National Institute for Health and Care Excellence

Suspected sepsis: recognition, diagnosis and early management

[G] Evidence reviews for intravenous fluids for resuscitation

NICE guideline NG253

Evidence reviews underpinning recommendation 1.8.4 to 1.8.9; 1.8.11 to 1.8.13 in the NICE guideline

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Guideline version (Final)

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Contents

1 Intravenous fluids for resuscitation

1.1 Review questions

RQ5.1: What is the most clinical and cost-effective intravenous fluid for resuscitation of people aged 16 or over with suspected sepsis?

RQ5.2: What is the most clinically and cost-effective volume and rate of administration for IV fluid for resuscitation in people aged 16 or over with suspected sepsis

1.1.1 Introduction

Fluid resuscitation is considered vital in the initial treatment and management of suspected sepsis and septic shock. Fluid resuscitation along with use of vasopressors is an area in which practice is evolving. There is a requirement for updated recommendations to guide clinicians on what volume of fluid should be given, what type and at what rate. This evidence review explores these factors.

1.1.2 Summary of the protocol

Table 1: RQ 5.1 Type of fluid PICOS inclusion criteria

Population	Inclusion: • Adults aged 16 or over with suspected sepsis in acute hospital* and ambulance settings who require resuscitation in the first 6 hours of care. *this could include hospital at home/virtual wards Exclusion: • People who are or have recently been pregnant
Interventions	The following intravenous fluids: Crystalloid – • Ringer's lactate (Hartmann's) • Plasmalyte A • Normal Saline (0.9%) Colloid – albumin

	• Human albumin solution • Fresh frozen plasma (FFP)
Comparator	Crystalloid – • Ringer's lactate (Hartmann's) • Plasmalyte A • Normal Saline (0.9%) Colloid – albumin • Human albumin solution • Fresh frozen plasma (FFP)
Outcomes	Primary outcomes: • All-cause mortality – in hospital and 30 days • Adverse events including but not limited to AKI Secondary outcomes: • Length of hospital stay • Admission to ICU • Organ system dysfunction • Pulmonary oedema
Study type	• Systematic reviews of RCTs • RCTs • Cohort studies (prospective and retrospective) if no RCTs are identified.

Table 2: RQ 5.2 Volume of fluid PICOS inclusion criteria

Population	Inclusion: • Adults aged 16 or over with suspected sepsis in acute hospital* and ambulance settings who require resuscitation in the first 6 hours of care. *this could include hospital at home/virtual wards Exclusion: • Children under the age of 16

	• People who are or have recently been pregnant
Interventions	• boluses of x ml/kg bodyweight / x minutes
Comparator	• boluses of x ml/kg bodyweight / x minutes
Outcomes	Primary outcomes: • Mortality (all cause, in hospital and at 30 days) • organ support (vasoactive drugs, mechanical ventilation, RRT) • signs that someone is not responding: tachycardia; level of consciousness; blood pressure decrease (clinical significance as defined by the study); respiratory rate; blood lactate; urine output; peripheral perfusion; blood gases • Fluid overload – hypervolemia as defined by the study • Adverse events including but not limited to AKI Secondary outcomes • Length of hospital stay • Admission to ICU • Length of ICU stay
Study type	• Systematic reviews of RCTs • RCTs • Cohort studies (prospective and retrospective) if no RCTs are identified.

For the full protocol see appendix A.

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 appendix L.

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

Relevant systematic reviews with meta-analysis for both questions 5.1 and 5.2 were found. A decision was taken to include the most recent reviews (n=2) with the most relevant primary papers. Systematic reviews were assessed for risk of bias using the ROBIS checklist. The risk of bias ratings given by review authors for primary includes

was used where this aligned with NICE methods and to inform the overall GRADE certainty rating. A risk of bias assessment of the primary papers included in the Beran et al (2022) systematic review was conducted by the NICE technical team as the author's own assessment did not use the Cochrane ROB2 tool as per NICE methods.

It was noted that the meta-analyses in the Beran et al (2022) systematic review (included for review question 5.1) contained data from trials conducted in both emergency department (ED) and intensive care units (ICU) for fluid resuscitation. A decision was taken to present the pooled data from this review directly with no added data, to give the committee a broad picture of the effectiveness of resuscitation fluids across these settings. However, a study was identified during this review (Jackson et al 2021) that undertook a post-hoc subgroup analysis from one of the included studies within Beran et al (2022) which focused on fluids started in an ED setting. Although this study design is an exclude, following discussion with the committee a decision was made to include Jackson et al (2021) as it provided useful data from an ED setting which directly maps to the scope of this topic. Data from this paper is presented separately (Table 12) for consideration alongside the findings of Beran et al (2022) and the risk of bias assessment takes into consideration the lack of proper randomisation in this analysis. The pooled data from Beran et al (2022) was rated down for indirectness in GRADE as it included data from an ICU setting. Similarly, the Sivapalan et al (2023) review (included for review question 5.2) contains data from both ED and ICU settings. The authors have undertaken a subgroup analysis for those fluids given in the first 6 hours of resuscitation and specifically in sepsis (not septic shock) populations in the emergency department.

1.1.3.1 Search methods

The searches for the effectiveness evidence were run on 15 08 2024. The following databases were searched: MEDLINE (Ovid), Embase (Ovid), the Cochrane Central Register of Controlled Trials (Wiley), the Cochrane Database of Systematic Reviews (Wiley), and Epistemonikos. Full search strategies for each database are provided in Appendix B.

The searches for the cost effectiveness evidence were run on 15 08 2024. The following databases were searched: MEDLINE (Ovid), Embase (Ovid), the EconLit (Ovid), and the International HTA database (INAHTA). The validated NICE Cost Utility Filter was used on MEDLINE and Embase.

A NICE senior information specialist (SIS) conducted the searches. The MEDLINE strategy was quality assured by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement.

1.1.3.2 Protocol deviations

The protocol excludes studies from non-OECD countries and those published before 2016 (the date of the last guideline search). A decision was agreed to include meta-analyses from systematic reviews that included some studies that were both non-OECD and pre-2016.

The protocol excludes post-hoc studies. A study was identified (Jackson et al 2021) that undertook a post-hoc subgroup analysis from one of the included studies within Beran et al (2022) which focused on fluids started in an ED setting. A decision was made to include Jackson et al (2021) as it provided useful data from an ED setting. Data from this paper is presented separately (Table 12) and the risk of bias assessment accounts for the lack of proper randomisation in this analysis.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 785 references (see appendix B for the literature search strategy).

These 785 references were screened at title and abstract level against the review protocol, with 704 excluded at this level. 10% of references were screened separately by two reviewers with 100% agreement.

The full texts of 81 systematic reviews of RCTs and RCTs were ordered for closer inspection. 4 of these studies met the criteria specified in the review protocol

(appendix A) including 2 systematic reviews (1 for fluid type [review question 5.1] and 1 for fluid volume [review question 5.2]) with 15 primary papers included within them and 2 RCTs (2 for fluid type [review question 5.1]). For a summary of the 4 included studies see table 3 and table 4.

The clinical evidence study selection is presented as a PRISMA diagram in appendix C.

See section 1.1.14 References – included studies for the full references of the included studies.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in appendix H.

1.1.5 Summary of studies included in the (effectiveness) evidence

Table 3 Summary of studies included in the effectiveness evidence for 5.1 – fluid type

Study details	Location	Population	Intervention	Comparison	Outcomes	Place of administration / initial resuscitation fluids received	Risk of bias
Beran 2022 – n=7599 from 8 RCTs included in the meta-analysis Study type: Systematic review	Review conducted in the USA See below for details of location and settings from primary papers included in this systematic review	Patients with sepsis as defined by included trials	Balanced Crystalloids	Normal Saline	Mortality Acute Kidney Injury RRT ICU length of stay	Contains primary papers from both Emergency Department and Intensive Care Units	High
Primary papers included in Beran 2022 systematic review:							
Annane 2013 n=594 Study type: RCT	France	Sepsis population (no further details)	Lactated Ringer	Normal Saline	Overall mortality 28/30 day mortality 90 day mortality	ICU	Moderate[2]

Study details	Location	Population	Intervention	Comparison	Outcomes	Place of administration / initial resuscitation fluids received	Risk of bias
90 days follow up							
Finfer 2022 n=2094 Study type: RCT 90 days follow up	Australia and New Zealand	Sepsis population (no further details)	Plasma-Lyte 148	Normal Saline	Overall mortality, 90 day mortality	ICU	Moderate[2]
Golla 2020 n=160 Study type: RCT 30 days follow up	India	Sepsis population SOFA: 7.64 ± 2.56/ 7.63 ± 2.49	Lactated Ringer	Normal Saline	Overall mortality 28/30 day mortality AKI Need for RRT	ED	Low[2]
Pagano 2020	Italy	Sepsis population SOFA: 5.9 (2.9)/6 (2.8)	Lactated Ringer	Normal Saline	Overall mortality Need for RRT	ED	High[2]

Study details	Location	Population	Intervention	Comparison	Outcomes	Place of administration / initial resuscitation fluids received	Risk of bias
n=84 Study type: RCT Follow up not reported							
Semler 2017 n=260 Study type: RCT 30 days follow up	USA	Sepsis population (no further details)	LR or Plasmalyte	Normal Saline	Overall mortality 28/30 day mortality	ICU	High[2]
Semler 2018 n=2336	USA	Sepsis population (no further details)	LR or Plasmalyte	Normal Saline	Overall mortality 28/30 day mortality	ICU and ED	High[2]

Study details	Location	Population	Intervention	Comparison	Outcomes	Place of administration / initial resuscitation fluids received	Risk of bias
Study type: RCT 30 days follow up							
Young 2015 n=84 Study type: RCT 90 days follow up	Australia and New Zealand	Sepsis population APACHE II: 14.1 (6.9)/14.1 (6.9)	Plasma-Lyte 148	Normal Saline	Overall mortality 90 day mortality AKI	ICU	High[2]
Zampieri 2021 n=1987 Study type: RCT	Brazil	Sepsis population (no further details)	Plasma-Lyte 148	Normal Saline	Overall mortality 90 day mortality	ICU	Moderate[2]

Study details	Location	Population	Intervention	Comparison	Outcomes	Place of administration / initial resuscitation fluids received	Risk of bias
90 days follow up							
RCTs not in the included systematic review:							
Gray 2024 n=300 Study type: RCT 90 days follow up	UK	Adult patients with sepsis and a National Early Warning Score 2 greater than or equal to five requiring IV fluids withing one hour of randomization	5% human albumin solution (HAS)	Balanced crystalloid (BC)	30-day mortality 90-day mortality In hospital mortality IV Vasopressors RRT[3] AKI[4] Invasive ventilation	ED 55% in HAS arm and 59% in BC arm received fluids prior to randomisation	High
Jackson[1] 2021 (based on Semler 2018 SMART trial data) n=1274	USA	Adults sepsis patients	Balanced crystalloid (lactated Ringer's solution or Plasma-Lyte A)	Normal saline	30-day in-hospital mortality ICU free days Ventilator free days Vasopressor free days Major adverse kidney events Receipt of new RRT[3]	ED	High

Study details	Location	Population	Intervention	Comparison	Outcomes	Place of administration / initial resuscitation fluids received	Risk of bias
Study type: Cluster randomised multiple crossover trial 30 days follow up					Stage 2 or > AKI developing after ICU admission		

1. Semler 2018 is the primary trial; Jackson 2021 is post hoc subgroup analysis of fluids started in the ED (please see methods section 1.1.3)
2. Risk of bias rating assessed by NICE team using the Cochrane ROB2 tool. Rating from the systematic review authors not used – see methods section 1.1.3

RRT = renal replacement therapy

AKI = acute kidney injury

LR = Lactated Ringer

ICU = intensive care unit

ED = emergency room

Table 4: Summary of studies included in the effectiveness evidence for 5.2 – fluid volume

Study details	Location	Population	Intervention	Comparison	Outcomes	Early vasopressor	Place of administration / initial resuscitation fluids received	Risk of bias
Sivapalan 2023 - N= 2076 from 7 RCTs Study type: Systematic review of RCTs	Review conducted in the Denmark See below for details of location and settings from primary papers included in this systematic review	Adult patients with sepsis (as defined in the original trials)	Lower fluid volumes (details provided in primary paper summary below)	Higher fluid volumes (details provided in primary paper summary below)	All-cause mortality Serious adverse events Ventilator free days Duration of vasopressor or inotropes Use of renal replacement therapy Acute kidney injury (AKI) incidence	(as per primary study details below)	ED and ICU	Low

