E. Included studies are referenced in full in section 1.1.14.

1.1.6 Summary of the prognostic evidence

1.1.6.1 NEWS and NEWS2 model summary

NEWS2 is the latest version of the National Early Warning Score (NEWS), first produced in 2012 and updated in December 2017, which improves the detection and response to clinical deterioration in adult and young people (16 and over), including those with sepsis, and is a key element of patient safety and improving patient outcomes.

1.1.6.1.1. The NEWS and NEWS2 scoring system

The National Early Warning Score (NEWS and NEWS2) is a system for scoring the physiological measurements that are routinely recorded at the patient's bedside and should be used as an aid to clinical assessment and not as a substitute for competent clinical judgement. The Royal College of Physicians recommends the use of the national early warning score to standardise the assessment of acute-illness severity when patients present in acute hospitals and also in the prehospital assessment i.e., by primary care and ambulance services. However, the use of national early warning score should not be used in children under 16 years or people who are pregnant because the physiological response to acute illness can be modified in children and by pregnancy.

1.1.6.1.2 Differences between NEWS and NEWS2 tools

In NEWS, oxygen saturations (SpO2) receive increasing weights for values of 95% or less, and oxygen therapy receives a flat weight (a score of 2 is added to the aggregate NEW score for any patient requiring supplemental oxygen). However, guidance for the management of patients with type II respiratory failure (T2RF) and those deemed at risk of T2RF before blood gas analysis, suggests lower SpO2 values (88–92%) should be targeted. Consequently, it is suggested that the NEWS SpO2 weighting system is inappropriate for patients with/at risk of T2RF.

NEWS2 includes several modifications to the NEWS vital sign weightings. To account for concerns about NEWS and T2RF, NEWS2 includes a new SpO2 scoring scale for patients with/at risk of T2RF. This scale, termed *SpO_2 scale 2* assigns weights at lower SpO_2 thresholds than NEWS and combines these lower thresholds with weights for the use of supplemental oxygen at higher SpO_2 levels, reflecting the concern of hyperoxia-induced hypercapnic respiratory failure.

The NEWS2 updates are outlined in the table below:

1	The recording of physiological parameters has been reordered to align with the Resuscitation Council (UK) ABCDE sequence
2	The ranges for the boundaries of each parameter score are now shown on the chart
3	The chart has a dedicated section (spo2 Scale 2) for use in patients with hypercapnic respiratory failure (usually due to COPD) who have clinically recommended oxygen saturation of 88–92%
4	The section of the chart for recording the rate of (L/min) and method/device for supplemental oxygen delivery has been improved
5	The importance of considering serious sepsis in patients with known or suspected infection, or at risk of infection, is emphasised. A new score of 5 or more is the key trigger threshold for urgent clinical review and action

6	The addition of 'new confusion' (which includes disorientation, delirium or any new alteration to mentation) to the AVPU score, which becomes ACVPU (where C represents confusion)
7	The chart has a new colour scheme, reflecting the fact that the original red amber–green colours were not ideal for staff with red/green colour blindness

To account for these differences, the evidence from studies that used the NEWS tool was downgraded for indirectness (see protocol, Appendix A).

1.1.6.2 Summary of primary outcomes included in the prognostic review

The measures of association for different NEWS risk cut-off points and patient outcomes at a specific time point are presented as odd ratios (ORs). ORs greater than 1 indicate that a particular outcome (e.g. ICU admission or 30-day mortality) is more likely to occur in the higher risk group relative to the lowest risk group. An OR > 1 means greater odds of association between the higher NEWS risk bands and the outcome.

The way the data was reported did not allow to statistically pool the outcome data. However, forest plots were used for the visualisation of the adjusted odds ratios (ORs) for different NEWS risk categories and the associated risk per outcome as reported in the modified GRADE tables. The MID threshold defined as a "line of no effect" was used to rate imprecision in GRADE. The forest plots are presented in Appendix F, with the detailed modified GRADE tables in Appendix G.

The summary of the modified GRADE tables for each study are presented below.

Study: Corfield et al, 2014

The aim of this study was to determine whether a single NEWS score in the ED was a useful predictor of outcome, either death or ICU admission. The total number of participants was N=2003, stratified into the following NEWS risk categories: 0-4; 5-6; 7-8; 9-20.

Data regarding ICU admission within 2 days and 30-day mortality for this study are presented on Table 3 and Table 4, respectively. Data is presented as ORs for the higher risk NEWS score categories (5-6; 7-8 and 9-20) relative to the lowest NEWS risk category (0-4).

Outcome: ICU admission

Table 3: Adjusted ORs for admission to ICU within 2 days in higher risk NEWS categories relative to the lowest NEWS risk category (0-4)

Outcome: ICU within 2 days	Sample size (higher vs lowest NEWS category)	Events (higher vs lowest NEWS category)	Measure of association Adjusted ORs [95% CI]	Quality	Interpretation of outcome measure*
NEWS score 5-6 vs NEWS score 0-4	N= 988 (459 vs 529)	14 vs 17	1.22 [0.59, 2.54]	Very Low**	Could not differentiate
NEWS score 7-8 vs NEWS score 0-4	N= 979 (450 vs 529)	20 vs 17	2.01 [1.02, 3.97]	Low***	NEWS score 7-8 associated with greater ICU admission

Outcome: ICU within 2 days	Sample size (higher vs lowest NEWS category)	Events (higher vs lowest NEWS category)	Measure of association Adjusted ORs [95% CI]	Quality	Interpretation of outcome measure*
NEWS score 9-20 vs NEWS score 0-4	N= 1094 (565 vs 529)	62 vs 17	5.76 [3.22, 10.31]	Low***	NEWS score 9-20 associated with greater ICU admission

*OR greater than 1 favours NEWS category 0-4
** Downgraded for Downgraded for high risk of bias, indirectness and imprecision
*** Downgraded for high risk of bias and indirectness
OR=odds ratio. CI=confidence interval. ICU=intensive care unit. NEWS=National Warning Score

Outcome: 30-day mortality

Table 4: Adjusted ORs for 30-day mortality in higher NEWS categories relative to the lowest risk category

Outcome: Mortality (30 days)	Sample size (higher vs lowest NEWS category)	Events (higher vs lowest NEWS category)	Measure of association Adjusted ORs [95% CI]	Quality	Interpretation of outcome measure *
NEWS score 5-6 vs NEWS score 0-4	N= 988 (459 vs 529)	52 vs 29	1.95 [1.21, 3.14]	Low**	NEWS score 5-6 associated with greater 30-day mortality
NEWS score 7-8 vs NEWS score 0-4	N= 979 (450 vs 529)	60 vs 29	2.26 [1.42, 3.61]	Low**	NEWS score 7-8 associated with greater 30-day mortality
NEWS score 9-20 vs NEWS score 0-4	N= 1094 (565 vs 529)	156 vs 29	5.64 [3.70, 8.60]	Low**	NEWS score 9-20 associated with greater 30-day mortality

*OR greater than 1 is associated with greater 30-day mortality in higher NEWS risk bands relative to the NEWS category 0-4
** Downgraded for high risk of bias and indirectness
OR=odds ratio. CI=confidence interval. NEWS=National Warning Score

Study: Hargreaves et al, 2020

This study aimed to assess whether change in NEWS (measured prehospital and ED) better predicted mortality and ICU admission than individual scores taken in isolation. The total number of participants assessed was N=1233, stratified into two NEWS risk categories: NEWS score of 5 and over and NEWS score smaller than 5.

Data regarding ICU admissions and 30-day mortality associated with persistent NEWS ≥ 5 score across all three settings (prehospital, ED and hospital wards) relative to the NEWS score <5 is presented on Table 5 and Table 6, respectively. Cases with persistently elevated NEWS ≥5 from either prehospital to ED or persisting at all three settings were compared with those cases whose NEWS resolved to <5 points on ED arrival.

The outcome data were reported as adjusted ORs and percentages. Authors did not report extractable format of data for calculation of the number of events in each risk category (NEWS≥5 vs NEWS<5) across the three settings (prehospital, ED and hospital wards).

Outcome: ICU admissions

ICU admission was 6% (n = 80) for the cohort (n=1233). In the group with a NEWS ≥5 prehospital and in the ED, ICU admission increased [8.3% vs. 1.8%, OR 5.0 (1.8–13.8); P < 0.001]. Data for ICU admissions in people with persistently elevated NEWS ≥ 5 score across all three settings (prehospital, ED and hospital ward) was not reported.

Table 5: Adjusted ORs for ICU admission associated with persistent elevation of NEWS ≥ 5 score (prehospital, prehospital + ED) relative to the resolved NEWS score <5 points on ED arrival

Outcome: ICU admission	ICU admission (%) NEWS ≥5 vs NEWS <5	Measure of association Adjusted ORs [95% CI]	Quality	Interpretation outcome measure*
Prehospital+ED NEWS ≥5 vs ED NEWS <5	8.3% vs 1.8%	5.0 [1.8, 13.8]	Moderate**	NEWS≥5 associated with greater ICU admission

*OR greater than 1 is associated with greater ICU admissions in NEWS ≥5 relative to the NEWS<5
** Downgraded for indirectness
OR=odds ratio. CI=confidence interval. ICU=intensive care unit. ED=emergency department. NEWS=National Warning Score

Outcome: 30-day mortality

Thirty-day mortality for the cohort was 18.6% (n = 229).

Table 6: Adjusted ORs for 30-day mortality associated with persistent elevation of NEWS ≥ 5 score (prehospital, prehospital + ED, prehospital + ED + ward admission) relative to the resolved NEWS score <5 points on ED arrival

Outcome: Mortality (30 days)	Sample size and Mortality (%) NEWS ≥5 vs NEWS <5	Measure of association Adjusted ORs [95% CI]	Quality	Interpretation of outcome measure*
Prehospital NEWS ≥5 vs NEWS <5	N=1233 19.6% vs 11.9%	1.80 [1.1, 3.0]	Moderate**	NEWS≥5 associated with greater 30-day mortality
Prehosp.+ED NEWS ≥5 vs ED NEWS <5	N=1074 22.1% vs 10.2%	2.5 [1.6, 4.0]	Moderate**	NEWS≥5 associated with greater 30-day mortality
Prehosp.+ED+Ward NEWS ≥5 vs ED NEWS <5	N=1015 32.1% vs 14.3%	2.8 [2.1, 3.9]	Moderate**	NEWS≥5 associated with greater 30-day mortality

*OR greater than 1 is associated with greater 30-day mortality in NEWS ≥5 relative to the NEWS<5
** Downgraded for indirectness
OR=odds ratio. CI=confidence interval. ED=emergency department. NEWS=National Warning Score

1.1.6.3 Summary of secondary outcomes

The guideline update committee did not specify any secondary outcomes of interest during protocol development. For details see Appendix A.

1.1.7 Economic evidence

1.1.7.1 Included studies

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see Appendix C). Only a small number of studies (n=359) were returned using the clinical effectiveness search strategy, and a further economic filter was not applied given the low number. An additional 2 studies were identified from other sources, giving a total of 361 studies retrieved from the search. Based on title and abstract screening, all 361 of the studies could confidently be excluded for this review question, and therefore no health economic studies were included.

1.1.7.2 Excluded studies

No relevant health economic studies were identified for this review question.

See also the health economic study selection flow chart in Appendix D.

1.1.8 Summary of included economic evidence

No relevant health economic studies were identified to be included.

1.1.9 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.10 Unit costs

No relevant unit costs were identified for this review question.

1.1.11 Evidence statements

There was no economic evidence relevant for this review question.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The committee members agreed that unscheduled admission to intensive care unit (ICU) and 30-day mortality are critical outcomes to assess the association between the different National Early Warning Score 2 (NEWS2) bands (0, 1-4, 5-6, 7-20) and the risk of severe illness or death in people with suspected sepsis aged 16 and over.

Health related quality of life, hospital readmission rates, unplanned critical care admission and mortality other than 30 days were also considered to be critical outcomes, however no evidence for these outcomes was found.

1.1.12.2 The quality of the evidence

No studies that used the NEWS2 tool to stratify the risk of severe illness or death in young people and adults (16 and over) with suspected sepsis were identified.

The certainty of the body of evidence for the association between the earlier version of the tool, namely NEWS bands (0, 1 to 4, 5 to 6, 7 or above) and risk of severe illness or death in adults and young people (16 and over) with suspected sepsis in acute hospital settings, ambulance trusts and acute mental health facilities ranged from very low to moderate. However, several factors were considered when linking the evidence to recommendations.