Study details	Location	Population	Intervention	Comparison	Outcomes	Early vasopressor	Place of administration / initial resuscitation fluids received	Risk of bias
					ICU Length of stay Hospital length of stay			
Primary papers included in Sivapalan 2023 systematic review subgroup analysis of 'early' fluid resuscitation[5]								
Shapiro 2023 (CLOVERS) n=1563 Study type: RCT Follow up: 90 days	USA	18 y of age, suspected or confirmed infection, sepsis-induced hypotension (SBP < 100 mm Hg or MAP < 65 mm Hg after at least 1 L of fluid Exclusion: inclusion criteria > 4 h or hospital admission > 24 h, received > 3 L of IV fluids, non-sepsis hypotension, non-sepsis	Total volume of resuscitation fluids over 24hrs: **Low = 500ml (0-1500)[2]** High = 2750 (2000-3615 Vasopressor as primary treatment for sepsis-induced hypotension and halt all bolus and	Total volume of resuscitation fluids over 24hrs: **High = 2750ml (2000-3615)[2]** Liberal protocol: halt maintenance Give initial 2 L followed by 500- mL boluses based on clinical triggers (e.g., tachycardia)	All-cause mortality (90 days) Serious Adverse events Ventilator free days Duration of mechanical ventilation Duration of vasopressor or inotropes	Yes	ED	Low[1]

Study details	Location	Population	Intervention	Comparison	Outcomes	Early vasopressor	Place of administration / initial resuscitation fluids received	Risk of bias
		severe volume depletion, pulmonary oedema or fluid overload, withdrawal of life support, protocol not possible because of physician's directives or immediate surgery, pregnancy, consent not obtainable	maintenance fluid; up to 2 L of total fluid at discretion of physicians Afterward, rescue fluids (500-Ml boluses) permitted for prespecified indications suggesting severe intravascular volume depletion	with rescue vasopressors October 2019 amended to initial 1 L if heart rate and BP stabilized and clinically volume repleted	Use of renal replacement therapy			
Jessen 2022[6] n=123 Study type: RCT	Denmark	≥18 y of age, unplanned ED admission, expected hospital stay > 24 h, sepsis (defined as infection suspected by	Total volume of resuscitation fluids over 24hrs: **Low = 0ml (0-600)[2]** 50-mL bolus could be given	Total volume of resuscitation fluids over 24hrs: **High = 1000ml (80 -2000)[2]**	All-cause mortality (90 days) Serious Adverse events	Not specified	ED	Low[1]

Study details	Location	Population	Intervention	Comparison	Outcomes	Early vasopressor	Place of administration / initial resuscitation fluids received	Risk of bias
Follow up: 90 days		physician, blood cultures, IV antibiotics administered or planned, and infection related increase in SOFA score > 2) Exclusion: received ≥ 500-mL IV fluids, vasopressor or invasive ventilation started before screening, severe bleeding, prior enrolment in the trial, pregnancy, survival expectancy < 24 h	if severe hypoperfusion or circulatory with lactate ≥ 4 mM, SBP < 90 mm Hg, urine < 0.1 mL/kg/h (first 4 h) or mottling score > 2 Correction of overt fluid losses or if oral/enteral fluid was contraindicated to correct dehydration or electrolyte imbalances or ensure total fluid input of 1 L/d	Standard care at physician's discretion	Use of renal replacement therapy AKI incidence ICU length of stay Hospital length of stay			

Study details	Location	Population	Intervention	Comparison	Outcomes	Early vasopressor	Place of administration / initial resuscitation fluids received	Risk of bias
			The protocol was paused if the patient underwent surgery during the first 24 h					
Macdonald 2018 (REFRESH) n=99 Study type: RCT Follow up: 90 days	Australia	≥18 y of age, ED, sepsis (Sepsis-3), SBP < 100 mm Hg despite minimum 1-L IV crystalloid within 1 h, possible to start study within 2 h Exclusion: non-sepsis hypotension requirement for fluid replacement transferals > 2 L IV fluids, acute surgery, < 18 y of age,	Total volume of resuscitation fluids over 6hrs: **Low: 550ml (0-1150)[2]** Vasopressor to MAP ≥ 65 mm Hg If altered perfusion: crystalloid bolus 250 mL allowed each hour	Total volume of resuscitation fluids over 6hrs: **High: 1535ml (1000-2200)[2]** Fluid bolus 1 L / If SBP < 90 mm Hg, MAP < 65 mm Hg further 500-mL bolus every 30 min If persistent hypotension:	All-cause mortality (90 days) Serious Adverse events Duration of mechanical ventilation Ventilator free days Duration of vasopressor or inotropes	Yes	ED	Low[1]

Study details	Location	Population	Intervention	Comparison	Outcomes	Early vasopressor	Place of administration / initial resuscitation fluids received	Risk of bias
		pregnancy, imminent death, patient wishes, fluids or vasopressors contraindicated	Up to 1 L additional IV fluid allowed as safety measure Maintenance fluid of max 2 mL/kg/h if required	NE to maintain MAP 65-70 mm Hg Maintenance fluid if required	Use of renal replacement therapy ICU Length of stay Hospital length of stay			
Douglas 2020 n=150 Study type: RCT Follow up: 30 days	USA / UK	18 y of age, anticipated ICU[7] admission, sepsis or septic shock (defined as ≥ 2 SIRS criteria and a suspected or documented infection), MAP ≤ 65 mm Hg after ≥ 1 L IV fluid and < 3 L, enrolment within	Total volume of resuscitation fluids over 72hrs post enrolment: **Low: 3231ml (1787-6990)[2]** PLR before any treatment of	Total volume of resuscitation fluids over 72hrs post enrolment: **High: 3567ml (1795?d-5350)[2]** Standard care at physician's	All-cause mortality (30 day) Serious Adverse events Duration of mechanical ventilation	Not specified	ICU	Moderate[1]

Study details	Location	Population	Intervention	Comparison	Outcomes	Early vasopressor	Place of administration / initial resuscitation fluids received	Risk of bias
		< 24 h of hospital arrival Exclusion: > 3 L IV fluid, do-not-resuscitate order, hemodynamic instability because of active haemorrhage, acute cerebral vascular event, acute coronary syndrome, acute pulmonary oedema, status asthmaticus, major cardiac arrhythmia, drug overdose, burn or trauma, status epilepticus, indication for	hypoperfusion / If SV > 10% / 500- mL IV fluid bolus / Reassess MAP/SBP If SV < 10% / Titrate pressors to MAP ≥ 65 mm Hg, repeat PLR after significant escalation	discretion. The use of dynamic fluid assessment to determine fluid responsiveness was prohibited	Duration of vasopressor or inotropes Use of renal replacement therapy ICU Length of stay Hospital length of stay			

Study details	Location	Population	Intervention	Comparison	Outcomes	Early vasopressor	Place of administration / initial resuscitation fluids received	Risk of bias
		immediate surgery, PLR contraindication, pregnancy, incarceration, transferred from another hospital						
Corl 2019 (RIFTS)[6] n=109 Study type: RCT Follow up: 60 days	USA	≥18 y of age, admitted to ICU from ED, sepsis (Sepsis-244 or deemed sepsis by attending physician), 1 L IV fluid, MAP < 65 mm Hg or lactate ≥ 4 mM Exclusion: primary diagnosis other than sepsis, fluid wasting condition, diagnosis requiring high-volume IV resuscitation,	Prior to randomisation + 72h study period **Low: 4140ml ±1660[3]** 72-h protocol: maximum 60 mL/ kg resuscitative IV fluids If weight > 100 kg max 6,000 mL allowed	Prior to randomisation + 72h study period **High: 4963ml ± 2362[3]** Usual care	All-cause mortality (30 and 60 day) Duration of mechanical ventilation Duration of vasopressor or inotropes Use of renal replacement therapy AKI incidence	Not specified	ICU	Low[1]

Study details	Location	Population	Intervention	Comparison	Outcomes	Early vasopressor	Place of administration / initial resuscitation fluids received	Risk of bias
		acute surgery or ECMO, pregnancy, incarcerated, received > 60 mL/kg IV fluid before randomization	IV fluids received before randomization included		ICU Length of stay			
Van Genderen 2015[6] n=30 Study type: RCT Follow up: 72 hours	The Netherlands	≥18 y of age, ICU, severe sepsis/septic shock (vasopressor requirement or lactate ≥ 3 mEq/L) Exclusion: hypothermia, Raynaud or peripheral vascular disease, acute coronary syndrome or pulmonary oedema, burn or	Overall fluids in 72hr study period: **Low: 7565ml (982)[4]** Fluid challenge 250 mL HES / If sufficient peripheral perfusion, discontinue fluids	Overall fluids in 72hr study period: **High: 10028ml (941)[4]** Fluid challenge 250 mL HES / Hemodynamic goals based on 2012 SSC	All-cause mortality	Not specified	ICU	High[1]

Study details	Location	Population	Intervention	Comparison	Outcomes	Early vasopressor	Place of administration / initial resuscitation fluids received	Risk of bias
		trauma, liver failure, cannulation contraindicated, aerobic cause of hyperlactatemia, neurologic insult, do not resuscitate, pregnancy, recent participation in another study, inability to start study ≥4 h						

Lanspa 2018 n=30 Study type: RCT Follow up: 28 days	USA	≥18 y of age, septic shock,44 CVC, and arterial catheter Exclusion: inclusion criteria > 6 h, moribund patient, pregnancy, incarceration, acute surgery, chest/abdominal pathology, contraindicating TTE, protocol not possible because of physician's or patient's directives	Total volume for resuscitation over 6 hour study period: **Low: 0 ml (0-2000)[2]** Both groups: hourly assessment for 6 h – if intervention then assessment after 30 min ECHO group: If MAP < 65 mm Hg and lactate clearance < 10% ECHO 1 L IV fluid if IVC collapsing, if IVC not collapsing increase NE, if myocardial dysfunction and MAP < 70	Total volume for resuscitation over 6 hour study period: **High: 1000ml (0-2000)** EGDT group: If CVP < 8 mm Hg 1 L IV fluid If MAP < 65 mm Hg Add/increase NE If Scvo2 < 70% Add/increase dobutamine	All-cause mortality Ventilator free days ICU Length of stay	Not specified	ICU[8]	Moderate[1]

			mm Hg add/increase dobutamine					

1. Risk of bias as assessed by review authors using Cochrane ROB2 for primary outcome of all-cause mortality
2. Data reported as median (IQR)
3. Data reported as mean (SD)
4. Data reported as mean (SE)
5. Authors define 'early' resuscitation subgroup as 'trials with early (≤ 6 h) start of protocolised resuscitation'
6. Fluid only interventions

ED = emergency department
ICU – intensive care unit
MAP = mean arterial pressure
SBP = systolic blood pressire
PL = passive leg raise
SIRS = systemic inflammatory response syndrome
HES = hydroxyethyl starches
EGDT = early goal directed therapy
ECHO = echocardiogram
TTE = transthoracic echocardiogram
CVC = central venous catheter
IVC = inferior vena cava
SSC = surviving sepsis campaign

See Appendix D – Effectiveness evidencefor full evidence tables

1.1.6 Summary of the effectiveness evidence

Interpreting the effectiveness evidence

For mortality outcomes the line of no effect (represented by 1.0 as mortality is a dichotomous outcomes) was used as a clinical decision threshold. The following criteria were used to interpret the effect (column of 'Interpretation of effect' below) in the summary GRADE tables with results divided into 2 groups as follows:

- The evidence showed that there is an effect if the 95% CI does not cross the line of no effect. Where there is an effect, we have stated the direction of the effect.

- The evidence could not differentiate between comparators if the 95% CI crosses the line of no effect. Where this is the case we have stated 'could not differentiate'.

Where default MIDs have been used (0.8 and 1.25) the following criteria were used to interpret the effect (column of 'Interpretation of effect' below) in the summary GRADE tables. The results were divided into 4 groups as follows:

- Where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect. (Where there is an effect, we will state the direction of the effect.)

- Where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence showed there is an effect, but it is less than the defined MID.

- Situations where the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no meaningful difference.

- In all other cases, we state that the evidence could not differentiate between the comparator

Table 5: Balanced Crystalloid vs Normal Saline (evidence from Beran 2022 systematic review)

No of studies	Study design	Intervention group (BC) (events/total)	Comparator (NS) (events/total)	Effect size (Risk ratio / mean difference) (95% CI)	Absolute effect	Interpretation of effect	Certainty
Overall mortality							
8[1]	RCT	450 / 970	498 / 1017	RR 0.92 (0.82, 1.02)	39 fewer per 1000 (88 fewer to 10 more)	Could not differentiate	Very low[6]
28 / 30 day-mortality							
4[4]	RCT	362 / 1414	569 / 1936	RR 0.87 (0.77, 0.97)	38 fewer per 1000 (68 fewer to 9 fewer)	Effect - favours balanced crystalloids	Very low[7]
Acute kidney injury							
2[2]	RCT	28 / 115	41 / 122	RR 0.71 (0.47, 1.06)	97 fewer per 1000 (178 fewer to 20 more)	Could not differentiate	Very low[7]
Need for RRT							
2[3]	RCT	12 / 115	18 / 129	RR 0.71 (0.36, 1.41)	41 fewer per 1000 (90 fewer to 57 more)	Could not differentiate	Very low[9]

1. Annane 2013, Finfer 2022, Golla 2020, Pagano 2020, Semler 2017, Semler 2018, Young 2015, Zampieri 2021
2. Golla 2020, Young 2015
3. Golla 2020, Pagano 2020
4. Annane 2013, Golla 2020, Semler 2017, Semler 2018
5. Annane 2013, Finfer 2022, Young 2015, Zampieri 2021

6. Rated down for risk of bias, inconsistency and indirectness
7. Rated down for risk of bias, indirectness and imprecision
8. Rated down for risk of bias and indirectness
9. Rated down for risk of bias and imprecision

Table 6: Subgroup analysis of Semler 2018 trial (Jackson 2021 paper) – fluids started in emergency department

No of studies	Study design	Intervention group (BC) (events/total)	Comparator (NS) (events/total)	Effect size (odds ratio) (95% CI)	Absolute effect	Interpretation of effect	Certainty
30 day in-hospital mortality							
1[2]	Cluster RCT	170 / 682	181 / 592	OR 0.68 (0.52, 0.89)[1]	Not estimable[5]	Effect - favours balanced crystalloids	Very low[3]
Major adverse kidney event within 30 days							
1[2]	Cluster RCT	236 / 682	233 / 592	OR 0.76 (0.59, 0.97)[1]	Not estimable[5]	Effect - favours balanced crystalloids	Very low[3]
Receipt of new RRT							
1[2]	Cluster RCT	47 / 614	50 / 524	OR 0.79 (0.52, 1.19)[1]	Not estimable[5]	Could not differentiate	Very low[4]

Stage 2 or greater AKI developing after ICU admission							
1[2]	Cluster RCT	163 / 614	155 / 524	OR 0.86 (0.66, 1.12)[1]	Not estimable[5]	Could not differentiate	Very low[4]

1. OR's in this post-hoc analysis adjusted for covariates age, sex, race, source of admission, receipt of mechanical ventilation, and receipt of vasopressors
2. Jackson 2021
3. Rated down for risk of bias and inconsistency
4. Rated down for risk of bias and inconsistency and imprecision
5. Not estimable for adjusted odds ratio
6. ORs of higher than 1.0 indicate a better outcome (i.e., more days alive and free from the specified therapy) with balanced crystalloids than with saline

Table 7: 5% human albumin solution vs balanced crystalloid

No of studies	Study design	Intervention group (HAS) (events/total)	Comparator (BC) (events/total)	Effect size (risk ratio, odds ratio. Mean difference) (95% CI)	Absolute effect	Interpretation of effect	Certainty
30-day mortality							
1[1]	RCT	31 / 147	32 / 149	RR 1.43 (0.87, 2.35)[2]	92 more per 1000 (28 fewer to 290 more)	Could not differentiate	Very low[3]
In-hospital mortality							

1[1]	RCT	29 / 147	23 / 149	RR 1.28 (0.78, 2.10)	43 more per 1000 (34 fewer to 169 more)	Could not differentiate	Very low[3]
RRT							
1[1]	RCT	1/147	2/149	RR 0.51 (0.05, 5.53)	6 fewer per 1000 (12 fewer to 59 more)	Could not differentiate	Very low[3]
AKI							
1[1]	RCT	36/147	30/149	RR 1.29 (0.74, 2.23)	58 more per 1000 (52 fewer to 247 more)	Could not differentiate	Very low[3]

1. Gray 2024
2. Authors present as an adjusted odds ratio of 1.54 (95% CI 0.84–2.83)
3. Rated down for risk of bias, inconsistency, indirectness and imprecision

Table 8: Lower vs Higher fluid volumes - evidence from Sivapalan SR subgroup early phase of sepsis fluid resuscitation

No of studies	Study design	Lower fluid volume (events/total)	Higher fluid volume (events/total)	Effect size (risk ratio, odds ratio. mean difference) (97% or 99% CI)	Absolute effect	Interpretation of effect	Certainty
All-cause mortality							
7[1]	RCT	235 / 1064	221 / 1012	RR 1.02 (97% CI 0.85, 1.22)	4 more per 1000 (33 fewer to 48 more)	Could not differentiate	Moderate[16]

Serious adverse events[2]							
4[3]	RCT	52 / 991	48 / 937	RR 0.95 (97% CI 0.64, 1.42)	3 fewer per 1000 (18 fewer to 21 more)	Could not differentiate	Very low[11]
Duration of mechanical ventilation[5]							
4[4]	RCT	n=921	n=878	MD -1.14 (99% CI -3.25, 0.97)	N/A	No meaningful difference	Very low[12]
Duration of vasopressor or inotropes[6]							
4[4]	RCT	n=958	n=918	MD 2.22 (99% CI -6.48, 10.92)	N/A	Could not differentiate	Very Low[13]
Use of renal replacement therapy							
5[7]	RCT	33 / 976	37 / 942	RR 0.72 (99% CI 0.30, 1.73)	11 fewer per 1000 (27 fewer to 28 more)	Could not differentiate	Very low[14]
Incidence of AKI							

2[8]	RCT	10 / 116	11 / 116	RR 0.92 (99% CI 0.32, 2.61)	8 fewer per 1000 (65 fewer to 153 more)	Could not differentiate	Very low[15]
ICU length of stay							
4[9]	RCT	N= 202	N = 158	MD -1.29 (97% CI -3.20, 0.62)	N/A	No meaningful difference	Moderate[16]
Hospital length of stay							
4[10]	RCT	n=268	n=214	MD 0.60 (97% CI -0.80, 1.99)	N/A	No meaningful difference	Moderate[16]

1. Jessen 2022, Douglas 2020, Corl 2019, Shapiro 2023, Van Genderen 2015, MacDonald 2018, Lanspa 2018
2. 'As defined in the original trials or any untoward medical occurrence that fulfils the International Council on Harmonization Guideline for Good Clinical Practice's definition'
3. Douglas 2020, Jessen 2022, Macdonald 2018, Shapiro 2023
4. Corl 2019, Douglas 2020, Shapiro 2023, MacDonald 2018
5. Unit of measurement = days
6. Unit of measurement = hours
7. Douglas 2020, Jessen 2022, Macdonald 2018, Shapiro 2023, Corl 2019
8. Jessen 2022, Corl 2019
9. Lanspa 2018, Douglas 2020, Corl 2019, Macdonald 2018
10. Douglas 2020, Corl 2019, Macdonald 2018, Jessen 2022
11. Rated down for risk of bias, indirectness and imprecision
12. Rated down for risk of bias, inconsistency and imprecision
13. Rated down for risk of bias, inconsistency and indirectness

14. Rated down for imprecision and indirectness
15. Rated down for risk of bias and imprecision
16. Rated down for indirectness

Table 9: Lower vs Higher fluid volumes - subgroup analysis of sepsis only (not septic shock) ED population

No of studies	Study design	Lower fluid volume (events/total)	Higher fluid volume (events/total)	Effect size (risk ratio, odds ratio. mean difference) (97% CI)	Absolute effect	Interpretation of effect	Certainty
All -cause mortality							
3[1]	RCT	188 / 877	187 / 880	RR 1.01 (97% CI 0.83, 1.23)	2 more per 1000 (36 fewer to 49 more)	Could not differentiate	Moderate[8]
Serious adverse events[2]							
3[1]	RCT	42 / 893	19 / 892	RR 1.02 (97% CI 0.66, 1.58)	0 more per 1000 (7 fewer to 12 more)	Could not differentiate	Very low[6]
Duration of mechanical ventilation[5]							
2[2]	RCT	n=823	n=820	MD -0.08 (99% CI -0.52, 0.35)	N/A	No meaningful difference	Moderate[8]

Duration of vasopressor or inotropes[6]							
2[2]	RCT	n=828	n=827	MD 0.00 (99% CI -0.33, 0.34)	N/A	No meaningful difference	Moderate[8]
Use of renal replacement therapy							
3[1]	RCT	28 / 849	28 / 849	RR 1.00 (99% CI 0.51, 1.96)	0 more per 1000 (16 fewer to 32 more)	Could not differentiate	Moderate[8]
Incidence of AKI							
1[3]	RCT	9 / 61	10 / 62	RR 0.91 (99% CI 0.31. 2.72)	14 fewer per 1000 (111 fewer to 277 more)	Could not differentiate	Very Low[7]
ICU length of stay							
1[4]	RCT	n= 50	n=49	MD 0.10 (97% CI -0.90, 1.10)	N/A	Could not differentiate	Very Low[7]
Hospital length of stay							
2[5]	RCT	n = 111	n= 112	MD 1.18 (97% CI -0.72, 3.08)	N/A	No meaningful difference	Moderate[8]

1. Jessen 2022, Shapiro 2023, MacDonald 2018
2. Shapiro 2023, MacDonald 2018
3. Jessen 2022
4. MacDonald 2018
5. MacDonald 2018, Jessen 2022
6. Rated down for risk of bias, indirectness and imprecision
7. Rated down for inconsistency, imprecision and indirectness
8. Rate down for indirectness

See appendix F for full GRADE tables

1.1.7 Economic evidence

A search was performed to identify published economic evaluations of relevance for both review questions 5.1 and 5.2 (see Appendix B – Literature search strategies). The search returned 350 studies, of which 350 could be excluded at title and abstract.

1.1.7.1 Included studies

No economic evidence was included for these review questions. See Appendix G – Economic evidence study selection.

1.1.7.2 Excluded studies

All studies were excluded at the title and abstract stage.

1.1.8 Summary of included economic evidence

No relevant economic evidence was identified for these review questions.

1.1.9 Economic model

These review questions were not prioritised for economic modelling.

1.1.10 Unit costs

Relevant unit costs for fluids for resuscitation are provided below to aid the consideration of cost effectiveness in the absence of published relevant economic evidence. Unit costs and costs for resuscitation based on 2000ml as aligned with the IV fluid guideline are presented in Table .

Table 10: UK costs of IV fluids

Resource	Fluid class	Volume (ml)	Unit costs (a)	Cost for resuscitation (2000ml)
0.9% Sodium Chloride (bag)	Crystalloid	1000	£2.16	£4.32
0.9% Sodium Chloride (polyethylene bottles)	Crystalloid	1000	£1.72	£3.44
Hartmann's Solution (ringers lactate)	Balanced Crystalloid	1000	£2.90[(b)]	£5.80
Albumin (5%)	HAS	100	£13.50	£270

Resource	Fluid class	Volume (ml)	Unit costs (a)	Cost for resuscitation (2000ml)
Albumin (5%)	HAS	250	£33.75	£270
Albumin (4.5%)	HAS	250	£30.37	£242.96
Albumin (4.5%)	HAS	500	£60.75	£243
Plasmalyte A[(c)]	-	-	-	-
Clinical Fresh Frozen Plasma (FFP)	-	275	£40.02[(d)]	-

a) BNF 2024
b) Midpoint between the highest and lowest cost (£2.16 to £3.64)
c) Unable to source this cost
d) NHS Blood and Transplant 2023-24
HAS: Human albumin solution

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

The committee agreed that a reduction in all-cause mortality was the primary outcome when considering someone's initial resuscitation, but that reduced risk of renal replacement therapy, acute kidney injury, serious adverse events, mechanical ventilation and vasopressor use were important markers of successful resuscitation. The committee agreed that pulmonary oedema, fluid overload and signs that someone is not responding were also important outcomes, but no evidence was found for these.