The indirect evidence presented on the NEWS tool was limited and comes from two retrospective cohort studies conducted in the UK (N=3236). The studies used different NEWS categories and cut-off points when assessing the risk of deterioration in adults with suspected sepsis. A meta-analysis could not be conducted due to the substantial variation of confounding factors used to adjust the reported ORs. Subgroup analysis was not possible due to insufficient data. One of the studies (Corfield et al, 2014) was included in the current NG51 guideline.

However, the committee agreed that although the NEWS2 update refines and improves the NEWS tool, it does not change its core principles and thus does not affect the stratification of people with suspected sepsis into appropriate bands. They agreed that the evidence could be used to inform the current review but accepted to downgrade the evidence for indirectness.

Furthermore, the committee agreed the study of Corfield et al, 2014 to be of a high risk of bias for two main reasons: 1) as authors failed to disclose baseline characteristics of participants in more details as only age and sex were reported, and 2) the reported odds ratios (ORs) were adjusted only for age, with no consideration for other important confounders such as underlying comorbidities and lactate level. The committee also accepted the modified approach used to GRADE the body of evidence and the default threshold cut-off points used to assess imprecision set at the line of no effect.

The committee also discussed recommendations for future research. Prospective cohort studies that assess the association of the different NEWS2 categories (0, 1-4, 5-6, 7 and over) and the risk of deterioration in people with suspected sepsis were warranted. Studies should include assessment of all critical outcomes such as mortality, ICU admission, health related

quality of life, hospital readmission rates, unplanned critical care admission and mortality time points other than 30 days.

In addition, a NEWS2 score of 3 in a single parameter was a matter of concern due to lack of evidence and uncertainties highlighted also by the AoMRC report. The committee decided that more evidence for a NEWS2 score of 3 in a single physiological parameter would help to identify the particular risk of organ deterioration and clarify the approach for management and treatment of this specific category of people with suspected or confirmed infection. Research recommendations are outlined in Appendix K.

1.1.12.3 Benefits and harms

Risk stratification

Failure to recognise or act on signs that a patient is deteriorating is a key patient safety issue. The aim of the NEWS2 as a track-and-trigger early warning score system is early recognition of people who have or who are in risk of developing a systemic response to infection that may be life-threatening. Furthermore, people with suspected sepsis may present in any clinical setting including prehospital (ambulance and mental health services), emergency departments (ED) and acute care hospitals. Hence, the recommendations made by the committee for people with suspected sepsis aged 16 and over have several benefits highlighted below.

Based on the evidence presented in this review the committee agreed that delays in detecting and consequently managing and treating sepsis increases morbidity and mortality. The evidence showed an increased risk of ICU admission and mortality in people with suspected sepsis aged 16 and over associated with a NEWS score of 5 or more and supports the findings of the AoMRC report. It is also in line with the clinical experience of the committee. In light of the lack of evidence, the committee agreed to make a consensus recommendation in support of the clinical decision support framework for initial evaluation of sepsis as outlined in the AoMRC report (Table 7). These four bands will determine further action and intervention, adapted to the likelihood of infection with urgency increasing with a higher band.

Table 7: Risk stratification of people aged 16 and over with suspected sepsis using the NEWS2 tool (based on AoMRC clinical decision support framework)

Risk category	Very low risk	Low risk	Moderate risk	High risk
NEWS2 score	NEWS2 score 0	NEWS2 score 1-4	NEWS2 score 5-6	NEWS2 score 7-20

By stratifying the risk in the above categories, people at risk of acute deterioration are recognised early, regardless of the setting (e.g., ambulance services, mental health facilities, ED or acute hospital wards) where the score was aggregated. The committee discussed the importance of clinical judgement when interpreting the NEWS2 scores. The committee agreed that the aggregate NEWS2 framework should be used as a tool to support clinical decision making when stratifying the risk of deterioration in people with suspected or confirmed infection and not to replace clinical judgement. A NEWS2 score should thus be interpreted within the context of patient's history and physical examination results and the consequent management and treatment plans should be tailored to the individual patient needs.

The committee discussed the lowest band of risk in the AoMRC framework with a NEWS2 score of 0. Concerns were raised by the committee that this indicates zero or no risk and precludes a need to take any action. The committee wished to emphasise that this lowest risk band (NEWS2 score 0) is still an indication of increased risk. It is important to ensure that

patients in this lowest band are not missed and should still receive routine NEWS2 monitoring based on local practice.

Furthermore, the committee emphasised that acute illness is a dynamic state for which treatment priorities must be adjusted accordingly. They also noted that clinicians should take into account when and where NEWS2 score is recorded such as in an ambulance or mental health facility and any potential delays in monitoring. They agreed to highlight this in a recommendation to consider any previous NEWS2 score and interventions and to evaluate the risk of severe illness or death from sepsis as being higher than suggested by their initial NEWS2 score.

The recommendation of the NEWS2 as a risk stratification tool was reinforced by the fact that the NEWS2 is already in use by most of the NHS acute care settings, EDs and prehospital setting (defined as ambulance services and mental health facilities) in England. The committee agreed that by recommending the NEWS2 to stratify risk of severe illness or death in people with suspected sepsis aged 16 and over in these settings, the consistency in the detection of and response to acute illness due to sepsis across acute hospitals, mental health facilities and ambulance services where NHS care is provided would be improved.

The committee agreed that a NEWS2 score of 3 in a single parameter may suggest an increased risk of organ dysfunction and further deterioration which could lead to a decision on change of frequency of monitoring or escalation of clinical care. While this category of a NEWS2 of 3 in a single parameter is classified as low-medium by the Royal College of Physicians, a separate classification in the AoMRC clinical framework does not exist. However, despite the lack of evidence, and based on their clinical expertise and experience, the committee members recommended that the risk of severe illness or death from sepsis for people with a NEWS2 score of 3 in a single parameter could be seen as being one level higher from the aggregated score bracket. This may require managing their condition as per a higher risk level than that suggested by their NEWS2 score alone. The committee considered this issue at length and believed strongly that a NEWS2 score of 3 in a single parameter is an important red flag indicating increased risk and that their recommendations should include the RCP classification.

The committee members did not highlight any potential harms that could be caused using the NEWS2 tool for risk stratification in people with suspected or confirmed infection. This is mainly due to the fact that recording physiological parameters is not an invasive procedure and makes part of the standard observation of people at risk of acute deterioration. Possible harms were likely to be associated with the management and treatment of people with suspected sepsis.

Communication of NEWS2 scores

Recording physiological parameters is now part of the NHS routine acute care and converting these separate measurements into a single aggregate score enables prompt and early recognition and subsequently timely management and treatment of people with suspected sepsis. Harm could result from having different scoring systems in use across the NHS when patients or staff move between services. The committee agreed that the use of a standardised tool that uses the same risk grades might improve communication and the recommendation of its use across ambulance, mental health and acute hospital settings was made. This recommendation is also supported with the fact that NHS England and NHS Improvement have already approved and recommended the use of NEWS2 as the early warning scoring system in people with suspected sepsis aged 16 and over in ambulance, mental health and acute hospital settings. Hence, this recommendation would ensure standardising the approach to detecting and grading the severity of acute illness in patients with an infection or at risk of infection and would improve adverse outcomes.

Overall, the committee concluded that the NEWS2 tool should be recommended for risk stratification and early detection in people aged 16 and over with suspected sepsis at risk of deterioration as it would prompt an appropriate prioritisation and planning across the care

pathway in-line with NEWS2 and improve patient safety. This would result with reduced morbidity and mortality from sepsis which ultimately could reduce NHS costs by reducing unnecessary ICU and critical care unit admissions, inappropriate treatment and length of hospital stay.

1.1.12.4 Cost effectiveness and resource use

No relevant economic evaluations were identified for this review question. The committee considered the resource implications of using NEWS2 tool for risk stratification. NEWS2 is already in widespread use in ambulance trusts and in acute trusts, and so the committee focused on discussing the implications of the recommended choice of NEWS2 thresholds and implementing these in practice.

The committee discussed an excess of ED admissions could be a potential consequence of the use of the NEWS2 tool. This would be an increased risk among ambulance teams who may not have the necessary experience to make a clinical judgement alongside the use of the NEWS2 scoring tool. The concern that this may lead to resource implications particularly within EDs was evaluated carefully by the committee during their decision making particularly considering the limited evidence. The committee weighed up the potential resource implications in terms of over triage compared to the severe consequences in terms of mortality and morbidity for cases of sepsis missed.

Based on the evidence, a persistent score of at least 5 was an indication of a higher risk of rapid deterioration. In light of ensuring these patients were seen in a timely manner while trying to prevent over burden in emergency departments, the committee agreed that where possible an assessment by a clinician with core competencies in the care of acutely ill patients is of high priority. When this is not possible, taking multiple measurements of NEWS2 score will provide a strong indicator of risk level.

The NICE (2020) Medtech innovation briefing (MIB205) for National Early Warning Score systems that alert to deteriorating adult patients in hospital estimated the time to assess the NEWS2 score to be either 150 seconds to 215 seconds depending on whether the integrated software was used or whether the score was calculated manually. The cost of a nurse on band 4 of the NHS pay scale per working hour is £32 (Personal Social Services Research Unit, 2021); assuming a time of 215 seconds to manually calculate the NEWS2, this costs an estimated £1.91 per patient, per observation set. Therefore, the use of multiple assessments over time is not expected to have a substantial resource impact because of the short duration of time to carry out the assessments.

Overall, the committee considered that any resource impact because of the recommendations would be low. Although the committee raised some concern about the potential resource impact within EDs, the benefit of a time-critical transfer in terms of reduced ICU and critical care unit admissions and durations of stay outweighed potential triage which could be seen in EDs. Additionally, the committee determined that recommending multiple score readings and sending a senior clinician for opinion would mitigate against any potential over triage.

1.1.12.5 Other factors the committee took into account

While anyone can develop sepsis and vigilance is therefore required in all clinical encounters, there are people whose risk is increased because of various reasons (personal characteristics, concurrent medical conditions or medicines). Therefore, the committee recognised that NEWS2 score of 5 or above poses an increased risk of severe illness or death in people with suspected sepsis which should then prompt timely face to face assessment by a senior clinical decision maker. This is based on the findings of Hargreaves et al (2020) which reported that a NEWS score of 5 or above was associated with greater ICU admission and greater 30-day mortality.

The committee considered settings and situations where there may be an absence of a clinician with core competencies in the care of acutely ill patients, such as ambulance and mental health facilities. The committee agreed to make a consensus recommendation to consider a time-critical transfer and pre-alerting the hospital. For management before and during transportation, a referral to local guidelines and protocols in relation to clinician's scope of practice, conveyance agreements, advanced care planning and end of life care planning was made. The committee considered this issue at length given the consequences of this recommendation with possible higher volume of referrals to EDs and acute hospital wards based on the cut-off point of 5 and above.

The committee also discussed what constitutes a senior clinical decision maker. In the previous version of the NG51 guideline a 'senior clinical decision maker' for people aged 18 years or over should be someone who is authorised to prescribe antibiotics, such as a doctor of grade CT3/ST3 or above or equivalent, such as an advanced nurse practitioner with antibiotic prescribing responsibilities, depending on local arrangements; a 'senior decision maker' for people aged 16–17 years is a paediatric or emergency care qualified doctor of grade ST4 or above or equivalent. After careful consideration, the committee agreed to use "clinician with core competencies in the care of acutely ill patients" to define the senior clinical decision maker in line with the Royal College of Physicians' definition.

Furthermore, the committee wished to highlight some important issues faced in rural areas, where transport to the nearest appropriate acute setting might take longer relative to urban areas. Considering the recognised higher risk of acute deterioration of people with suspected sepsis and persistent elevation of NEWS2 ≥5 score which would require timely management and treatment, this was of a particular concern. The committee addressed this issue by amending an existing recommendation in the NG51 guideline outlining that in locations where time before admission to the emergency department (including transfer time) is more than one hour to ensure that ambulance services have mechanisms in place to give antibiotics to people with high-risk criteria.