1.1.11.2 The certainty of the evidence

The committee agreed that the certainty of the evidence for fluid type was very low, due to a high risk of bias (many of the trials were a small subgroup analyses of sepsis patients in critically ill populations therefore reducing the strength of the randomisation process), indirectness (many of the trials were in ICU populations and fell outside of the initial resuscitation period of the guideline) and imprecision (wide confidence intervals likely linked to small sample sizes). They also noted that the trials included in the Beran 2022 systematic review did not measure chloride. They noted that the certainty of the evidence for 5% human albumin solution compared to balanced crystalloids was very low, it came from one feasibility RCT that was unblinded and not powered to detect a statistically significant difference between arms.

The committee agreed that the certainty of the evidence for different volumes of fluid ranged from very low to moderate for some outcomes, being rated down for indirectness (many of the interventions in each 'lower' or 'higher' fluid arms were not fluids only for resuscitation and were complex haemodynamic protocols) and there were concerns about the risk of bias of the studies. They noted that the volume of fluids administered differed within the same ('lower volume' or 'higher volume') arm in the meta-analysis due to differences between the resuscitation protocols. They commented that in most of the studies initial resuscitation fluids had already been given prior to randomisation and that the volume of total fluids was measured at different timepoints with some falling outside of the initial resuscitation period.

1.1.11.3 Benefits and harms

When discussing the evidence on what type of fluid to use, the committee discussed that being too prescriptive for initial resuscitation could result in a delay to someone receiving fluids if that specific type is not stocked. They noted that different services carried different types of fluids, with ambulance services only stocking 0.9% saline whereas emergency departments, some in-patient areas, and ICUs will stock other fluids in addition to saline. Although the evidence favoured balanced crystalloids in one post-hoc subgroup analysis from a trial, the committee felt that the most important aspect of early resuscitation was that people receive intravenous fluids as soon as it is apparent that they are needed. Services should use whatever is available in order not to delay treatment, but with a preference for balanced solutions where possible. They discussed the possibility of making recommendations for using specific fluids depending on the indication. They noted that there was no evidence for this, and given this recommendation's remit is to cover early resuscitation across different settings, they would be unable to make the recommendations this nuanced. They agreed that changing the fluid type depending on someone's biochemistry or other clinical indications could be done at a later point. The committee discussed and agreed to remove the wording about sodium range from the existing recommendation as they felt

this was not meaningful given all isotonic solutions used in the UK would contain sodium within that range (130 to 154 mmol/litre).

In relation to the evidence on 5% human albumin solution (HAS) the committee discussed that the feasibility RCT included in the review could not differentiate between 5% HAS and balanced crystalloids, though they also discussed that it was not powered to detect a difference between the two arms. They further discussed the existing recommendation on HAS, particularly with reference to changing practice in this area, and the availability and cost implications. They noted that the original evidence used for this recommendation was based on quite a specific population, that of septic shock patients in ICU with hypoalbuminemia. They discussed their concerns with extrapolating this to other situations such as initial fluid resuscitation in emergency departments, wards or ambulances and noted that the noted that the original guideline committee also had concerns with this. They also noted that one other study in the original evidence was unable to differentiate between albumin and crystalloids for 90-day mortality. They agreed that HAS, was more expensive than other solutions, that practice had moved on from using it for initial resuscitation in people with sepsis. Furthermore, it is not stocked in some services. For these reasons they removed the previous recommendation to consider HAS for people with sepsis or septic shock.

When discussing the evidence for lower or higher fluid volumes, the committee noted that the evidence presented to them showed no statistically significant difference between the two approaches. Although a subgroup analysis of fluids given in the emergency department was conducted, in most studies the populations had already been given an initial bolus of fluid for resuscitation. This raised concerns about the direct applicability of the evidence to the recommendations they were updating. On discussing the volume of the initial fluid bolus, the committee agreed that this will be determined by the individual's current clinical situation and that in some instances less fluids would be better and in others more might be required. The committee commented that the emphasis on this initial phase of

resuscitation should be on the timely reassessment of the patient after each bolus is delivered. They recommended a staggered approach be taken by delivering an initial 250ml bolus over 10-15 minutes, reassessing and if required further 250ml boluses up to 1000ml. At this point they agreed with the existing recommendation to seek advice from a senior clinical decision maker before giving any more fluids. The committee also commented that any decision to give further boluses should take into account fluids that had already been given to people in a previous setting, for example if fluids are given in an ambulance this should be considered when giving further fluids in the emergency department.

1.1.11.4 Cost effectiveness and resource use

No published economic evidence was available for the committee to review. The committee considered the costs of the fluid options included within the scope of this guideline update and acknowledged Albumin was much more expensive compared to the crystalloids. The committee discussed the evidence suggested crystalloids are the most effective at reducing mortality, in particular balanced crystalloids, suggesting the use of Hartmann's solution compared with 0.9% sodium chloride. However, the committee agreed that the evidence suggesting balanced crystalloids was weak and replacing the use of 0.9% sodium chloride with Hartmann's solution could have a large resource impact, particularly in the ambulance setting where predominately only 0.9% sodium chloride is carried.

The costs associated with replacing the fluid use and additional training for settings where Hartmann's solution is not currently available was not considered justifiable given the relatively small benefits based on weak evidence. The committee agreed that when Hartmann's is available, such as in an emergency department, based on the evidence showing benefit then a balanced crystalloid such as Hartmann's solution should be used.

The committee discussed tailoring the use of specific fluids based on how a patient presents based on their electrolytes. The committee agreed that whilst

there may be some benefit to tailoring fluids, given this evidence was out of scope they were unable to make such recommendations for which there could be resource implications.

The committee discussed the effectiveness evidence associated with human albumin solution (HAS) did not show it to be more effective (though the evidence was limited and of low certainty). They further noted the additional costs of using HAS compared with crystalloids and resource use in terms of additional staff time required for prescribing, storage and giving of blood transfusion. They noted the limited evidence underpinning this recommendation in the previous guideline which was also specifically in a septic shock population in ICU. They further discussed that practice in this area has moved on and that HAS is infrequently used. The committee therefore agreed that the recommendation for considering the use of HAS should be removed for people with sepsis or septic shock.

The committee discussed the clinical importance of not overloading someone with fluids and by giving 250ml initially before reassessing whether more fluids are required. Although reassessing patients for whether further fluids are required may lead to a slight increase in nurse staffing time, these costs may be offset by improved outcomes such as a reduction in fluid overload. Additionally, this may lead to a decrease in costs because of a reduction in the quantity of fluid used. The committee weighed the risks of patient harms of overloading with fluids compared with the additional senior staff time required for assessment. The committee agreed that after 1000ml advice should be sought from a senior clinical decision maker.

Overall, the committee did not anticipate a large resource impact as a result of these recommendations. The committee mitigated against any potentially large resource impact by phrasing the recommendation as to use balanced crystalloids when available to avoid a potentially large resource impact within the ambulance and prehospital settings. The committee discussed that many services would not stock HAS and whilst not using HAS would reduce costs,

given it is not widely used, cost savings are expected to be small. Given previously the recommendation stated that a senior clinical decision maker should attend in person if there were no signs of improvement following repeated boluses up to 1000ml, there is no resource impact anticipated from this recommendation as it adds clarity and potentially reduces earlier requirement of senior input.

1.1.11.5 Other factors the committee took into account

The previous recommendation stated that a senior clinical decision maker should attend in person if there were no signs of improvement following repeated boluses up to 1000ml. The committee agreed that this could potentially delay further treatment and could be resource intensive; they therefore amended the recommendation to get advice from a senior clinical decision maker.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.8.4 to 1.8.9; and 1.8.11 to 1.8.13. Other evidence supporting these recommendations can be found in the evidence review F: Indicators of organ hypoperfusion in people with suspected sepsis and evidence review G: safety of peripheral administration of vasopressor.

1.1.13 References – included studies

1.1.13.1 Effectiveness

Beran, Azizullah, Altorok, Nehaya, Srour, Omar et al. (2022) Balanced Crystalloids versus Normal Saline in Adults with Sepsis: A Comprehensive Systematic Review and Meta-Analysis. Journal of clinical medicine 11(7)

Gray, Alasdair J, Oatey, Katherine, Grahamslaw, Julia et al. (2024) Albumin Versus Balanced Crystalloid for the Early Resuscitation of Sepsis: An Open Parallel-Group Randomized Feasibility Trial. The ABC-Sepsis Trial. Critical care medicine

Jackson, Karen E, Wang, Li, Casey, Jonathan D et al. (2021) Effect of Early Balanced Crystalloids Before ICU Admission on Sepsis Outcomes. Chest 159(2): 585-595

Sivapalan P, Ellekjaer KL, Jessen MK et al. (2023) Lower vs Higher Fluid Volumes in Adult Patients With Sepsis: An Updated Systematic Review With Meta-Analysis and Trial Sequential Analysis. Chest 164(4): 892-912

1.1.13.2 Economic

No economic evidence was identified for these review questions.

1.1.15 References – other

National Institute for Health and care Excellence (NICE). British National Formulary (BNF). Published 2024. Accessed February, 2024. https://bnf.nice.org.uk/

NHS blood and transplant. Published 2023. Accessed September 2024. https://hospital.blood.co.uk/components/portfolio-and-prices

Appendices

Appendix A – Review protocols

Review protocol for fluid type (5.1)

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Clinical and cost effectiveness of type of IV fluids for resuscitation in people aged 16 or over with suspected sepsis.
2.	Review question(s)	What is the most clinical and cost-effective intravenous fluid for resuscitation of people aged 16 or over with suspected sepsis?
3.	Objective	To determine the clinical and cost effectiveness of different types of fluid for resuscitation in people aged 16 or 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 • Epistemonikos • MEDLINE in process Searches will be restricted by: • 2016 • English Language • Human studies • Conference abstracts excluded • OECD countries

		The full search strategies will be reported in the final review in accordance with the PRISMA-S reporting guide.
5.	Condition or domain being studied	Suspected sepsis
6.	Population	Inclusion: • Adults aged 16 or over with suspected sepsis in acute hospital* and ambulance settings who require resuscitation in the first 6 hours of care. *this could include hospital at home/virtual wards Exclusion: • Children under the age of 16 • People who are or have recently been pregnant
7.	Intervention	*Type of IV Fluid – Specifically:* Crystalloid – • Ringer's lactate (Hartmann's) • Plasmalyte A • Normal Saline (0.9%) Colloid – albumin • Human albumin solution • Fresh frozen plasma (FFP)
8.	Comparator	*Type of IV Fluid – Specifically:* Crystalloid – • Plasmalyte A • Normal Saline (0.9%) Colloid – albumin • Human albumin solution • FFP
9.	Types of study to be included	• Systematic reviews of RCTs • RCTs • Cohort studies (prospective and retrospective) if no RCTs are identified.

10.	Other exclusion criteria	• All other study types for example conference abstracts, editorials/letters, studies not published in English and study pre-prints. • Studies reporting data without confidence intervals or data that cannot be used to calculate confidence intervals.
11.	Context	During the previous update of the sepsis guideline that published in January 2024, the committee indicated that there is insufficient detail in the current sepsis guideline to guide clinicians as to when to start and stop fluids, what volume and what type of fluid is appropriate. The current recommendations in this area are taken from the NICE guideline on intravenous fluid therapy in adults in hospital.
12.	Primary outcomes (critical outcomes)	• All cause mortality – in hospital and 30 days • Adverse events including but not limited to AKI
13.	Secondary outcomes (important outcomes)	Length of hospital stay Admission to ICU Organ system dysfunction Pulmonary oedema
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 6.2). Study investigators may be contacted for missing data where time and resources allow.

		Where appropriate, this review will make use of the priority screening functionality within the EPPI-reviewer software. At least 50% of the data set will be screened and we will stop screening after that if we screen more than 250 records without an include
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the Cochrane ROB-2 checklist for RCTs, ROBIS for systematic reviews and ROBINS-I for cohort studies as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	**Approach to meta-analysis** Pairwise meta-analyses will be performed in Cochrane RevMan Web. A pooled relative risk will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. A pooled mean difference will be calculated for continuous outcomes (using the inverse variance method) when the same scale will be used to measure an outcome across different studies. Where different studies presented continuous data measuring the same outcome but using different numerical scales these outcomes will be all converted to the same scale before meta-analysis is conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data will be analysed using standardised mean differences (SMDs, Hedges' g). Fixed effects models will be fitted unless there is significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$, when random effects models will be used instead. Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced

<table>
<tr><td></td><td></td><td colspan="3">to graphically assess the potential for publication bias.

GRADE will be used to assess the quality of any pair-wise analysis of outcomes. Outcomes using evidence from RCTs will be rated as high quality initially and downgraded from this point. Reasons for upgrading the certainty of the evidence will also be considered.</td></tr>
<tr><td>17.</td><td>Analysis of sub-groups</td><td colspan="3">People with heart failure prior to sepsis

People developing sepsis post-operatively</td></tr>
<tr><td>18.</td><td>Type and method of review</td><td colspan="3">☒ Intervention
☐ Diagnostic
☐ Prognostic
☐ Qualitative
☐ Epidemiologic
☐ Service Delivery
☐ Other (please specify)</td></tr>
<tr><td>19.</td><td>Language</td><td colspan="3">English</td></tr>
<tr><td>20.</td><td>Country</td><td colspan="3">England</td></tr>
<tr><td>21.</td><td>Anticipated or actual start date</td><td colspan="3">June 2024</td></tr>
<tr><td>22.</td><td>Anticipated completion date</td><td colspan="3">tbc</td></tr>
<tr><td rowspan="4">23.</td><td rowspan="4">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☐</td><td>☐</td></tr>
<tr><td>Piloting of the study selection process</td><td>☐</td><td>☐</td></tr>
<tr><td>Formal screening of search</td><td>☐</td><td>☐</td></tr>
</table>

		results against eligibility criteria		
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** sepsisupdate@nice.org.uk **5b Named contact e-mail** sepsisupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and Guideline Development Team B		
25.	Review team members	From the Centre for Guidelines: • Guideline lead: Emma McFarlane • Technical analyst: Anthony Gildea • Senior technical analyst: James Jagroo • Health Economist: Lindsay Claxton • Senior Information specialist: Lynda Ayiku		
26.	Funding sources/sponsor	This systematic review is being completed by the guideline development team 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: tbc
29.	Other registration details	N/A
30.	Reference/URL for published protocol	tbc
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, Intravenous, IV, Fluids, mortality
33.	Details of existing review of same topic by same authors	This is a new review question that will update Sepsis: recognition, diagnosis and early management NG51
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued

35..	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

Review protocol for fluid volume (5.2)

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Clinical and cost effectiveness of different volumes and rates of IV fluids for resuscitation in people aged 16 or over with suspected sepsis.
2.	Review question(s)	What is the most clinically and cost-effective volume and rate of administration for IV fluid for resuscitation in people aged 16 or over with suspected sepsis
3.	Objective	To determine the clinical and cost effectiveness of different volumes and different rates of IV fluids for resuscitation in people aged 16 or 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 • Epistemonikos • MEDLINE in process Searches will be restricted by: • 2016

		• English Language • Human studies • Conference abstracts excluded • OECD countries The full search strategies will be reported in the final review in accordance with the PRISMA-S reporting guide.
5.	Condition or domain being studied	Suspected sepsis
6.	Population	Inclusion: • Adults aged 16 or over with suspected sepsis in acute hospital* and ambulance settings *this could include hospital at home/virtual wards Exclusion: • Children under the age of 16 • People who are or have recently been pregnant
7.	Intervention	• boluses of x ml/kg bodyweight / x minutes
8.	Comparator	• boluses of x ml/kg bodyweight / at different rates
9.	Types of study to be included	• Systematic reviews of RCTs • RCTs • Cohort studies (prospective and retrospective) if no RCTs are identified.
10.	Other exclusion criteria	• All other study types for example conference abstracts, editorials/letters, studies not published in English and study pre-prints. • Studies reporting data without confidence intervals or data that cannot be used to calculate confidence intervals.

11.	Context	During the previous update of the sepsis guideline that published in January 2024, the committee indicated that there is insufficient detail in the current sepsis guideline to guide clinicians as to when to start and stop fluids, what volume and what type of fluid is appropriate. The current recommendations in this area are taken from the NICE guideline on intravenous fluid therapy in adults in hospital.
12.	Primary outcomes (critical outcomes)	• Mortality (all cause, in hospital and at 30 days • organ support (vasoactive drugs, mechanical ventilation, RRT) • signs that someone is not responding: tachycardia; level of consciousness; blood pressure decrease (clinical significance as defined by the study); respiratory rate; blood lactate; urine output; peripheral perfusion; blood gases • Fluid overload – hypervolemia as defined by the study • Adverse events including but not limited to AKI
13.	Secondary outcomes (important outcomes)	• Length of hospital stay • Admission to ICU • Length of ICU stay
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 6.2). Study investigators may be contacted for missing data where time and resources allow. Where appropriate, this review will make use of the priority screening functionality within the EPPI-reviewer software. At least 50% of the data set will be screened and we will stop screening after that if we screen more than 250 records without an include
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the Cochrane ROB-2 checklist for RCTs, ROBIS for systematic review and ROBINS-I for cohort studies as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	**Approach to meta-analysis** Pairwise meta-analyses will be performed in Cochrane RevMan Web. A pooled relative risk will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. A pooled mean difference will be calculated for continuous outcomes (using the inverse variance method) when the same scale will be used to measure an outcome across different studies. Where different studies presented continuous data measuring the same outcome but using different numerical scales these outcomes will be all converted to the same scale before meta-analysis is conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data will be analysed using standardised mean differences (SMDs, Hedges' g). Fixed effects models will be fitted unless there is significant statistical heterogeneity in the meta-

		analysis, defined as $I^2 \geq 50\%$, when random effects models will be used instead. Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically assess the potential for publication bias. GRADE will be used to assess the quality of any pair-wise analysis of outcomes. Outcomes using evidence from RCTs will be rated as high quality initially and downgraded from this point. Reasons for upgrading the certainty of the evidence will also be considered.		
17.	Analysis of sub-groups	People with heart failure prior to developing sepsis Post operative patients		
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	June 2024		
22.	Anticipated completion date	tbc		
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** sepsisupdate@nice.org.uk **5b Named contact e-mail** sepsisupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and Guideline Development Team B		
25.	Review team members	From the Centre for Guidelines: • Guideline lead: Emma McFarlane • Technical analyst: Anthony Gildea • Senior technical analyst: James Jagroo • Health Economist: Lindsay Claxton • Senior Information specialist: Lynda Ayiku		
26.	Funding sources/sponsor	This systematic review is being completed by the guideline development team 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: tbc
29.	Other registration details	N/A
30.	Reference/URL for published protocol	tbc
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, Intravenous, IV, Fluids, mortality
33.	Details of existing review of same topic by same authors	This is a new review question that will update Sepsis: recognition, diagnosis and early management NG51
34.	Current review status	☒ Ongoing

		☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

Background and development

Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches for the evidence review.

The principal search strategies were 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.

The MEDLINE strategies below were quality assured (QA) by a trained NICE SIS. All translated search strategies were peer reviewed by another SIS to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

This search report is based on the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

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 search terms for the sepsis population from '(A) Evidence reviews for stratifying risk of severe illness or death from sepsis' in NG51 (Jan 2024) were used to inform the population terms for the search strategy.

Search limits and other restrictions

Formats

Limits were applied in adherence to standard NICE practice (as set out in the Identifying the evidence chapter of the manual) and the eligibility criteria listed in the review protocol to exclude:

- Animal studies
- Conference abstracts and posters
- Registry entries for ongoing clinical trials or those that contain no results
- Papers not published in the English language.

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.

Date limits

A date limit of 2016 to 2024 was applied, as stated in the review protocol.

Search filters and classifiers

Effectiveness searches

Systematic reviews filters:

Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. BMC Medical Research Methodology, 12(1), 51.

- In MEDLINE, the standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.
- In Embase, the standard NICE modifications were used: pubmed.tw added to line medline.tw.

Cohort studies terms:

Terms for cohort studies were used from the observational studies filters. The terms used for observational studies are standard NICE practice that have been developed in house.

Randomised controlled trials filters:

The MEDLINE RCT filter was McMaster Therapy – Medline - "best balance of sensitivity and specificity" version.

The standard NICE modifications were used: the MeSH heading *randomized controlled trial/*, which is equivalent *to randomized controlled trial.pt* was exploded to capture newer, narrower *terms equivalence trial/ and pragmatic clinical trial*. The free-text term *randomized.mp* was also changed to the (more inclusive) alternative *randomi?ed.mp.* to capture both UK and US spellings.

Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.

The Embase RCT filter was McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *Journal of the Medical Library Association*, 94(1), 41-47.

OECD countries geographic search filters:

The OECD countries filters were used without modification: Ayiku, L., Hudson, T., Williams, C., Levay, P., & Jacob, C. (2021). The NICE OECD countries' geographic search filters: Part 2 - Validation of the MEDLINE and Embase (Ovid) filters. *Journal of the Medical Library Association*, 109(4), 583–589.

Cost effectiveness searches

In line with the review protocol, the sensitive version of the validated NICE cost utility filter was used in the MEDLINE and Embase strategies without amendment.

- Hubbard W et al. (2022) Development and validation of paired MEDLINE and Embase search filters for cost-utility studies. *BMC Medical Research Methodology*, 22(1), 310.

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

- Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Note: Several modifications have been made to these filters over the years that are standard NICE practice.

Effectiveness searches

Database results

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
Cochrane Database of Systematic Reviews (CDSR)	15th Aug 2024	Wiley	Issue 8 of 12, August 2024	0
Cochrane Central Register of Controlled Trials (CENTRAL)	15th Aug 2024	Wiley	Issue 7 of 12, July 2024	322
Embase	15th Aug 2024	Ovid	Embase <1974 to 2024 August 14>	634
Epistemonikos	15th Aug 2024	Epistemonikos	Searched 15th Aug 2024	11
MEDLINE ALL	15th Aug 2024	Ovid	Ovid MEDLINE(R) ALL <1946 to August 14, 2024>	365

Search strategy history

Database name: MEDLINE ALL

Searches
Database: Ovid MEDLINE(R) ALL <1946 to August 14, 2024> Search Strategy: ---------- 1 exp sepsis/ (147096) 2 sepsis.ti,ab. (126082) 3 blood-borne pathogens/ (3052) 4 (blood* adj2 (pathogen* or poison*)).ti,ab. (3498) 5 exp systemic inflammatory response syndrome/ (155521) 6 'systemic inflammatory response syndrome*'.tw. (6095) 7 sirs.ti,ab. (6871) 8 (septicaemi* or septicemi*).ti,ab. (22674) 9 ((septic or cryptic) adj2 shock).ti,ab. (28806) 10 (pyaemi* or pyemi* or pyohemi*).ti,ab. (260) 11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab. (74914) 12 (hypotension adj3 induced adj3 hypoperfusion).ti,ab. (7) 13 or/1-12 (295150)

Searches
14 exp Administration, Intravenous/ (149862)
15 Fluid therapy/ (22264)
16 plasma substitutes/ (6802)
17 exp crystalloid solutions/ (5088)
18 ringer's solution/ (1006)
19 dextrans/ (25494)
20 (intravenous* or iv or i-v).tw. (831788)
21 (fluid* or drip*).tw. (596265)
22 (crystalloid* or Hartmann* or Ringer* or saline* or colloid* or album* or dextran* or plasma* or FFP or hypertonic* or sodium*).tw. (1883045)
23 or/14-22 (3115518)
24 Resuscitation/ (29007)
25 (resuscit* or reanimat* or re-animat* or reviv* or restor*).tw. (495421)
26 or/24-25 (503975)
27 13 and 23 and 26 (4797)
28 (MEDLINE or pubmed).tw. (370701)
29 systematic review.tw. (312507)
30 systematic review.pt. (270106)
31 meta-analysis.pt. (206230)

Searches
32 intervention$.ti. (219002)
33 or/28-32 (766849)
34 27 and 33 (240)
35 exp Randomized Controlled Trial/ (620617)
36 randomi?ed.mp. (1135424)
37 placebo.mp. (259014)
38 or/35-37 (1203656)
39 27 and 38 (832)
40 34 or 39 (957)
41 afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or