The committee gave special consideration for people with neutropenic sepsis such as those on anti-cancer treatment and immunosuppressant therapies as sepsis shares many of the same immunosuppressant mechanisms (increased production of the immunosuppressant inflammatory factors such as cytokine interleukin 10, T regulatory cells, myeloid derived suppressor cells, and PD-1 and PD-L1 with T-cell exhaustion). These processes were thought to be similar among all people with neutropenic sepsis, regardless of its aetiology e.g., anti-cancer treatment, transplants or congenital causes. The committee considered that people with suspected neutropenic sepsis are a very high-risk category separate to those with suspected sepsis without neutropenia and thus require targeted management and treatment. Hence, based on this urgency and the very high risk of further deterioration, for all people with neutropenic sepsis regardless of its cause, referral to the guideline Neutropenic sepsis: prevention and management in people with cancer was made.

No other consideration, such as those of an ethical and equality nature were anticipated because the risk stratification using the NEWS2 tool is decided by the measurement of physiological parameters of people with suspected sepsis with equipment that is already available and widely used across NHS England hospital and ambulance trusts.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.1 - 1.5.5, 1.6.3, 1.6.4, 1.7.2 and 1.10.1 and research recommendation 2 of the NG51 guideline. Research recommendations are detailed in Appendix K of this evidence review.

1.1.14 References

Effectiveness

Corfield, Alasdair R, Lees, Fiona, Zealley, Ian et al. (2014) Utility of a single early warning score in patients with sepsis in the emergency department. *Emergency medicine journal: EMJ* 31(6): 482-7.

Hargreaves, Duncan Sebastian, de Carvalho, Joshua Lucas Jarman, Smith, Laura et al. (2020) Persistently elevated early warning scores and lactate identifies patients at high risk of mortality in suspected sepsis. *European journal of emergency medicine: official journal of the European Society for Emergency Medicine* 27(2): 125-131.#

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NICE (2020) Medtech innovation briefing (MIB205), National early warning score systems that alert to deteriorating adult patients in hospital. Published online 2020. Available at: https://www.nice.org.uk/advice/mib205/resources/national-early-warning-score-systems-that-alert-to-deteriorating-adult-patients-in-hospital-pdf-2285965392761797

Personal Social Services Research Unit. Unit Costs of Health and Social Care 2021. Published online 2021. Available at: https://www.pssru.ac.uk/project-pages/unit-costs/

Appendices

Appendix A – Review protocols

Review protocol for stratifying risk of severe illness or death from sepsis.

ID	Field	Content
0.	PROSPERO registration number	CRD42022344711
1.	Review title	Stratifying risk of severe illness or death from sepsis.
2.	Review question	In adults and young people (16 and over) with suspected sepsis in acute hospital settings, ambulance trusts and acute mental health facilities, what is the association between NEWS2 bands (0, 1 to 4, 5 to 6, 7 or above) and risk of severe illness or death?
3.	Objective	To assess the association between NEWS2 bands (0, 1 to 4, 5 to 6, greater than 7) and risk of mortality and severe illness in adults and young people (16 and over) with suspected sepsis.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • From 2012 onwards • English language

		• Human studies The full search strategies will be published in the final review. Note: As the evidence base for NEWS2 tool is expected to be small, studies on NEWS tool will also be included as indirect evidence (these studies will be downgraded for indirectness in the GRADE analysis).
5.	Condition or domain being studied	Sepsis: recognition, diagnosis and early management Domain: risk stratification of adults and young people (16 and over) with suspected sepsis
6.	Population	Inclusion: Adults and young people (16 and over) with suspected sepsis presenting to: • acute hospital settings • ambulance trusts • acute mental health facilities Exclusion: • Children (15 and under) • Pregnant and recently pregnant women (women who have given birth or had a termination of pregnancy or miscarriage in the past 4 weeks) • People undergoing anticancer treatment with suspected or confirmed neutropenic sepsis • Primary care setting Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection (Sepsis 3 definition). Note: To ensure that all relevant studies are captured, studies that have defined sepsis according to the Sepsis 1 (Bone et al., 1992) and Sepsis 2 (Levy et al., 2003) definitions will also be included.

		Note: In the current NG51 guideline, recommendations are made for young people and adults (12 and over), therefore this must be accounted for when making new recommendations for age16 and over. Note: In pregnant and recently pregnant women with suspected sepsis, the MEWS tool is used. Note: For people undergoing anticancer treatment with suspected or confirmed neutropenic sepsis a cross reference to the NICE CG151 Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients will be made.
7.	Intervention/Exposure/Test	NEWS/NEWS2 risk brackets recommended in the AoMRC statement on the initial antimicrobial treatment of sepsis (0, 1 to 4, 5 to 6, 7 or above)
8.	Measures of association	This review is going to investigate the association of the initial NEWS2 risk bracket (0, 1 to 4, 5 to 6, 7 and above) in adults and young people (16+) with suspected sepsis with the critical outcomes listed below. Outcome measures: • Adjusted relative risk (RR) or odds ratio (OR) (and ultimately risk difference) for patient outcomes listed above for those in higher risk groups relative to the lowest risk group measured at a specific time point • Adjusted hazard ratios (HRs) if outcomes are measured over time for those in higher risk groups relative to the lowest risk group
9.	Types of study to be included	• Prospective cohort studies • Systematic reviews of these studies If sufficient evidence is not found: • Retrospective cohort studies Note: comparisons of NEWS and NESW2 tool with other existing and verified tools will not be considered.

10.	Other exclusion criteria	• Non-randomised studies • Non-English language
11.	Context	This review is part of an update of the NICE guideline on Sepsis: recognition, diagnosis and early management (NG51). This guideline update will cover NEWS 2 tool used in young people and adults of 16 years and over presenting to ambulance trusts, acute mental health facilities and acute hospital settings in which NHS care is received. This review will focus on the risk stratification of patients with suspected sepsis triggered by the report from the Academy of Medical Royal Colleges (AoMRC). To help stratify risk of deterioration in adults with suspected sepsis the report recommends the use of the UK's National Early Warning System 2 (NEWS2) scale to identify and respond to patients at risk of acute deterioration. NHS England and NHS Improvement endorse the use of NEWS2, and it is now widely used in acute and ambulance settings.
12.	Primary outcomes (critical outcomes)	• Mortality (e.g. in-hospital mortality, mortality due to sepsis, all-cause mortality measured at 28 days or nearest time point, or as reported in individual studies e.g., 2 days, 28 days, 3 months, 6 months, 9 months, 12 months) • Escalation of care (e.g. increase in NEWS2 score/band, involvement of senior consultant, intensive care unit admission, rehospitalisation or as reported in individual studies) • Hospital readmission rates • Unplanned critical care admission • Health related quality of life (measured by EQ5D or SF-36 or other validated questionnaires)
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).

15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Individual cohort studies and non-randomised studies presenting data on association will be quality assessed using the QUIPS check list. Systematic reviews will be assessed using the ROBIS check list.
16.	Strategy for data synthesis	Data on all included studies will be extracted into evidence tables. Where statistically possible, a meta-analytic approach will be used to give an overall summary effect. Data synthesis for association data (defined as measures of association between one or more factors (which could be either a single variable or a group of variables) and an outcome variable will be implemented. A pairwise meta-analysis of adjusted ORs and RRs will be conducted when possible. Adjusted ORs, HRs and RRs from multivariate models will only be pooled if the same set of factors are used across multiple studies and if the same thresholds to measure factors are used across studies. Where appropriate, HRs will be pooled using the generic inverse-variance method. When meta-analysis is not possible, a narrative approach for data synthesis will be used. All key outcomes from evidence will be presented in GRADE profiles and further summarised in evidence statements. As appropriate GRADE tables for association studies do not exist, to assess the quality of evidence, a modified approach using the GRADE framework will be applied.
17.	Analysis of sub-groups	• Age (young people, adults, and older adults) • People who are approaching the end of their life • People with COVID-19 and suspected sepsis • The type of tool used (NEWS and NEWS2) Statistical heterogeneity will be calculated using the 'Q' statistic with P value set at $P < 0.05$ and will be quantified by the calculation of the I^2 statistic for heterogeneity. If there are sufficient studies, sensitivity analyses will be used to explore, quantify, and control for sources of heterogeneity between studies by excluding studies at high and unclear risk of bias to

		ensure our conclusions are robust. If there are sufficient studies, sensitivity analysis based on sepsis definition (Sepsis 1, 2 or 3) will be performed.		
18.	Type and method of review	☐ Intervention ☐ Diagnostic ☒ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify) Review of association studies		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	6th July		
22.	Anticipated completion date			
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐

		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** Guideline Development Team **5b Named contact e-mail** Sepsis@nice.org.uk **5c Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and Guideline Development Team		
25.	Review team members	From the Guideline Development Team: • Caroline Mulvihill • Teuta Gjuladin-Hellon • Kirsty Hounsell • Daniel Tuvey • Jonathan Littler		
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Development Team, Centre for Guidelines which receives funding from NICE.		

27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=344711&fbclid=IwAR1cv_P9-Bt6w9VlmAwzrjhJfNp7cRZTD2uvm8hw3Wj_iDNztPzoLecJBwU
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Sepsis, risk stratification, NEWS2
33.	Details of existing review of same topic by same authors	

34.	Current review status	☐ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]
36.	Details of final publication	www.nice.org.uk

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Health economic review protocol

No health economic review protocol is included for this review question.

Appendix B – Methods

Literature search, screening, and study selection

Search methods

The searches for the prognostic evidence were run on 30th July 2022. The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley); Cochrane Database of Systematic Reviews (CDSR) (Wiley); Embase (OVID); Medline (OVID). MEDLINE Epub Ahead-of-Print (OVID).

The database searches were supplemented with additional search methods. Searches for grey literature were also undertaken on websites covering government, charities and related organisations.

The searches for the cost effectiveness evidence were run on 30th July. The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley); Cochrane Database of Systematic Reviews (CDSR) (Wiley); EconLit (OVID); Embase (OVID); International HTA database (INAHTA); Medline (OVID). MEDLINE Epub Ahead-of-Print (OVID).

Detailed search strategies for each database and method are provided in Appendix C.

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstracts of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstracts can be stopped, assuming a defined threshold for the proportion of relevant papers which it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- In every review, at least 50% of the identified abstracts (or 1,000 records, if that is a greater number) were always screened.

- After this point, the number of included studies was recorded after every 1,000 records were screened. If, assuming studies were to be found in the remainder of the dataset at the same rate as in that 1,000 records (for example, if 5 includes were found, every subsequent 1,000 records would contain 5 includes), it was estimated that at least 95% of the includable studies in the database had been identified, then the screening was stopped.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of potentially relevant systematic reviews were searched to identify any papers not identified through the primary search.

Incorporating published systematic reviews

For all review questions where a literature search was undertaken looking for a particular study design, systematic reviews containing studies of that design were also included. All potentially eligible studies from those systematic reviews were screened to identify any additional relevant primary studies not found as part of the initial search. However, during this process, systematic reviews or included primary studies that met the eligibility criteria were not identified during the full-text screening.

Evidence of prognostic association studies

In this guideline, association studies are defined as those reporting data showing an association of a predictor (either a single variable or a group of variables) and an outcome variable, where the data are not reported in terms of outcome classification (i.e. diagnostic/prognostic accuracy). Data were reported as adjusted odds ratios (ORs) as were measured at a specific time-point. Data reported in terms of model fit or predictive accuracy were not assessed. Odds ratios were calculated when studies did not report any of the measures of interest (hazard ratios, risk ratios or odds ratios) but reported extractable data for the calculation of odds ratios.

Quality assessment

The Quality In Prognosis Studies (QUIPS) tool to assess risk of bias in prognostic factor cohort studies. The QUIPS tool uses six important domains that are critically appraised when evaluating validity and bias in studies of prognostic factors:

- Study participation
- Study attrition
- Prognostic factor measurement
- Outcome measurement
- Study confounding
- Statistical analysis and reporting

Each domain includes multiple items that are judged separately. Based on the ratings of the included items, a conclusive judgment of the risk of bias within each domain is made and expressed on a three-grade scale (high, moderate or low risk of bias).

Therefore, each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.

- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.

- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, predictors and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, predictors and/or outcomes.

- Partially indirect – Important deviations from the protocol in one of the population, predictors and/or outcomes.
- Indirect – Important deviations f Each domain was assessed as being at low, high or unclear risk of bias.

Quality assessment and directness are presented in Appendix E.

Methods for combining predictive modelling evidence

Combining the evidence from univariate analyses (hazard ratios using the inverse-variance method, and odds ratios or risk ratios using the Mantel Haenszel method) was not performed due to the different NEWS risk categories (cut-off points) and different confounding factors used in the included studies. Forest plots were generated in RevMan5 to visualise the association of different risk categories with corresponding outcomes for each study and are presented in Appendix F.

Minimal clinically important differences (MIDs)

The Guideline Committee did not prospectively define clinical decision thresholds for association outcomes based on the degree of association that would be considered clinically important for decision making. Therefore, the Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline, however none were identified.

In cases where the minimal clinically important difference thresholds could not be identified in the COMET data base and committee were unable to define a clinical decision threshold by consensus, the line of no effect was used at the clinical decision threshold for the purpose of rating imprecision in GRADE.

Modified GRADE for predictive evidence

GRADE has not been developed for use with predictive studies; therefore, a modified approach was applied using the GRADE framework. Data from cohort studies was initially rated as high quality with the quality of the evidence for each outcome then downgraded or not from this initial point.

Table 8: Rationale for downgrading quality of evidence for predictive modelling questions

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.

GRADE criteria	Reasons for downgrading quality
	Extremely serious: If greater than 33.3% of the weight in a meta-analysis came from studies at critical risk of bias, the outcome was downgraded three levels Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e., the outcome was not statistically significant). If relative risk could not be estimated (due to zero events in both arms), outcome was downgraded for very serious imprecision as effect size could not be calculated. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if either of the following conditions were met:

- Data showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Summary of evidence is presented in section 1.1.5. This summarises the effect size, quality of evidence and interpretation of the evidence in relation to the significance of the data.

The full GRADE tables can be found in Appendix G.

Publication bias

Publication bias was not assessed due to the small number of included studies (n=2).

Appendix C – Literature search strategies

Evidence review for stratifying risk of severe illness or death from sepsis.

Background and development

Search design and peer review

A NICE information specialist conducted the literature searches for the evidence review. The searches were run on 30 June 2022. This search report is compliant with the requirements of PRISMA-S.

The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The sepsis terms were based on the strategy used for Sepsis: recognition, diagnosis and early management (2017) NICE guideline 51.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

The search was limited from 2012 to 2022 as defined in the review protocol.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Key decisions

The review protocols were only interested in evidence related to one assessment tool (NEWS and NEWS 2) as opposed to the multiple tools that were included in the original guideline (Sepsis: recognition, diagnosis and early management (2017) NICE guideline 51). The scoping search (March 2022) identified less than 500 records in Medline and just over 100 in Medline in Process, which was a very small evidence base. The original guideline search included a set of umbrella terms for assessment tools and a set of named tools. As the review protocols only wanted evidence on NEWS and NEWS2 the broader set of umbrella terms nor the set of name tools were not included in the search strategy. To maximise the number of NEWS and NEWS2 results, the strategy was kept short and focused with 2 sets (sepsis AND news/news2).

Due to the small number of results from the effectiveness search it was decided not to apply a cost-effectiveness filter to the cost-effectiveness searches.

Clinical/public health searches

Main search – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	30/06/22	Wiley	Issue 6 of 12, June 2022	10
Cochrane Database of Systematic Reviews (CDSR)	30/06/22	Wiley	Issue 6 of 12, June 2022	1
Embase	30/06/22	Ovid	Embase 1996 to 2022 June 29	353
MEDLINE	30/06/22	Ovid	Ovid MEDLINE(R) 1996 to June 29, 2022	138
MEDLINE Epub Ahead-of-Print	30/06/22	Ovid	Ovid MEDLINE(R) Epub Ahead of Print June 29, 2022	7

Main search – Additional methods

Additional method	Date searched	No. of results downloaded
Web searching	4-5 July 2022	19

Search strategy history

Database name: Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor: [Sepsis] explode all trees 4918
#2 sepsis:ti,ab,kw 12176
#3 MeSH descriptor: [Blood-Borne Pathogens] this term only 30
#4 (blood* near/2 (pathogen* or poison*)):ti,ab,kw 329
#5 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees 5312
#6 "systemic inflammatory response syndrome*":ti,ab,kw 1167
#7 sirs:ti,ab,kw 794
#8 (septicaemi* or septicemi*):ti,ab,kw 1075
#9 ((septic or cryptic) near/2 shock):ti,ab,kw 3417
#10 (pyaemi* or pyemi* or pyohemi*):ti,ab,kw 8
#11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*):ti,ab,kw 6146
#12 (hypotension near/3 induced near/3 hypoperfusion) 1
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 21320
#15 ("National Early Warning Score*"):ti,ab,kw (Word variations have been searched) 121
#16 ("National Early Warning Score* 2"):ti,ab,kw (Word variations have been searched) 34

#17 (NEWS2):ti,ab,kw (Word variations have been searched) 51
#18 (NEWS):ti,ab,kw (Word variations have been searched) 2813
#19 #15 or #16 or #17 or #18 2877
#20 #13 and #19 with Cochrane Library publication date Between Jan 2012 and Jun 2022 25
#21 #13 and #19 with Publication Year from 2012 to 2022, in Trials 20
#22 "conference":pt or (clinicaltrials or trialsearch):so 599319
#23 #20 not #22 1
#24 #21 not #22 10
#25 ("systemic inflammatory response syndrome*"):ti,ab,kw (Word variations have been searched) 1170

Database name: Cochrane Database of Systematic Reviews (CDSR)

#1 MeSH descriptor: [Sepsis] explode all trees 4918
#2 sepsis:ti,ab,kw 12176
#3 MeSH descriptor: [Blood-Borne Pathogens] this term only 30
#4 (blood* near/2 (pathogen* or poison*)):ti,ab,kw 329
#5 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees 5312
#6 "systemic inflammatory response syndrome*":ti,ab,kw 1167
#7 sirs:ti,ab,kw 794
#8 (septicaemi* or septicemi*):ti,ab,kw 1075
#9 ((septic or cryptic) near/2 shock):ti,ab,kw 3417
#10 (pyaemi* or pyemi* or pyohemi*):ti,ab,kw 8
#11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*):ti,ab,kw 6146
#12 (hypotension near/3 induced near/3 hypoperfusion) 1
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 21320
#15 ("National Early Warning Score*"):ti,ab,kw (Word variations have been searched) 121
#16 ("National Early Warning Score* 2"):ti,ab,kw (Word variations have been searched) 34
#17 (NEWS2):ti,ab,kw (Word variations have been searched) 51
#18 (NEWS):ti,ab,kw (Word variations have been searched) 2813
#19 #15 or #16 or #17 or #18 2877
#20 #13 and #19 with Cochrane Library publication date Between Jan 2012 and Jun 2022 25
#21 #13 and #19 with Publication Year from 2012 to 2022, in Trials 20
#22 "conference":pt or (clinicaltrials or trialsearch):so 599319
#23 #20 not #22 1
#24 #21 not #22 10
#25 ("systemic inflammatory response syndrome*"):ti,ab,kw (Word variations have been searched) 1170

Database name: Embase

1	exp sepsis/	272511
2	sepsis.ti,ab.	152596
3	bloodborne bacterium/	1921
4	(blood* adj2 (pathogen* or poison*)).ti,ab.	3583

5	exp systemic inflammatory response syndrome/	283102
6	'systemic inflammatory response syndrome*'.ti,ab.	7991
7	sirs.ti,ab.	10649
8	(septicaemi* or septicemi*).ti,ab.	16169
9	((septic or cryptic) adj2 shock).ti,ab.	37554
10	(pyaemi* or pyemi* or pyohemi*).ti,ab.	80
11	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab.	79492
12	(hypotension adj3 induced adj3 hypoperfusion).ti,ab.	6
13	or/1-12	373042
14	"National Early Warning Score*".ti,ab,kw.	787
15	"National Early Warning Score* 2".ti,ab,kw.	119
16	NEWS2.ti,ab,kw.	204
17	NEWS.ti,ab,kw.	25102
18	National Early Warning Score/	308
19	or/14-18	25512
20	13 and 19	422
21	limit 20 to yr="2012 -Current"	358
22	limit 21 to english language	353
23	Animals/ not (Humans/ and Animals/)	576993
24	22 not 23	353

Database name: MEDLINE

1	exp sepsis/	101110
2	sepsis.ti,ab.	78657
3	blood-borne pathogens/	2719
4	(blood* adj2 (pathogen* or poison*)).ti,ab.	2302
5	exp systemic inflammatory response syndrome/	108074
6	'systemic inflammatory response syndrome*'.ti,ab.	4745
7	sirs.ti,ab.	5229
8	(septicaemi* or septicemi*).ti,ab.	10082
9	((septic or cryptic) adj2 shock).ti,ab.	18638
10	(pyaemi* or pyemi* or pyohemi*).ti,ab.	47
11	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab.	47902
12	(hypotension adj3 induced adj3 hypoperfusion).ti,ab.	3
13	or/1-12	184174
14	"National Early Warning Score*".ti,ab,kw.	431

15	"National Early Warning Score* 2".ti,ab,kw.	74
16	NEWS2.ti,ab,kw.	116
17	NEWS.ti,ab,kw.	13435
18	or/14-17	13643
19	13 and 18	164
20	limit 19 to yr="2012 -Current"	145
21	limit 20 to english language	138
22	Animals/ not (Humans/ and Animals/)	2802987
23	21 not 22	138

Database name: MEDLINE Epub Ahead-of-Print

1	sepsis.ti,ab.	1264
2	(blood* adj2 (pathogen* or poison*)).ti,ab.	32
3	'systemic inflammatory response syndrome*'.ti,ab.	58
4	sirs.ti,ab.	74
5	(septicaemi* or septicemi*).ti,ab.	101
6	((septic or cryptic) adj2 shock).ti,ab.	267
7	(pyaemi* or pyemi* or pyohemi*).ti,ab.	0
8	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab.	515
9	(hypotension adj3 induced adj3 hypoperfusion).ti,ab.	0
10	or/1-9	2068
11	"National Early Warning Score*".ti,ab,kw.	17
12	"National Early Warning Score* 2".ti,ab,kw.	7
13	NEWS2.ti,ab,kw.	12
14	NEWS.ti,ab,kw.	820
15	or/11-14	834
16	10 and 15	7
17	limit 16 to yr="2012 -Current"	7
18	limit 17 to english language	7

Additional search methods

Source name: NHS England

Name	NHS England
URL	https://www.england.nhs.uk/
Date searched	04/07/22
Segment or dates covered by search,	2017 onwards

including any specific sections browsed	
Search terms	Sepsis AND (NEWS or NEWS2) + date range (from 01/01/17)
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	Browsed for relevance
No. of results	6

Source name: Department of Health and Social Care

Name	Department of Health and Social Care
URL	https://www.gov.uk/
Date searched	05/07/22
Segment or dates covered by search, including any specific sections browsed	Search function: Health and social care as topic
Search terms	Sepsis AND (news or news2)
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	Any result referring to NEWS or NEWS2
No. of results	0

Source name: Royal College of Physicians

Name	Royal College of Physicians
URL	https://www.rcplondon.ac.uk/
Date searched	04/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards
Search terms	Sepsis
How the results were selected [state how many results you reviewed if you did not check them all	Reviewed 34 results

e.g. the first 100 results or the first 10 pages]	
No. of results	8

Source name: Royal College of Emergency Medicine

Name	Royal College of Emergency Medicine
URL	https://rcem.ac.uk/
Date searched	04/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards
Search terms	Sepsis
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	Any result referring to NEWS or NEWS2
No. of results	1

Source name: Sepsis Trust

Name	Sepsis Trust
URL	Home - Sepsis Trust
Date searched	05/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards
Search terms	Browsed "Professional resources"
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	Any result referring to NEWS or NEWS2
No. of results	3

Source name: Surviving Sepsis Campaign

Name	Surviving Sepsis Campaign
URL	Surviving Sepsis Campaign (SSC) | SCCM
Date searched	05/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards
Search terms	Browsed: Guidelines and bundles; Tools and education
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	Any result referring to NEWS or NEWS2
No. of results	1

Source name: Sepsis Alliance

Name	Sepsis Alliance
URL	Sepsis Alliance
Date searched	05/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards. Browsed: Sepsis information guides;
Search terms	-
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	Any result referring to NEWS or NEWS2
No. of results	0