Searches
lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/ (1362187) 42 "organisation for economic co-operation and development"/ (622) 43 australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/ (3581748) 44 european union/ (18126)

Searches
45 developed countries/ (21606)
46 or/42-45 (3598213)
47 41 not 46 (1270768)
48 40 not 47 (933)
49 limit 48 to english language (876)
50 animals/ not humans/ (5214574)
51 49 not 50 (658)
52 limit 51 to yr="2016 -Current" (365)

Database name: Embase

Searches
Database: Embase <1974 to 2024 August 14>
Search Strategy:
1 exp sepsis/ (359910)
2 sepsis.ti,ab. (197862)
3 bloodborne bacterium/ (2195)
4 (blood* adj2 (pathogen* or poison*)).ti,ab. (4578)
5 exp systemic inflammatory response syndrome/ (374249)
6 'systemic inflammatory response syndrome*'.ti,ab. (9053)

Searches
7 sirs.ti,ab. (12231)
8 (septicaemi* or septicemi*).ti,ab. (26706)
9 ((septic or cryptic) adj2 shock).ti,ab. (47344)
10 (pyaemi* or pyemi* or pyohemi*).ti,ab. (136)
11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab. (104458)
12 (hypotension adj3 induced adj3 hypoperfusion).ti,ab. (8)
13 or/1-12 (497129)
14 exp intravenous drug administration/ (393125)
15 fluid therapy/ or fluid resuscitation/ (43776)
16 sodium chloride/ (236673)
17 exp plasma substitute/ (76675)
18 exp crystalloid/ (11065)
19 calcium chloride plus potassium chloride plus sodium chloride/ (113)
20 acetic acid plus gluconate sodium plus magnesium chloride plus potassium chloride plus sodium chloride/ (802)
21 colloid/ (31108)
22 infusion fluid/ (20124)
23 (intravenous* or iv or i-v).tw. (1193188)
24 (fluid* or drip*).tw. (756241)

Searches
25 (crystalloid* or Hartmann* or Ringer* or saline* or colloid* or album* or dextran* or plasma* or FFP or hypertonic* or sodium*).tw. (2392890)
26 or/14-25 (4312543)
27 resuscitation/ (140227)
28 (resuscit* or reanimat* or re-animat* or reviv* or restor*).tw. (623290)
29 or/27-28 (685729)
30 13 and 26 and 29 (10640)
31 fluid resuscitation/ (18637)
32 13 and 31 (6360)
33 30 or 32 (13361)
34 (MEDLINE or pubmed).tw. (461209)
35 exp systematic review/ or systematic review.tw. (574087)
36 meta-analysis/ (327985)
37 intervention$.ti. (288477)
38 or/34-37 (1072135)
39 random:.tw. (2111766)
40 placebo:.mp. (544590)
41 double-blind:.tw. (255266)
42 or/39-41 (2396750)

Searches
43 38 or 42 (3138512) 44 33 and 43 (2238) 45 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/

Searches
or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ (1801477)
46 exp "organisation for economic co-operation and development"/ (3085)
47 exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/ (3918138)
48 european union/ (32599)
49 developed country/ (36437)
50 or/46-49 (3953274)
51 45 not 50 (1640579)
52 44 not 51 (2180)
53 limit 52 to english language (2078)
54 nonhuman/ not human/ (5514339)

Searches
55 53 not 54 (1700)
56 limit 55 to yr="2016 -Current" (912)
57 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (6005191)
58 56 not 57 (634)

Database name: Cochrane CENTRAL

Searches
#1 MeSH descriptor: [Sepsis] explode all trees 6535
#2 sepsis:ti,ab,kw 14366
#3 MeSH descriptor: [Blood-Borne Pathogens] this term only 38
#4 (blood* near/2 (pathogen* or poison*)):ti,ab,kw 382
#5 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees 7071
#6 systemic inflammatory response syndrome*:ti,ab,kw 1799
#7 (septicaemi* or septicemi*):ti,ab,kw 1056
#8 sirs:ti,ab,kw 947
#9 ((septic or cryptic) near/2 shock):ti,ab,kw4099
#10 (pyaemi* or pyemi* or pyohemi*):ti,ab,kw 7
#11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*):ti,ab,kw 6839

Searches
#12 (hypotension near/3 induced near/3 hypoperfusion):ti,ab,kw 2
#13 {or #1-#12} 25115
#14 MeSH descriptor: [Administration, Intravenous] explode all trees 22890
#15 MeSH descriptor: [Fluid Therapy] this term only 2231
#16 MeSH descriptor: [Plasma Substitutes] this term only 666
#17 MeSH descriptor: [Crystalloid Solutions] explode all trees 1101
#18 MeSH descriptor: [Ringer's Solution] this term only 116
#19 MeSH descriptor: [Dextrans] this term only 594
#20 (intravenous* or iv or i-v):ti,ab,kw 181581
#21 (fluid* or drip*):ti,ab,kw 42706
#22 (crystalloid* or Hartmann* or Ringer* or saline* or colloid* or album* or dextran* or plasma* or FFP or hypertonic* or sodium*):ti,ab,kw 220006
#23 {or #14-#22} 384885
#24 MeSH descriptor: [Resuscitation] this term only 966
#25 (resuscit* or reanimat* or re-animat* or reviv* or restor*):ti,ab,kw 35781
#26 {or #24-#25} 35781
#27 #13 and #23 and #26 1225
#28 "conference":pt or (clinicaltrials or trialsearch):so 770307

Searches
#29 #27 not #28 with Publication Year from 2016 to 2024, with Cochrane Library publication date Between Jan 2016 and Aug 2024, in Trials 322 (322 results CENTRAL)

Database name: CDSR

Searches
#1 MeSH descriptor: [Sepsis] explode all trees 6535
#2 sepsis:ti,ab,kw 14366
#3 MeSH descriptor: [Blood-Borne Pathogens] this term only 38
#4 (blood* near/2 (pathogen* or poison*)):ti,ab,kw 382
#5 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees 7071
#6 systemic inflammatory response syndrome*:ti,ab,kw 1799
#7 (septicaemi* or septicemi*):ti,ab,kw 1056
#8 sirs:ti,ab,kw 947
#9 ((septic or cryptic) near/2 shock):ti,ab,kw4099
#10 (pyaemi* or pyemi* or pyohemi*):ti,ab,kw 7
#11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*):ti,ab,kw 6839
#12 (hypotension near/3 induced near/3 hypoperfusion):ti,ab,kw 2
#13 {or #1-#12} 25115

Searches
#14 MeSH descriptor: [Administration, Intravenous] explode all trees 22890
#15 MeSH descriptor: [Fluid Therapy] this term only 2231
#16 MeSH descriptor: [Plasma Substitutes] this term only 666
#17 MeSH descriptor: [Crystalloid Solutions] explode all trees 1101
#18 MeSH descriptor: [Ringer's Solution] this term only 116
#19 MeSH descriptor: [Dextrans] this term only 594
#20 (intravenous* or iv or i-v):ti,ab,kw 181581
#21 (fluid* or drip*):ti,ab,kw 42706
#22 (crystalloid* or Hartmann* or Ringer* or saline* or colloid* or album* or dextran* or plasma* or FFP or hypertonic* or sodium*):ti,ab,kw 220006
#23 {or #14-#22} 384885
#24 MeSH descriptor: [Resuscitation] this term only 966
#25 (resuscit* or reanimat* or re-animat* or reviv* or restor*):ti,ab,kw 35781
#26 {or #24-#25} 35781
#27 #13 and #23 and #26 1225
#28 "conference":pt or (clinicaltrials or trialsearch):so 770307
#29 #27 not #28 with Publication Year from 2016 to 2024, with Cochrane Library publication date Between Jan 2016 and Aug 2024, in Trials 322 (0 results CDSR)

Database name: Epistemonikos

Searches
(title:((title:(sepsis OR systemic inflammatory response syndrome* OR sirs OR septi* OR crypti* OR pyaemi* OR pyemi* OR pyohemi* OR bacteremi* OR bacteraemi* OR fungemi* OR fungaemi* OR parasitemi* OR parasitaemi* OR viremi* OR viraemi*) OR abstract:(sepsis OR systemic inflammatory response syndrome* OR sirs OR septi* OR crypti* OR pyaemi* OR pyemi* OR pyohemi* OR bacteremi* OR bacteraemi* OR fungemi* OR fungaemi* OR parasitemi* OR parasitaemi* OR viremi* OR viraemi*)) AND (title:(intravenous* OR iv OR i-v OR fluid* OR drip* OR crystalloid* OR Hartmann* OR Ringer* OR saline* OR colloid* OR album* OR dextran* OR plasma* OR FFP OR hypertonic* OR sodium*) OR abstract:(intravenous* OR iv OR i-v OR fluid* OR drip* OR crystalloid* OR Hartmann* OR Ringer* OR saline* OR colloid* OR album* OR dextran* OR plasma* OR FFP OR hypertonic* OR sodium*)) AND (title:(resuscit* OR reanimat* OR re-animat* OR reviv* OR restor*) OR abstract:(resuscit* OR reanimat* OR re-animat* OR reviv* OR restor*))) OR abstract:((title:(sepsis OR systemic inflammatory response syndrome* OR sirs OR septi* OR crypti* OR pyaemi* OR pyemi* OR pyohemi* OR bacteremi* OR bacteraemi* OR fungemi* OR fungaemi* OR parasitemi* OR parasitaemi* OR viremi* OR viraemi*) OR abstract:(sepsis OR systemic inflammatory response syndrome* OR sirs OR septi* OR crypti* OR pyaemi* OR pyemi* OR pyohemi* OR bacteremi* OR bacteraemi* OR fungemi* OR fungaemi* OR parasitemi* OR parasitaemi* OR viremi* OR viraemi*)) AND (title:(intravenous* OR iv OR i-v OR fluid* OR drip* OR crystalloid* OR Hartmann* OR Ringer* OR saline* OR colloid* OR album* OR dextran* OR plasma* OR FFP OR hypertonic* OR sodium*) OR abstract:(intravenous* OR iv OR i-v OR fluid* OR drip* OR crystalloid* OR Hartmann* OR Ringer* OR saline* OR colloid* OR album* OR dextran* OR plasma* OR FFP OR hypertonic* OR sodium*)) AND (title:(resuscit* OR reanimat* OR re-animat* OR reviv* OR restor*) OR abstract:(resuscit* OR

Searches
reanimat* OR re-animat* OR reviv* OR restor*)))) = 11 results (limited to SRs and 2016+)

Cost-effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
EconLit	15th Aug 2024	OVID	Econlit <1886 to August 1, 2024>	0
Embase	15th Aug 2024	Ovid	Embase <1974 to 2024 August 14>	338
INAHTA	15th Aug 2024	INAHTA	Searched 15th Aug 2024	0
MEDLINE	15th Aug 2024	Ovid	Ovid MEDLINE(R) ALL <1946 to August 14, 2024>	105

Search strategy history

Database name: MEDLINE ALL

Searches
Database: Ovid MEDLINE(R) ALL <1946 to August 14, 2024> Search Strategy: ---------- 1 exp sepsis/ (147096) 2 sepsis.ti,ab. (126082) 3 blood-borne pathogens/ (3052) 4 (blood* adj2 (pathogen* or poison*)).ti,ab. (3498) 5 exp systemic inflammatory response syndrome/ (155521) 6 'systemic inflammatory response syndrome*'.tw. (6095) 7 sirs.ti,ab. (6871) 8 (septicaemi* or septicemi*).ti,ab. (22674) 9 ((septic or cryptic) adj2 shock).ti,ab. (28806) 10 (pyaemi* or pyemi* or pyohemi*).ti,ab. (260) 11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab. (74914) 12 (hypotension adj3 induced adj3 hypoperfusion).ti,ab. (7) 13 or/1-12 (295150) 14 exp Administration, Intravenous/ (149862)