Source name: Sepsis Research

Name	Sepsis Research
URL	https://sepsisresearch.org.uk/
Date searched	05/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards

Search terms	NEWS or NEWS2
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	No relevant results
No. of results	0

Source name: First Response

Name	First Response
URL	https://www.firstresponse.org.uk/medical-training/news2
Date searched	05/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards
Search terms	Browsed: Medical training: NEWS2
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	No relevant results
No. of results	0

Source name: TRIP (Turning Research into Practice) database

Name	TRIP (Turning Research into Practice) database
URL	https://www.tripdatabase.com/
Date searched	05/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards
Search terms	Sepsis AND (news OR news2)
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	Browsed first 50 results
No. of results	0

Source name: FERN (Find Evidence, Retrieve Now)

Name	FERN (Find Evidence, Retrieve Now)
URL	Internal NICE database
Date searched	05/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards
Search terms	Sepsis AND (news or news2)
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	Browsed first 100 results for references to NEWS or NEWS2
No. of results	1

Source name: Google

Name	Google
URL	https://www.google.co.uk/
Date searched	05/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards
Search terms	Sepsis AND (news or news2)
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	Browsed first 100 results for references to NEWS or NEWS2
No. of results	5

Cost-effectiveness searches

Main search – Databases

EconLit	30/06/22	OVID	Econlit 1886 to June 23, 2022	0
Embase	30/06/22	Ovid	Embase 1996 to 2022 June 29	353
INAHTA	30/06/22	INAHTA	-	5
MEDLINE	30/06/22	Ovid	Ovid MEDLINE(R) 1996 to June 29, 2022	138
MEDLINE Epub Ahead-of-Print	30/06/22	Ovid	Ovid MEDLINE(R) Epub Ahead of Print June 29, 2022	7
Cochrane Central Register of Controlled Trials (CENTRAL)	30/06/22	Wiley	Issue 6 of 12, June 2022	10
Cochrane Database of Systematic Reviews (CDSR)	30/06/22	Wiley	Issue 6 of 12, June 2022	1

Search strategy history

Database name: EconLit

1	sepsis.ti,ab.	18
2	(blood* adj2 (pathogen* or poison*)).ti,ab.	0
3	'systemic inflammatory response syndrome*'.ti,ab.	0
4	sirs.ti,ab.	13
5	(septicaemi* or septicemi*).ti,ab.	2
6	((septic or cryptic) adj2 shock).ti,ab.	1
7	(pyaemi* or pyemi* or pyohemi*).ti,ab.	0
8	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab.	7
9	(hypotension adj3 induced adj3 hypoperfusion).ti,ab.	0
10	or/1-9	40
11	"National Early Warning Score*".ti,ab,kw.	1
12	"National Early Warning Score* 2".ti,ab,kw.	0
13	NEWS2.ti,ab,kw.	0
14	NEWS.ti,ab,kw.	9211
15	or/11-14	9211
16	10 and 15	0
17	limit 16 to yr="2012 -Current"	0

Database name: Embase

1	exp sepsis/	272511
2	sepsis.ti,ab.	152596
3	bloodborne bacterium/	1921
4	(blood* adj2 (pathogen* or poison*)).ti,ab.	3583
5	exp systemic inflammatory response syndrome/	283102
6	'systemic inflammatory response syndrome*'.ti,ab.	7991
7	sirs.ti,ab.	10649
8	(septicaemi* or septicemi*).ti,ab.	16169
9	((septic or cryptic) adj2 shock).ti,ab.	37554
10	(pyaemi* or pyemi* or pyohemi*).ti,ab.	80
11	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab.	79492
12	(hypotension adj3 induced adj3 hypoperfusion).ti,ab.	6
13	or/1-12	373042
14	"National Early Warning Score*".ti,ab,kw.	787
15	"National Early Warning Score* 2".ti,ab,kw.	119
16	NEWS2.ti,ab,kw.	204
17	NEWS.ti,ab,kw.	25102
18	National Early Warning Score/	308
19	or/14-18	25512
20	13 and 19	422
21	limit 20 to yr="2012 -Current"	358
22	limit 21 to english language	353
23	Animals/ not (Humans/ and Animals/)	576993
24	22 not 23	353

Database name: INAHTA

((NEWS)[abs]) OR ((NEWS)[title]) OR ((NEWS)[abs]) OR ((NEWS2)[abs]) OR ((NEWS2)[title]) OR (("National Early Warning Score 2")[title]) OR (("National Early Warning Score 2")[abs]) OR (("National Early Warning Score")[abs]) OR (("National Early Warning Score")[title])

Database name: MEDLINE

1	exp sepsis/	101110
2	sepsis.ti,ab.	78657
3	blood-borne pathogens/	2719

4	(blood* adj2 (pathogen* or poison*)).ti,ab.	2302
5	exp systemic inflammatory response syndrome/	108074
6	'systemic inflammatory response syndrome*'.ti,ab.	4745
7	sirs.ti,ab.	5229
8	(septicaemi* or septicemi*).ti,ab.	10082
9	((septic or cryptic) adj2 shock).ti,ab.	18638
10	(pyaemi* or pyemi* or pyohemi*).ti,ab.	47
11	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab.	47902
12	(hypotension adj3 induced adj3 hypoperfusion).ti,ab.	3
13	or/1-12	184174
14	"National Early Warning Score*".ti,ab,kw.	431
15	"National Early Warning Score* 2".ti,ab,kw.	74
16	NEWS2.ti,ab,kw.	116
17	NEWS.ti,ab,kw.	13435
18	or/14-17	13643
19	13 and 18	164
20	limit 19 to yr="2012 -Current"	145
21	limit 20 to english language	138
22	Animals/ not (Humans/ and Animals/)	2802987
23	21 not 22	138

Database name: MEDLINE Epub Ahead-of-Print

1	sepsis.ti,ab.	1264
2	(blood* adj2 (pathogen* or poison*)).ti,ab.	32
3	'systemic inflammatory response syndrome*'.ti,ab.	58
4	sirs.ti,ab.	74
5	(septicaemi* or septicemi*).ti,ab.	101
6	((septic or cryptic) adj2 shock).ti,ab.	267
7	(pyaemi* or pyemi* or pyohemi*).ti,ab.	0
8	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab.	515
9	(hypotension adj3 induced adj3 hypoperfusion).ti,ab.	0
10	or/1-9	2068
11	"National Early Warning Score*".ti,ab,kw.	17
12	"National Early Warning Score* 2".ti,ab,kw.	7
13	NEWS2.ti,ab,kw.	12

14	NEWS.ti,ab,kw.	820
15	or/11-14	834
16	10 and 15	7
17	limit 16 to yr="2012 -Current"	7
18	limit 17 to english language	7

Database name: Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor: [Sepsis] explode all trees 4918
#2 sepsis:ti,ab,kw 12176
#3 MeSH descriptor: [Blood-Borne Pathogens] this term only 30
#4 (blood* near/2 (pathogen* or poison*)):ti,ab,kw 329
#5 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees 5312
#6 "systemic inflammatory response syndrome*":ti,ab,kw 1167
#7 sirs:ti,ab,kw 794
#8 (septicaemi* or septicemi*):ti,ab,kw 1075
#9 ((septic or cryptic) near/2 shock):ti,ab,kw 3417
#10 (pyaemi* or pyemi* or pyohemi*):ti,ab,kw 8
#11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*):ti,ab,kw 6146
#12 (hypotension near/3 induced near/3 hypoperfusion) 1
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 21320
#15 ("National Early Warning Score*"):ti,ab,kw (Word variations have been searched) 121
#16 ("National Early Warning Score* 2"):ti,ab,kw (Word variations have been searched) 34
#17 (NEWS2):ti,ab,kw (Word variations have been searched) 51
#18 (NEWS):ti,ab,kw (Word variations have been searched) 2813
#19 #15 or #16 or #17 or #18 2877
#20 #13 and #19 with Cochrane Library publication date Between Jan 2012 and Jun 2022 25
#21 #13 and #19 with Publication Year from 2012 to 2022, in Trials 20
#22 "conference":pt or (clinicaltrials or trialsearch):so 599319
#23 #20 not #22 1
#24 #21 not #22 10
#25 ("systemic inflammatory response syndrome*"):ti,ab,kw (Word variations have been searched) 1170

Database name: Cochrane Database of Systematic Reviews (CDSR)

#1 MeSH descriptor: [Sepsis] explode all trees 4918
#2 sepsis:ti,ab,kw 12176
#3 MeSH descriptor: [Blood-Borne Pathogens] this term only 30
#4 (blood* near/2 (pathogen* or poison*)):ti,ab,kw 329
#5 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees 5312
#6 "systemic inflammatory response syndrome*":ti,ab,kw 1167
#7 sirs:ti,ab,kw 794
#8 (septicaemi* or septicemi*):ti,ab,kw 1075

#9 ((septic or cryptic) near/2 shock):ti,ab,kw 3417
#10 (pyaemi* or pyemi* or pyohemi*):ti,ab,kw 8
#11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*):ti,ab,kw 6146
#12 (hypotension near/3 induced near/3 hypoperfusion) 1
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 21320
#15 ("National Early Warning Score*"):ti,ab,kw (Word variations have been searched) 121
#16 ("National Early Warning Score* 2"):ti,ab,kw (Word variations have been searched) 34
#17 (NEWS2):ti,ab,kw (Word variations have been searched) 51
#18 (NEWS):ti,ab,kw (Word variations have been searched) 2813
#19 #15 or #16 or #17 or #18 2877
#20 #13 and #19 with Cochrane Library publication date Between Jan 2012 and Jun 2022 25
#21 #13 and #19 with Publication Year from 2012 to 2022, in Trials 20
#22 "conference":pt or (clinicaltrials or trialsearch):so 599319
#23 #20 not #22 1
#24 #21 not #22 10
#25 ("systemic inflammatory response syndrome*"):ti,ab,kw (Word variations have been searched) 1170

Appendix D – Prognostic evidence study selection

Figure 1: Flow chart of clinical study selection for the review of stratifying risk of severe illness or death from sepsis