Searches
15 Fluid therapy/ (22264)
16 plasma substitutes/ (6802)
17 exp crystalloid solutions/ (5088)
18 ringer's solution/ (1006)
19 dextrans/ (25494)
20 (intravenous* or iv or i-v).tw. (831788)
21 (fluid* or drip*).tw. (596265)
22 (crystalloid* or Hartmann* or Ringer* or saline* or colloid* or album* or dextran* or plasma* or FFP or hypertonic* or sodium*).tw. (1883045)
23 or/14-22 (3115518)
24 Resuscitation/ (29007)
25 (resuscit* or reanimat* or re-animat* or reviv* or restor*).tw. (495421)
26 or/24-25 (503975)
27 13 and 23 and 26 (4797)
28 Economics/ (27539)
29 exp "Costs and Cost Analysis"/ (272390)
30 Economics, Dental/ (1922)
31 exp Economics, Hospital/ (25940)
32 exp Economics, Medical/ (14442)

Searches	
33	Economics, Nursing/ (4013)
34	Economics, Pharmaceutical/ (3144)
35	Budgets/ (11838)
36	exp Models, Economic/ (16465)
37	Markov Chains/ (16360)
38	Monte Carlo Method/ (33177)
39	Decision Trees/ (12299)
40	econom$.tw. (442234)
41	cba.tw. (11442)
42	cea.tw. (28171)
43	cua.tw. (1514)
44	markov$.tw. (33750)
45	(monte adj carlo).tw. (62269)
46	(decision adj3 (tree$ or analys$)).tw. (33326)
47	(cost or costs or costing$ or costly or costed).tw. (802355)
48	(price$ or pricing$).tw. (57262)
49	budget$.tw. (37944)
50	expenditure$.tw. (72485)
51	(value adj3 (money or monetary)).tw. (3403)

Searches
52 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (4656)
53 or/28-52 (1537933)
54 "Quality of Life"/ (291929)
55 quality of life.tw. (410050)
56 "Value of Life"/ (5829)
57 Quality-Adjusted Life Years/ (16702)
58 quality adjusted life.tw. (18710)
59 (qaly$ or qald$ or qale$ or qtime$).tw. (15664)
60 disability adjusted life.tw. (6267)
61 daly$.tw. (5622)
62 Health Status Indicators/ (24135)
63 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (32093)
64 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2798)
65 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (8151)
66 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (42)

Searches
67 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (467)
68 (euroqol or euro qol or eq5d or eq 5d).tw. (18549)
69 (qol or hql or hqol or hrqol).tw. (79963)
70 (hye or hyes).tw. (77)
71 health$ year$ equivalent$.tw. (40)
72 utilit$.tw. (290943)
73 (hui or hui1 or hui2 or hui3).tw. (2110)
74 disutili$.tw. (690)
75 rosser.tw. (111)
76 quality of wellbeing.tw. (53)
77 quality of well-being.tw. (515)
78 qwb.tw. (219)
79 willingness to pay.tw. (9528)
80 standard gamble$.tw. (921)
81 time trade off.tw. (1456)
82 time tradeoff.tw. (269)
83 tto.tw. (1498)
84 or/54-83 (810962)

Searches
85 Cost-Benefit Analysis/ (95391)
86 Quality-Adjusted Life Years/ (16702)
87 Markov Chains/ (16360)
88 exp Models, Economic/ (16465)
89 cost*.ti. (151682)
90 (cost* adj2 utilit*).tw. (8226)
91 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (297657)
92 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (50667)
93 (qualit* adj2 adjust* adj2 life*).tw. (19087)
94 QALY*.tw. (15496)
95 (incremental* adj2 cost*).tw. (18587)
96 ICER.tw. (6620)
97 utilities.tw. (9996)
98 markov*.tw. (33750)
99 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (56914)
100 ((utility or effective*) adj2 analys*).tw. (26776)

Searches
101 (willing* adj2 pay*).tw. (10743) 102 (EQ5D* or EQ-5D*).tw. (14794) 103 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (4322) 104 (european* adj2 quality adj3 ("5" or five)).tw. (789) 105 or/85-104 (533380) 106 53 or 84 or 105 (2272219) 107 27 and 106 (222) 108 limit 107 to english language (214) 109 limit 108 to yr="2016 -Current" (105)

Database name: Embase

Searches
Database: Embase <1974 to 2024 August 14> Search Strategy: --- 1 exp sepsis/ (359910) 2 sepsis.ti,ab. (197862)

Searches
3 bloodborne bacterium/ (2195)
4 (blood* adj2 (pathogen* or poison*)).ti,ab. (4578)
5 exp systemic inflammatory response syndrome/ (374249)
6 'systemic inflammatory response syndrome*'.ti,ab. (9053)
7 sirs.ti,ab. (12231)
8 (septicaemi* or septicemi*).ti,ab. (26706)
9 ((septic or cryptic) adj2 shock).ti,ab. (47344)
10 (pyaemi* or pyemi* or pyohemi*).ti,ab. (136)
11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab. (104458)
12 (hypotension adj3 induced adj3 hypoperfusion).ti,ab. (8)
13 or/1-12 (497129)
14 exp intravenous drug administration/ (393125)
15 fluid therapy/ or fluid resuscitation/ (43776)
16 sodium chloride/ (236673)
17 exp plasma substitute/ (76675)
18 exp crystalloid/ (11065)
19 calcium chloride plus potassium chloride plus sodium chloride/ (113)
20 acetic acid plus gluconate sodium plus magnesium chloride plus potassium chloride plus sodium chloride/ (802)

Searches
21 colloid/ (31108)
22 infusion fluid/ (20124)
23 (intravenous* or iv or i-v).tw. (1193188)
24 (fluid* or drip*).tw. (756241)
25 (crystalloid* or Hartmann* or Ringer* or saline* or colloid* or album* or dextran* or plasma* or FFP or hypertonic* or sodium*).tw. (2392890)
26 or/14-25 (4312543)
27 resuscitation/ (140227)
28 (resuscit* or reanimat* or re-animat* or reviv* or restor*).tw. (623290)
29 or/27-28 (685729)
30 13 and 26 and 29 (10640)
31 fluid resuscitation/ (18637)
32 13 and 31 (6360)
33 30 or 32 (13361)
34 exp Health Economics/ (1089694)
35 exp "Health Care Cost"/ (357166)
36 exp Pharmacoeconomics/ (245722)
37 Monte Carlo Method/ (54556)
38 Decision Tree/ (25576)

Searches	
39	econom$.tw. (536105)
40	cba.tw. (14663)
41	cea.tw. (43601)
42	cua.tw. (1994)
43	markov$.tw. (42597)
44	(monte adj carlo).tw. (65108)
45	(decision adj3 (tree$ or analys$)).tw. (44160)
46	(cost or costs or costing$ or costly or costed).tw. (1066042)
47	(price$ or pricing$).tw. (78135)
48	budget$.tw. (50101)
49	expenditure$.tw. (95908)
50	(value adj3 (money or monetary)).tw. (4570)
51	(pharmacoeconomic$ or (pharmaco adj economic$)).tw. (9980)
52	or/34-51 (2405227)
53	"Quality of Life"/ (682359)
54	Quality Adjusted Life Year/ (38240)
55	Quality of Life Index/ (3310)
56	Short Form 36/ (42772)
57	Health Status/ (159840)

Searches
58 quality of life.tw. (642390)
59 quality adjusted life.tw. (28555)
60 (qaly$ or qald$ or qale$ or qtime$).tw. (28946)
61 disability adjusted life.tw. (7558)
62 daly$.tw. (7241)
63 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (52216)
64 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (3135)
65 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (12944)
66 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (74)
67 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (548)
68 (euroqol or euro qol or eq5d or eq 5d).tw. (33299)
69 (qol or hql or hqol or hrqol).tw. (141810)
70 (hye or hyes).tw. (194)
71 health$ year$ equivalent$.tw. (41)
72 utilit$.tw. (406226)

Searches
73 (hui or hui1 or hui2 or hui3).tw. (3391)
74 disutili$.tw. (1386)
75 rosser.tw. (146)
76 quality of wellbeing.tw. (80)
77 quality of well-being.tw. (595)
78 qwb.tw. (276)
79 willingness to pay.tw. (14282)
80 standard gamble$.tw. (1223)
81 time trade off.tw. (2171)
82 time tradeoff.tw. (323)
83 tto.tw. (2384)
84 or/53-83 (1403520)
85 cost utility analysis/ (13140)
86 quality adjusted life year/ (38240)
87 cost*.ti. (204063)
88 (cost* adj2 utilit*).tw. (13568)
89 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (410303)

Searches
90 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (70896)
91 (qualit* adj2 adjust* adj2 life*).tw. (29223)
92 QALY*.tw. (28660)
93 (incremental* adj2 cost*).tw. (30593)
94 ICER.tw. (14120)
95 utilities.tw. (15997)
96 markov*.tw. (42597)
97 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (76644)
98 ((utility or effective*) adj2 analys*).tw. (40342)
99 (willing* adj2 pay*).tw. (15993)
100 (EQ5D* or EQ-5D*).tw. (28352)
101 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (5824)
102 (european* adj2 quality adj3 ("5" or five)).tw. (1092)
103 or/85-102 (673349)
104 52 or 84 or 103 (3632369)
105 33 and 104 (891)
106 limit 105 to english language (871)

Searches
107 limit 106 to yr="2016 -Current" (514) 108 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (6005191) 109 107 not 108 (338)

Database name: EconLit

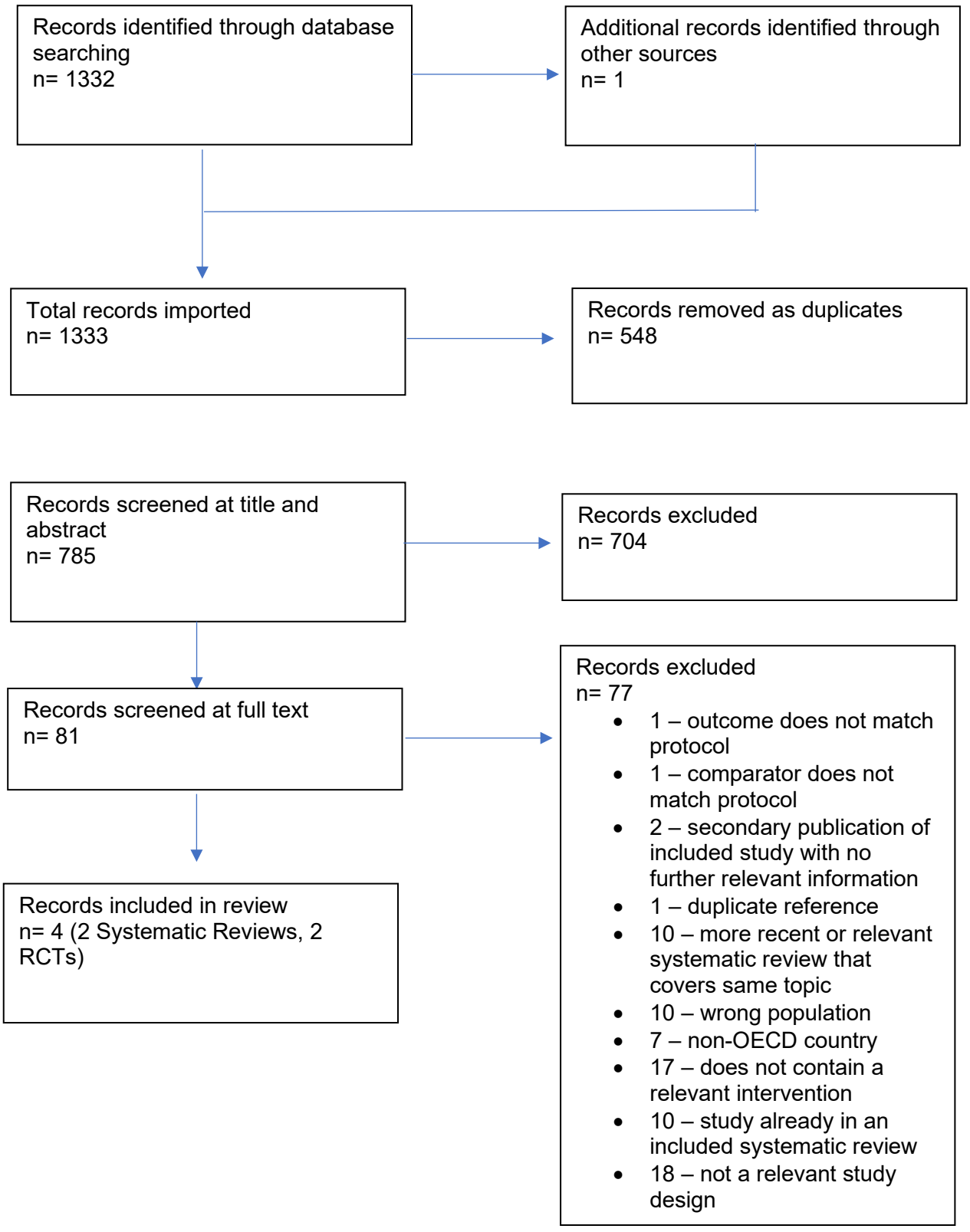
Searches
Database: Econlit <1886 to August 1, 2024> Search Strategy: --- 1 [exp sepsis/] (0) 2 sepsis.ti,ab. (24) 3 [blood-borne pathogens/] (0) 4 (blood* adj2 (pathogen* or poison*)).ti,ab. (0) 5 [exp systemic inflammatory response syndrome/] (0) 6 'systemic inflammatory response syndrome*'.tw. (0) 7 sirs.ti,ab. (20) 8 (septicaemi* or septicemi*).ti,ab. (2) 9 ((septic or cryptic) adj2 shock).ti,ab. (2) 10 (pyaemi* or pyemi* or pyohemi*).ti,ab. (0)