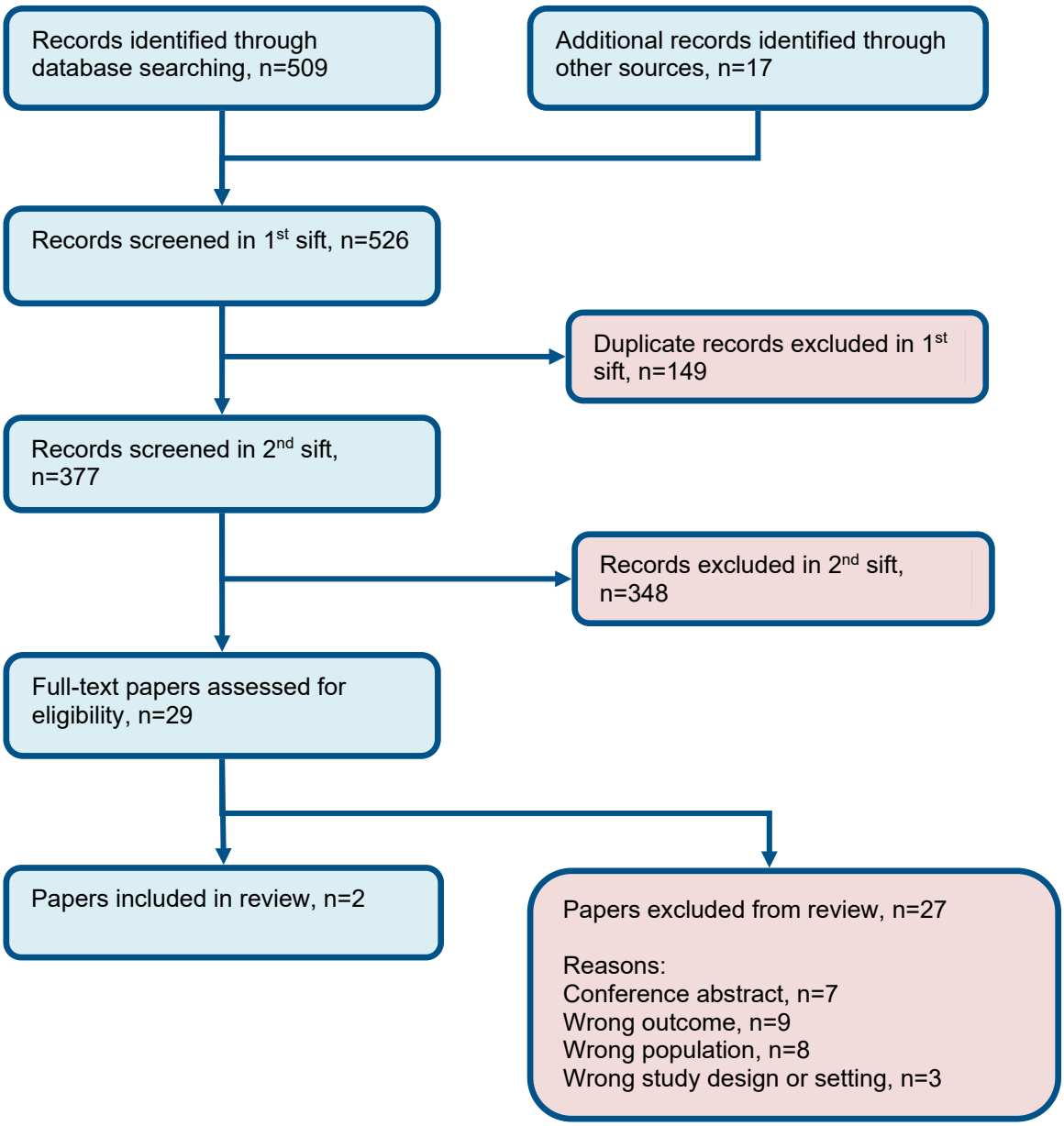
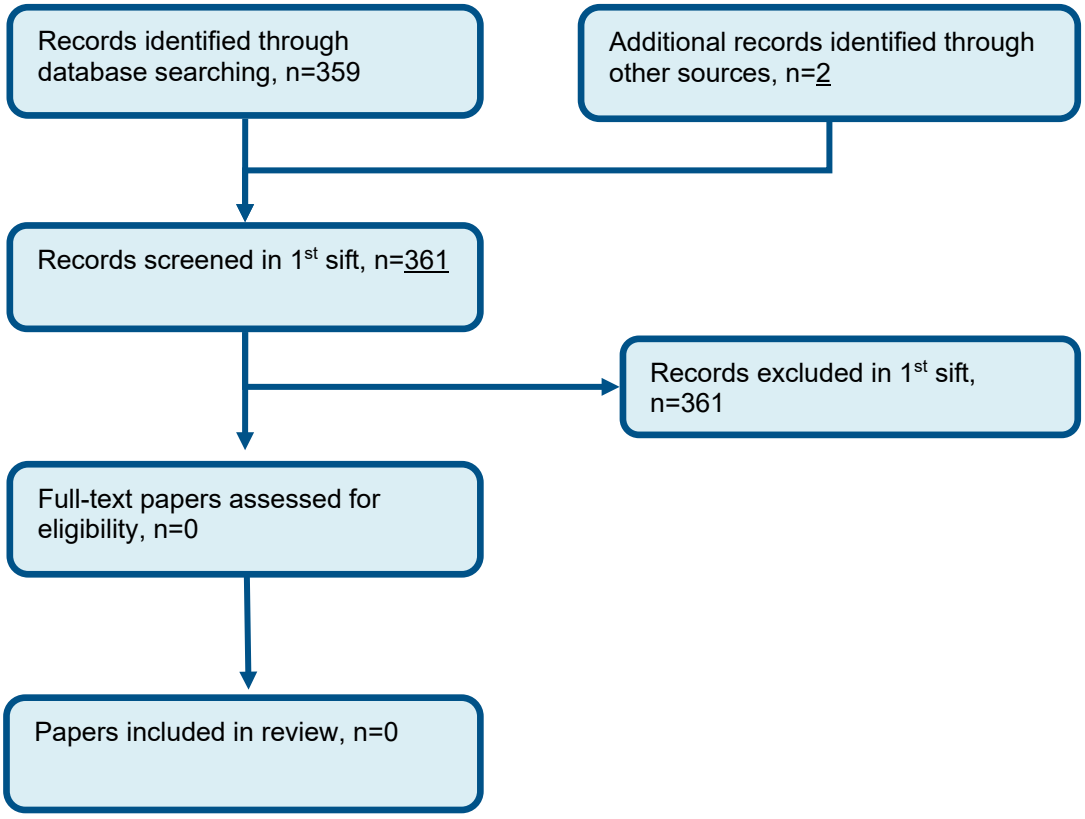


Figure 2: Flow chart of economic study selection for the review of stratifying risk of severe illness or death from sepsis



Appendix E – Evidence tables

Table 9: Corfield et al, 2014

Bibliographic Reference	Corfield, Alasdair R; Lees, Fiona; Zealley, Ian; Houston, Gordon; Dickie, Sarah; Ward, Kirsty; McGuffie, Crawford; Scottish Trauma Audit Group Sepsis Steering, Group; Utility of a single early warning score in patients with sepsis in the emergency department.; Emergency medicine journal: EMJ; 2014; vol. 31 (no. 6); 482-7

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location: Scotland, UK Study setting:20 district general and teaching hospital EDs Study dates: March and May 2009 Sources of funding: Not reported
Inclusion criteria	• Adult patients (>16 years) presenting to EDs • Suspicion or confirmation of infection within 2 days of attendance • Two or more of the following physiological derangements: temperature >38.3°C or <36°C; heart rate >90 bpm; respiratory rate >20/min; white cell count of >12 000/µl or <4000/µl or >10% immature forms; acutely altered mental status; systolic blood pressure <90 mm Hg; and blood glucose >7.7 mmol/l (in the absence of diabetes).
Exclusion criteria	Non-infective cause for attendance such as acute cardiac ischaemia, trauma or stroke presenting to EDs
Number of participants and recruitment methods	A total of 5285 patients fulfilled the entry criteria. Data were collected retrospectively by local audit coordinators at each hospital on a variety of demographic, physiological, process and outcome variables using a standardised proforma. Where available, patient observations taken on attendance were recorded. Hospital information systems were then interrogated to ascertain whether the patient had an inpatient stay of at least 2 days. Of the 5285 patients identified, complete data were collected for 3890 (74%). For the purposes of this analysis, only patients who presented with or developed signs of sepsis prior to leaving the ED were included (N=2489). In this sample of 2489 patients, patients were excluded if they did not have a full set of observations made as part of their first set of observations. This resulted in a final sample size of 2003
Length of follow-up	All patients were followed to discharge or death.
Loss to follow up	None. Patients who died within the first 2 days, and who therefore may have been omitted from data collection, were identified retrospectively using General Register Office Scotland records.

Outcome(s) of interest	ICU admission within 2 days of attendance 30-day mortality (in hospital).
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	NEWS categories: 0–4; 5–6; 7–8; 9–20
Covariates adjusted for in the multivariable regression modelling	Age
Additional comments	None

Population characteristics

Characteristic	**Study (N = 2003)**
Female Sample size	n = 1054; % = 53
Male Sample size	n = 949; % = 47
Mean age (SD) Median (IQR)	72 (59 to 81)
NEWS Median (IQR)	7 (4 to 9)

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	**Question**	**Answer**
Study participation	Summary Study participation	Moderate risk of bias *(Only age and sex reported at baseline)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias

Section	Question	Answer
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Outcomes adjusted only for age. No other confounding factors considered.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(No other confounding factors accounted for and missing baseline data)*
Overall risk of bias and directness	Directness	Indirectly applicable

Table 10: Hargreaves et al, 2020

Bibliographic Reference	Hargreaves, Duncan Sebastian; de Carvalho, Joshua Lucas Jarman; Smith, Laura; Picton, Graham; Venn, Richard; Hodgson, Luke Eliot; Persistently elevated early warning scores and lactate identifies patients at high risk of mortality in suspected sepsis.; European journal of emergency medicine: official journal of the European Society for Emergency Medicine; 2020; vol. 27 (no. 2); 125-131

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location: UK Study setting: two UK non-specialist hospitals and South-East Coast Ambulance Service. Study dates: 2015-2017 Sources of funding: Not reported
Inclusion criteria	'Suspicion of sepsis' alert (combining expert opinion and national guidelines) 'Suspicion of sepsis' screen by the triage ED nurse consisting of 3 stages: (1) suspicion of infection based on presenting history; (2) ambulance and triage assessment; (3) either ≥2 systemic inflammatory response syndrome (SIRS) criteria as or a NEWS ≥5 points
Exclusion criteria	Cases not brought in by ambulance (i.e., walk-ins) and incomplete ambulance observation data

Number of participants and recruitment methods	N=1233 Prospective data collection with a retrospective notes review over 2 years (2015–2017) in two UK non specialist hospitals.
Length of follow-up	30-day
Loss to follow up	None. Those discharged before day 30 were checked by administrative staff against death registers and GP records before being recorded as alive.
Outcome(s) of interest	30-day mortality (prehospital, ED and hospital ward) Intensive care admission Length of stay (days)
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	NEWS≥5 vs NEWS<5
Covariates adjusted for in the multivariable regression modelling	Lactate levels
Additional comments	No other confounding factors mentioned

Population characteristics

Characteristic	**Study (N = 1233)**
Female Sample size	n = 564; % = 46
Male Sample size	n = 669; % = 54
Mean age (SD) Median (IQR)	79 (68 to 86)
Congestive cardiac failure Sample size	n = 193; % = 17
Diabetes Sample size	n = 307; % = 26
Vascular disease	n = 308; % = 26

Characteristic	Study (N = 1233)
Sample size	
Liver disease Sample size	n = 37
Prehospital NEWS score Median (IQR)	8 (6 to 10)
ED NEWS score Median (IQR)	6 (4 to 8)
Ward admission NEWS score Median (IQR)	3 (2 to 6)

Coding and source	Suspected sepsis (N = 1293)
Sepsis Sample size	n = 189
Infection Sample size	n = 895
Respiratory Sample size	n = 541; % = 44
Urinary Sample size	n = 188; % = 15
Suspected source not documented in ED record Sample size	n = 408; % = 33
Skin/soft tissue Sample size	n = 48; % = 4
Abdominal/pelvic Sample size	n = 37; % = 3
Head and neck/dental Sample size	n = 4; % = 0

Coding and source	Suspected sepsis (N = 1293)
Central nervous system Sample size	n = 3; % = 0
Musculoskeletal Sample size	n = 2; % = 0
Neutropenia Sample size	n = 1; % = 0

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Low risk of bias *(Logistic regression was performed using backward stepwise selection starting with 11 variables including age, change in NEWS, ED lactate, past medical history and acute kidney injury*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Indirectly applicable

ED = emergency department; ICU = intensive care unit; NEWS = National Early Warning Score

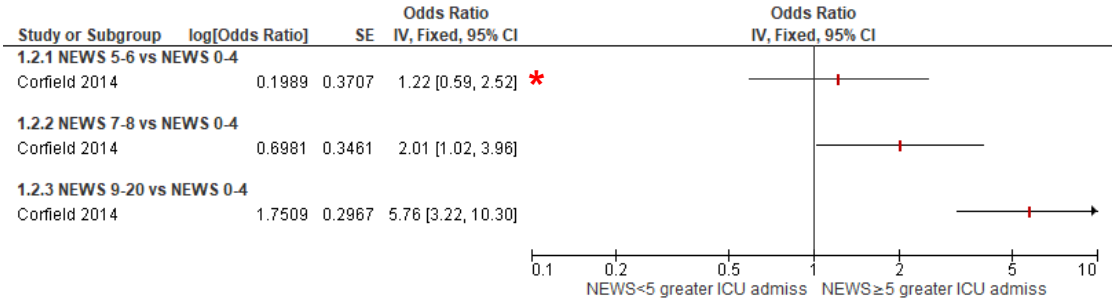
Appendix F – Forest plots

Forest plots of the association of different NEWS risk categories and primary outcomes in each included study are listed below:

Outcome: ICU admission

Study: Corfield et al, 2014

Figure 3: Forest plot of adjusted ORs for admission to ICU within 2 days associated with higher risk NEWS categories (5-6; 7-8 and 9-20) relative to the lowest risk NEWS category (0-4)



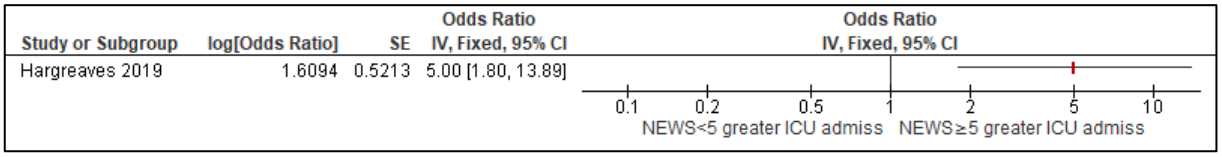
Note: OR greater than 1 is associated with greater ICU admission in higher NEWS risk bands relative to the NEWS band 0-4

*Could not differentiate (95%CI crosses the line of MID)

OR=odds ratio. ICU=intensive care unit. NEWS=National Warning Score

Study: Hargreaves et al, 2020

Figure 4: Forest plot of adjusted ORs for admission to ICU associated with persistent elevation of NEWS ≥ 5 score (prehospital, prehospital + ED, prehospital + ED + ward admission) relative to the resolved NEWS score <5 points on ED arrival



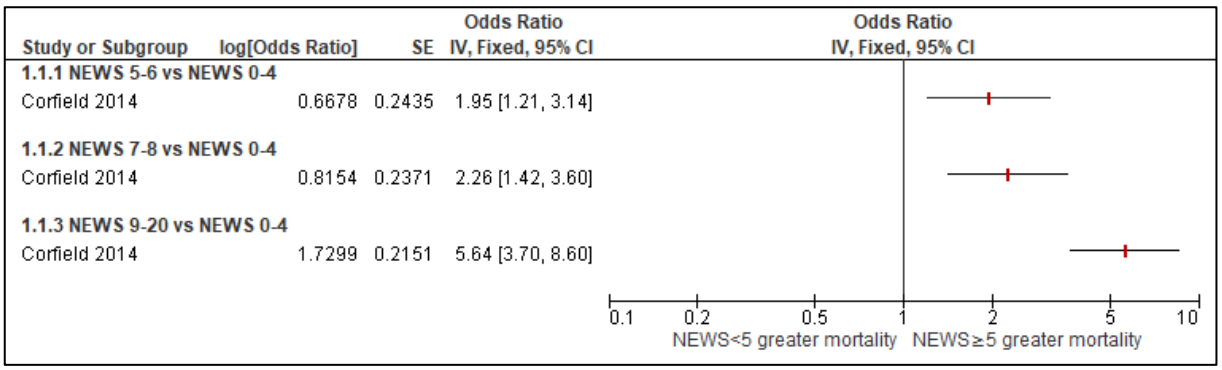
Note: OR greater than 1 is associated with greater 30-day mortality in NEWS≥5 relative to NEWS<5

OR=odds ratio. ICU=intensive care unit. NEWS=National Warning Score

Outcome: 30-day mortality

Study: Corfield et al, 2014

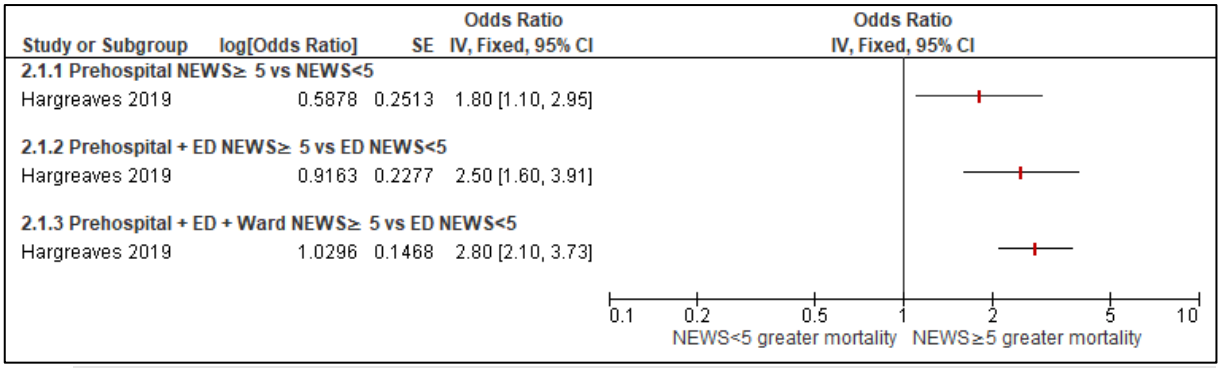
Figure 5: Forest plot of adjusted ORs for 30-day mortality associated with higher risk NEWS categories (5-6; 7-8 and 9-20) relative to the lowest risk NEWS category (0-4)



Note: OR greater than 1 is associated with greater 30-day mortality in higher NEWS risk bands relative to the NEWS band 0-4
OR=odds ratio. NEWS=National Warning Score

Study: Hargreaves et al, 2020

Figure 6: Forest plot of adjusted ORs for 30-day mortality associated with persistent elevation of NEWS ≥ 5 score (prehospital, prehospital + ED, prehospital + ED + hospital ward) relative to the resolved NEWS score <5 points



Notes: *OR greater than 1 is associated with greater 30-day mortality in NEWS ≥5 relative to NEWS<5
OR=odds ratio. ED=emergency department. NEWS=National Warning Score

Appendix G – modified GRADE tables for prognostic association studies

The modified GRADE tables are presented separately for each study.

Outcome: ICU admission

Study: Corfield et al, 2014

Table 11: Adjusted ORs for admission to ICU within 2 days associated with higher risk NEWS categories (5-6; 7-8 and 9-20) relative to the lowest risk NEWS category (0-4)

Study design	Sample size	MID	Measure of association: adjusted ORs (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
ICU (within 2 day) admissions: NEWS score 5-6 vs NEWS score 0-4 (OR>1 associated with greater ICU admissions in NEWS 5-6 relative to NEWS score 0-4)								
Retrospective cohort study	N= 987 (458 vs 529)	Line of no effect	1.22 [0.59, 2.54]	Serious[1]	NA[2]	Serious[3]	Serious[4]	⊕OOO Very low
ICU (within 2 day) admissions: NEWS score 7-8 vs NEWS score 0-4 (OR>1 associated with greater ICU admissions in NEWS 7-8 relative to NEWS score 0-4)								
Retrospective cohort study	N=979 (450 vs 529)	Line of no effect	2.01 [1.02, 3.97]	Serious[1]	NA[2]	Serious[3]	Not serious	⊕⊕OO Low
ICU (within 2 day) admissions: NEWS score 9-20 vs NEWS score 0-4 (OR>1 associated with greater ICU admissions in NEWS 9-20 relative to NEWS score 0-4)								
Retrospective cohort study	N=1094 (565 vs 529)	Line of no effect	5.76 [3.22, 10.31]	Serious[1]	NA[2]	Serious[3]	Not serious	⊕⊕OO Low

OR= odds ratio. CI=confidence interval. NA = not applicable. ICU=intensive care unit. NEWS=National Early Warning Score

1. Missing baseline characteristics; confounding factors other than age not accounted for
2. Only one study, inconsistency not applicable
3. Downgraded for indirectness as data assessed using the NEWS tool (as per protocol, Appendix A)
4. Downgraded by 1 increment as 95% CI crosses the end of the defined MID

Study: Hargreaves et al, 2020

Table 12: Adjusted ORs for admission to ICU associated with persistent elevation of NEWS ≥ 5 score (prehospital, prehospital + ED, prehospital + ED + ward admission) relative to the resolved NEWS score <5 points on ED arrival

Study design	Sample size*	MIDs	Measure of association: adjusted ORs (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
ICU admission: Prehospital + ED NEWS ≥5 vs ED NEWS <5 (OR>1 associated with greater ICU admission in NEWS ≥5 relative to NEWS<5)								
Retrospective cohort study	8.3% vs 1.8%	Line of no effect	1.95 [1.21, 3.14]	Not serious	NA[1]	Serious[2]	Not serious	⊕⊕⊕O Moderate

*Sample size could not be calculated
OR= odds ratio. CI=confidence interval.NA = not applicable. NEWS=National Early Warning Score. ICU=intensive care unit. ED=emergency department
1. Only one study, inconsistency not applicable
3. Downgraded for indirectness as data assessed using the NEWS tool (as per protocol, Appendix A)

Outcome: 30-day mortality

Study: Corfield et al, 2014

Table 13: Adjusted ORs for 30-day mortality associated with higher risk NEWS categories (5-6; 7-8 and 9-20) relative to the lowest risk NEWS category (0-4)

Study design	Sample size	MIDs	Measure of association: adjusted ORs (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
30-day mortality: NEWS score 5-6 vs NEWS score 0-4 (OR>1 associated with greater 30-day mortality in NEWS 5-6 relative to NEWS score 0-4)								
Retrospective cohort study	N= 987 (458 vs 529)	Line of no effect	1.95 [1.21, 3.14]	Serious[1]	NA[2]	Serious[3]	Not serious	⊕⊕OO Low
30-day mortality: NEWS score 7-8 vs NEWS score 0-4 (OR>1 associated with greater 30-day mortality in NEWS 7-8 relative to NEWS score 0-4)								
Retrospective cohort study	N=979 (450 vs 529)	Line of no effect	2.26 [1.42, 3.61]	Serious[1]	NA[2]	Serious[3]	Not serious	⊕⊕OO Low
30-day mortality: NEWS score 9-20 vs NEWS score 0-4 (OR>1 associated with greater 30-day mortality in NEWS 9-20 relative to NEWS score 0-4)								
Retrospective cohort study	N=1094 (565 vs 529)	Line of no effect	5.64 [3.70, 8.60]	Serious[1]	NA[2]	Serious[3]	Not serious	⊕⊕OO Low

OR= odds ratio. CI=confidence interval. NA = not applicable. ICU=intensive care unit. NEWS=National Early Warning Score
1. Missing baseline characteristics; confounding factors other than age not accounted for
2. Only one study, inconsistency not applicable
3. Downgraded for indirectness as data assessed using the NEWS tool (as per protocol, Appendix A)

Study: Hargreaves et al, 2020

Table 14: Adjusted ORs for 30-day mortality associated with persistent elevation of NEWS ≥ 5 score (prehospital, prehospital + ED, prehospital + ED + ward admission) relative to the resolved NEWS score <5 points on ED arrival

Study design	Sample size	MIDs	Measure of association: adjusted ORs (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
30-day mortality: Prehospital NEWS ≥5 vs NEWS <5 (OR>1 associated with greater 30-day mortality in NEWS ≥5 relative to NEWS<5)								
Retrospective cohort study	N= 1233 11.9% vs 19.6%	Line of no effect	1.80 [1.1, 3.0]	Not serious	NA[1]	Serious[2]	Not serious	⊕⊕⊕O Moderate
30-day mortality: Prehospital + ED NEWS ≥5 vs ED NEWS <5 (OR>1 associated with greater 30-day mortality in NEWS ≥5 relative to NEWS<5)								
Retrospective cohort study	N=1074 10.2% vs 22.1%	Line of no effect	2.5 [1.6, 4.0]	Not serious	NA[1]	Serious[2]	Not serious	⊕⊕⊕O Moderate
30-day mortality: Prehospital + ED + ward NEWS ≥5 vs ED NEWS <5 (OR>1 associated with greater 30-day mortality in NEWS ≥5 relative to NEWS<5)								
Retrospective cohort study	N=1015 14.3% vs 32.1%	Line of no effect	2.8 [2.1, 3.9	Not serious	NA[1]	Serious[2]	Not serious	⊕⊕⊕O Moderate

OR= odds ratio. CI=confidence interval.NA = not applicable. NEWS=National Early Warning Score. ED=emergency department
1. Only one study, inconsistency not applicable
2. Downgraded for indirectness as data assessed using the NEWS tool (as per protocol, Appendix A)

Appendix H – Economic evidence tables

There are no included studies in this review question.

Appendix I – Health economic model

Original health economic modelling was not prioritised for this review question.

Appendix J – Excluded studies

Clinical studies

Table 14:Lis of excluded studies at full-text stage and reasons for exclusion

Study (N=27)	Code [Reason]
Almutary, A., Althunayyan, S., Alenazi, K. et al. (2020) National early warning score (NEWS) as prognostic triage tool for septic patients. Infection and Drug Resistance 13: 3843-3851	- Study does not contain outcomes of interest *Sensitivity, specificity, and area under the curve (AUC) to predict hyperlactatemia, admission to ICU and intrahospital mortality*
Chiscano, L., Ruiz, J., Algarte, R. et al. (2020) Hospital clinical alert capacity. Prediction of evolution to sepsis/ septic shock. Capacicritic study. Intensive Care Medicine Experimental 8(suppl2)	- Conference abstract
Corfield, A.R., Lees, F., Houston, G. et al. (2012) Early warning scores in sepsis: Utility of a single early warning score in the emergency department?. Intensive Care Medicine 38(suppl1): 296-s297	- Conference abstract
Farenden, Scott; Gamble, David; Welch, John (2017) Impact of implementation of the National Early Warning Score on patients and staff. British journal of hospital medicine (London, England : 2005) 78(3): 132-136	- Does not contain a population of interest *Not sepsis: NEWS identified high-risk ward patients referred to critical care without increasing workload or worsening outcomes*
Gauntlett, L., Hall, K., Kakollu, M. et al. (2016) National Early Warning Score (NEWS) of 3 as a trigger for initiating sepsis screening tool for early identification of sepsis in patients presenting to the emergency department: A prospective observational study. Journal of the Intensive Care Society 17(4supplement1): 103-104	- Conference abstract
Grudzinska, Frances S, Aldridge, Kerrie, Hughes, Sian et al. (2019) Early identification of severe community-acquired pneumonia: a retrospective observational study. BMJ open respiratory research 6(1): e000438	- Does not contain a population of interest *Not a population with or suspected sepsis: People with community acquired pneumonia, no suspicion of sepsis as inclusion criteria*
Hamilton, F, Arnold, D, Baird, A et al. (2018) Early Warning Scores do not accurately predict mortality in sepsis: A meta-analysis and systematic review of the literature. The Journal of infection 76(3): 241-248	- Study does not contain any relevant predictive values *Only sensitivity and specificity, ROC curve*
Hancock, Chris (2015) A national quality improvement initiative for reducing harm and death from sepsis in Wales. Intensive & critical care nursing 31(2): 100-5	- Not a relevant study design *Rapid Response to Acute Illness (RRAILS) Programme - a quality and service improvement initiative*
Keep, J W, Messmer, A S, Sladden, R et al. (2016) National early warning score at Emergency Department triage may allow earlier identification	- Study does not contain any relevant predictive values *sensitivity, specificity, AUC.*

Study (N=27)	Code [Reason]
of patients with severe sepsis and septic shock: a retrospective observational study. Emergency medicine journal : EMJ 33(1): 37-41	
Kopczynska, Maja, Unwin, Harry, Pugh, Richard J et al. (2021) Four consecutive yearly point-prevalence studies in Wales indicate lack of improvement in sepsis care on the wards. Scientific reports 11(1): 16222	- Study does not contain outcomes of interest
Lim, Wan Tin, Fang, Andrew Hs, Loo, Chian Min et al. (2019) Use of the National Early Warning Score (NEWS) to Identify Acutely Deteriorating Patients with Sepsis in Acute Medical Ward. Annals of the Academy of Medicine, Singapore 48(5): 145-149	- Data not reported in an extractable format *Study combined all events within 24 hrs and reported combined events rate*
Lyons, H. and Trimmings, A. (2017) Retrospective study over a 12-month period looking at the national early warning score as a screening tool for patients with sepsis admitted to intensive care. Critical Care 21(1supplement1)	- Conference abstract
Maciver, Marina (2021) Pre-hospital use of early warning scores to improve detection and outcomes of sepsis. British journal of community nursing 26(3): 122-129	- Not a relevant setting *systematic narrative review - primary care setting*
Nannan Panday, R S, Minderhoud, T C, Alam, N et al. (2017) Prognostic value of early warning scores in the emergency department (ED) and acute medical unit (AMU): A narrative review. European journal of internal medicine 45: 20-31	- Does not contain a population of interest *Not a population with or suspected sepsis: patients at risk of deterioration*
Nieves Ortega, Ricardo, Rosin, Christiane, Bingisser, Roland et al. (2019) Clinical Scores and Formal Triage for Screening of Sepsis and Adverse Outcomes on Arrival in an Emergency Department All-Comer Cohort. The Journal of emergency medicine 57(4): 453-460e2	- Study does not use the risk tool of interest *qSOFA measured at presentation was used as a tool to identify sepsis in an all-comer cohort of ED patient and then compared with NEWS and other tool.*
Prothero, L.S. and Foster, T. (2015) Can the pre-hospital care of patients with comorbidity of sepsis and hyperglycaemiabe improved?. Diabetic Medicine 32(suppl1): 199	- Conference abstract
Pullyblank, Anne, Tavare, Alison, Little, Hannah et al. (2020) Implementation of the National Early Warning Score in patients with suspicion of sepsis: evaluation of a system-wide quality improvement project. The British journal of general practice : the journal of the Royal College of General Practitioners 70(695): e381-e388	- Not a relevant study design *quality audit and implementation of Sepsis 6*
Sabir, Lisa; Ramlakhan, Shammi; Goodacre, Steve (2022) Comparison of qSOFA and Hospital Early Warning Scores for prognosis in suspected sepsis in emergency department patients: a	- Study does not contain outcomes of interest *systematic review: comparison of different sepsis tools, sensitivity and specificity, AUC*

Study (N=27)	Code [Reason]
systematic review. Emergency medicine journal : EMJ 39(4): 284-294	
Scott, Lauren J, Redmond, Niamh M, Tavare, Alison et al. (2020) Association between National Early Warning Scores in primary care and clinical outcomes: an observational study in UK primary and secondary care. The British journal of general practice : the journal of the Royal College of General Practitioners 70(695): e374-e380	- Does not contain a population of interest *Not sepsis: study includes critically ill patients*
Silcock, Daniel J, Corfield, Alasdair R, Staines, Harry et al. (2019) Superior performance of National Early Warning Score compared with quick Sepsis-related Organ Failure Assessment Score in predicting adverse outcomes: a retrospective observational study of patients in the prehospital setting. European journal of emergency medicine : official journal of the European Society for Emergency Medicine 26(6): 433-439	- Does not contain a population of interest *Not sepsis: study includes critically ill patients*
Sutherland, Mark E, Yarmis, Samantha J, Lemkin, Daniel L et al. (2020) National Early Warning Score Is Modestly Predictive of Care Escalation after Emergency Department-to-Floor Admission. The Journal of emergency medicine 58(6): 882-891	- Does not contain a population of interest *Not sepsis or suspected sepsis: predicting early, unplanned escalation of care in patients admitted to the hospital from the emergency department*
Szakmany, T., Burke, O., Leon, Smith et al. (2014) Delivery of sepsis 6 by critical care outreach on the general wards: Impact on outcome. Critical Care Medicine 42(12suppl1): a1588	- Conference abstract
Szakmany, T., Ellis, G., Lundin, R. et al. (2014) Size of sepsis in wales: Feasibility pilot. Critical Care Medicine 42(12suppl1): a1446	- Study does not contain outcomes of interest *outcomes presented per people with and without sepsis with a median NEWS score*
Szakmany, Tamas, Lundin, Robert M, Sharif, Ben et al. (2016) Sepsis Prevalence and Outcome on the General Wards and Emergency Departments in Wales: Results of a Multi-Centre, Observational, Point Prevalence Study. PloS one 11(12): e0167230	- Conference abstract
Williams, Teresa A, Tohira, Hideo, Finn, Judith et al. (2016) The ability of early warning scores (EWS) to detect critical illness in the prehospital setting: A systematic review. Resuscitation 102: 35-43	- Does not contain a population of interest *Examines whether early warning scores (EWS) can accurately predict critical illness in the prehospital setting and affect patient outcomes.*
Zheng, H., Chen, L., Wu, S. et al. (2021) National early warning score in predicting severe adverse outcomes of emergency medicine patients: A retrospective cohort study. Journal of Multidisciplinary Healthcare 14: 2067-2078	- Does not contain a population of interest *Critical emergency patients in ED triage*

Study (N=27)	Code [Reason]
Zhou, H.-j.; Lan, T.-f.; Guo, S.-b. (2020) Outcome prediction value of National Early Warning Score in septic patients with community-acquired pneumonia in emergency department: A single-center retrospective cohort study. World Journal of Emergency Medicine 11(4): 206-215	- Study does not contain any relevant predictive values *Sensitivity, specificity, ROC curves to compare NEWS2 with other predictive sepsis tools*

Health Economic studies

No published health economic studies met the inclusion criteria.

Appendix K – Research recommendations – full details

[NICE's process and methods guide for research recommendations sets out how research recommendations are developed in response to gaps in the evidence.

K.1 Research recommendation

In adults and young people (16 and over) with suspected sepsis in acute hospital settings, ambulance trusts and acute mental health facilities, what is the association between NEWS2 bands (0, 1 to 4, 5 to 6, 7 or above) and risk of severe illness or death?

As a separate subgroup, the following research recommendation was made:

In adults and young people (16 and over) with suspected sepsis in acute hospital settings, ambulance trusts and acute mental health facilities, what is the association between the NEWS2 score of 3 in a single parameter and risk of severe illness or death?

K.1.1 Why this is important

NEWS2 has been introduced in 2017 and is widely used across the NHS prehospital and acute care settings. However, evidence on NEWS2 tool was not found. There is only indirect and very scarce data based on the earlier version of the tool (NEWS, published in 2012) on the association between NEWS bands and risk of severe illness or death as well as long term complications associated with severe sepsis. It is important to investigate the success, safety and possible implications on patients and staff of using the NEWS2 tool to stratify the risk of severe illness or death over a 5- to 10-year period. As a specific subgroup within this population, the category of a NEWS2 score of 3 in a single category was also of a great concern and lack of data around its stratification and possible risk of deterioration remains uncertain. Data regarding the categorisation of the risk of a NEWS2 score of 3 in one parameter is scarce and interpretation contradictory.

K.1.2 Rationale for research recommendation

Importance to 'patients' or the population	Little is known about the association between NEWS2 bands (0, 1 to 4, 5 to 6, 7 or above) and risk of severe illness or death in adults and young people (16 and over) with suspected sepsis presenting to acute hospital settings, ambulance trusts and acute mental health facilities. In particular little evidence exists about the association between a NEWS2 score of 3 in a single parameter and risk of severe illness or death in adults and young people (16 and over) with suspected sepsis presenting to acute hospital settings, ambulance trusts and acute mental health facilities as a separate subgroup of people with suspected sepsis. This would clarify existing uncertainties regarding outcomes such as health-related quality of life, ICU and critical care admission, long or short-term mortality for which no direct or indirect evidence was found.
Relevance to NICE guidance	The NEWS2 tool has been considered in this guideline but there was no data on different

	NEWS2 bands and associated short or long-term risk of severe illness or death. Findings would generate prognostic association data which could feed into future guideline updates and more specific evidence-based recommendations.
Relevance to the NHS	The findings would ensure a more structured approach to the management and treatment of people with suspected sepsis and their risk of acute illness and death. Early recognition and timely management has the potential to decrease morbidity and mortality and reduce NHS cost incurred due to delayed or inappropriate management. This in turn may involve ICU or critical care admission and length of hospital stay.
National priorities	High
Current evidence base	As highlighted data on the NEWS2 tool and association of different NEWS2 categories and risk of severe deterioration was not found.
Equality considerations	None known

K.1.3 Modified PICO table

Population	Adults and young people (16 and over) with suspected sepsis presenting to acute hospital settings, ambulance trusts and acute mental health facilities.
Test	NEWS2 bands (0-4, 5-6, 7-20) Subgroup: NEWS2 =3 in a single parameter
Measure of association	Adjusted ORs or RRs (for outcomes measured at a specific time point) Adjusted HR (for outcomes measured over time) All measure of association compared to the lowest NEWS2 band (0-4)
Outcomes	• Mortality (e.g., in-hospital mortality, mortality due to sepsis, all-cause mortality measured at 28 days or nearest time point, or as reported in individual studies e.g., 2 days, 28 days, 3 months, 6 months, 9 months, 12 months) • Escalation of care (e.g., increase in NEWS2 score/band, involvement of senior consultant, intensive care unit admission, rehospitalisation or as reported in individual studies) • Hospital readmission rates • Unplanned critical care admission • Health related quality of life (measured by EQ5D or SF-36 or other validated questionnaires)
Study design	Prospective cohort studies, retrospective cohort studies, longitudinal studies

Timeframe	Long term
Additional information	None