Searches
11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab. (8)
12 (hypotension adj3 induced adj3 hypoperfusion).ti,ab. (0)
13 or/1-12 (54)
14 [exp Administration, Intravenous/] (0)
15 [Fluid therapy/] (0)
16 [plasma substitutes/] (0)
17 [exp crystalloid solutions/] (0)
18 [ringer's solution/] (0)
19 [dextrans/] (0)
20 (intravenous* or iv or i-v).tw. (7593)
21 (fluid* or drip*).tw. (1258)
22 (crystalloid* or Hartmann* or Ringer* or saline* or colloid* or album* or dextran* or plasma* or FFP or hypertonic* or sodium*).tw. (448)
23 or/14-22 (9284)
24 [Resuscitation/] (0)
25 (resuscit* or reanimat* or re-animat* or reviv* or restor*).tw. (8939)
26 or/24-25 (8939)
27 13 and 23 and 26 (0)
28 limit 27 to yr="2016 -Current" (0)

Database name: INAHTA

Searches
(sepsis OR systemic inflammatory response syndrome* OR sirs OR septi* OR crypti* OR pyaemi* OR pyemi* OR pyohemi* OR bacteremi* OR bacteraemi* OR fungemi* OR fungaemi* OR parasitemi* OR parasitaemi* OR viremi* OR viraemi*) AND (intravenous* or iv or i-v or fluid* or drip* or crystalloid* or Hartmann* or Ringer* or saline* or colloid* or album* or dextran* or plasma* or FFP or hypertonic* or sodium*) AND (resuscit* or reanimat* or re-animat* or reviv* or restor*) FROM 2016 TO 2024 0 results

Appendix C – Effectiveness evidence study selection



Appendix D – Effectiveness evidence

Beran, 2022

Bibliographic Reference	Beran, Azizullah; Altorok, Nehaya; Srour, Omar; Malhas, Saif-Eddin; Khokher, Waleed; Mhanna, Mohammed; Ayesh, Hazem; Aladamat, Nameer; Abuhelwa, Ziad; Srour, Khaled; Mahmood, Asif; Altorok, Nezam; Taleb, Mohammad; Assaly, Ragheb; Balanced Crystalloids versus Normal Saline in Adults with Sepsis: A Comprehensive Systematic Review and Meta-Analysis.; Journal of clinical medicine; 2022; vol. 11 (no. 7)

Study Characteristics

Study design	Systematic review
Study details	Dates searched Inception to 22 January 2022. Databases searched PubMed, EMBASE, and Web of Sciences Sources of funding No external funding
Inclusion criteria	Peer-reviewed cohort studies or randomized controlled trials (RCTs), that compared BC to NS, in patients with sepsis, and reported the outcomes of interest.
Exclusion criteria	Conference abstracts. Studies not meeting outlined inclusion criteria. Randomized trials of BC versus NS in critically ill patients were included only if they reported dedicated outcomes in a subgroup of patients with sepsis
Intervention(s)	Balanced crystalloids (BC) Normal saline (NS)
Number of studies included in the systematic review	Primary outcomes: Mortality (at longest follow-up, 28/30 day, 90-day) and acute kidney injury (AKI). Secondary outcomes: The need for renal replacement therapy (RRT) and intensive care unit (ICU) length of stay (LOS) were .
Studies from the systematic review that are not relevant for	The guideline is focused on the early management of sepsis (up to 6 hours) which was thought to be in the emergency department (ED). For this review findings for both ED and intensive care unit (ICU) were considered with a secondary analysis of an included study (Semler et al 2018 [Jackson et al 2021]) which focuses on ED also included and extracted for ED specific data.

use in the current review	

Study arms

Balanced crystalloids (BC) (N = 9752)

Fluids received in emergency department (ED) and Intensive care units (ICU)

Normal saline (NS) (N = 10577)

Fluids received in emergency department (ED) and Intensive care units (ICU)

Critical appraisal - ROBIS checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	High *(The review used the Jadad score and did not justify ROB ratings. Studies which would have been rated as high risk or moderate risk of bias were classified as low risk of bias in this review. Studies where only a proportion of patients were included were sepsis patients were also included, and there were no prespecified inclusion or analysis plans of these mixed population studies. Analysis plans: There were no details on whether studies will be analysed as ACA, per protocol or ITT, or how missing data will be handled. Review pooled RCTs with cohort studies, and did not distinguish these for some subgroups analysed. No evidence the authors made any adjustment for the clustering effect in their data taken from cluster RCTs)*
Overall study ratings	Applicability as a source of data	Partially applicable *(Population: The bigger RCTs studies recruited ICU patients, and sepsis patients were a subgroup (as small as about 10% of total study population)Setting: Included non-OECD countries. ICU-setting and non-OECD high weightage on meta-analysis AG to adjust this based on the results used?)*

Gray, 2024

Bibliographic Reference	Gray, Alasdair J; Oatey, Katherine; Grahamslaw, Julia; Irvine, Sian; Cafferkey, John; Kennel, Titouan; Norrie, John; Walsh, Tim; Lone, Nazir; Horner, Daniel; Appelboam, Andy; Hall, Peter; Skipworth, Richard J E; Bell, Derek; Rooney, Kevin; Shankar-Hari, Manu; Corfield, Alasdair R; Albumin Versus Balanced Crystalloid for the Early Resuscitation of Sepsis: An Open Parallel-Group Randomized Feasibility Trial. The ABC-Sepsis Trial.; Critical care medicine; 2024

Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	N/A
Trial registration number and/or trial name	NCT04540094; EudraCT Number 2020-013520-18
Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	Emergency departments in 15 U.K. National Health Service (NHS) hospitals.
Study dates	Participants recruited from 01 June 2021 to 06 June 2022.
Sources of funding	Grant provided by the Jon Moulton Charitable Trust.
Inclusion criteria	Clinically suspected or proven infection as the primary reason for hospital attendance NEWS 2 greater than or equal to 5 Treating clinician determined that IV fluid resuscitation was required to be commenced within 1 hour of assessment
Intervention(s)	5% Human Albumin Solution (HAS) was started as soon as possible. If participants were receiving HAS or Balanced Crystalloid fluid before randomization and were allocated the alternative fluid, the pre-randomization fluid was stopped. The protocol stated that in the first 6 hours following randomization, no other IV fluid apart from the trial allocation should be administered for resuscitation.
Comparator	Balanced Crystalloid was started as soon as possible. If participants were receiving HAS or Balanced Crystalloid fluid before randomization and were allocated the alternative fluid, the pre-randomization fluid was stopped. The protocol stated that in the first 6 hours following randomization, no other IV fluid apart from the trial allocation should be administered for resuscitation.

Outcome measures	30-day mortality
Number of participants	N=300
Duration of follow-up	30 days and 90 days
Loss to follow-up	N=0 excluded from the analysis;
Methods of analysis	Mixed-effects logistic regression adjusting for site and prespecified prognostic baseline covariates (age, active cancer, and heart failure).
Additional comments	

Study arms

5% Human Albumin Solution (HAS) (N = 150)

Balanced Crystalloid (N = 150)

Characteristics

Arm-level characteristics

Characteristic	5% Human Albumin Solution (HAS) (N = 150)	Balanced Crystalloid (N = 150)
% Female Nominal	53	47
Mean age (SD) Mean (SD)	70 (15)	69 (17)
Chronic kidney disease Nominal	17	21
Cancer Nominal	20	19
Chronic obstructive pulmonary disaorder Nominal	37	37
Myocardial infarction	27	21

Characteristic	5% Human Albumin Solution (HAS) (N = 150)	Balanced Crystalloid (N = 150)
Nominal		
Time from hospital arrival to treatment allocation (Minutes) Median (IQR)	88 (60 to 144)	84 (55 to 129)
Mortality at 30 days (Total number) Nominal	31	22
In-hospital mortality (index admission) (Total number) Nominal	29	23
Acute kidney injury (Total number) Defined using NICE criteria Nominal	36	30
Pulmonary edema (Total number) Nominal	22	30
Length of hospital stay (days) Median (IQR)	6 (3 to 13)	6 (3 to 15)
ICU admission (Total number) Nominal	22	17
Allergy and anaphylaxis (Total number) Nominal	0	1

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(This is an open-label study where clinicians were aware of the study allocation. There is a high risk that the clinicians preferred crystalloids (which was the standard fluid used), with a disproportionate number of patients in HAS deviating from protocol and receiving crystalloids within the first 6 hours. This deviation from protocol probably affected the volume of HAS administered (lower) and 22.6% patients crossed over.)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Of the 1303 potential participants assessed, only 801 did not meet enrollment criteria. Authors noted that the recruitment rate (23%) is similar to many other emergency care trial)*

Jackson, 2021

Bibliographic Reference	Jackson, Karen E; Wang, Li; Casey, Jonathan D; Bernard, Gordon R; Self, Wesley H; Rice, Todd W; Semler, Matthew W; Effect of Early Balanced Crystalloids Before ICU Admission on Sepsis Outcomes.; Chest; 2021; vol. 159 (no. 2); 585-595

Study details

Secondary publication of another included study- see primary study for details	Jackson et al (2021) is a secondary publication of Semler et al 2018 which was not identified in the main sift but subsequently identified and used to inform the risk of bias and data extraction undertaken.
Other publications associated with this study included in review	N/A
Trial registration number and/or trial name	Not outlined - secondary analysis of the SMART trial: Semler et al 2018 (NCT02444988 and NCT02547779)
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	University medical centre; Emergency department and Intensive care units (ICU)
Study dates	June 2015 and April 2017 (ICU data collected from June 2015 to December 2015; ED and ICU data collected from January 2016 to March 2017)
Sources of funding	National Institutes of Health (NIH) [Grant T32HL087738-12] and National Heart, Lung, and Blood Institute (NHLBI) [Grant K12HL133117]; NIH [Grant R34HL105869], National Center for Advancing Translational Sciences (NCATS) [Grant UL1 RR 024975], and NHLBI [Grant U01 HL 123033]; NHLBI [Grant K23HL143053].

Inclusion criteria	Diagnosis of Sepsis Admission to ICU Admission to ED and ICU
Exclusion criteria	No diagnosis of Sepsis
Intervention(s)	ICU population: Balanced crystalloids (treating physician's choice of lactated Ringer's or Plasma-Lyte A). • Mean volume of balanced crystalloid administered in the 24 hour before ICU admission was 492 +/-957 mL • Mean volume of Saline administered in the 24 hour before ICU admission was 560 +/- 976 mL ED and ICU population: Balanced crystalloids (treating physician's choice of lactated Ringer's or Plasma-Lyte A) • Mean volume of balanced crystalloid administered in the 24 h before ICU admission was 1,109 +/- 1,682 mL • Mean volume of saline administered in the 24 h before ICU admission was 145 +/-532 mL
Comparator	ICU population: Saline • Mean volume of saline administered in the 24 h before ICU admission was 613 +/- 1015 mL • Mean volume of balanced crystalloid administered in the 24 hour before ICU admission was 523 +/- 1,063 mL ED and ICU population: Saline • Mean volume of balanced crystalloid administered in the 24 hour before ICU admission 1,135 +/- 1,524 mL • Mean volume of saline administered in the 24 h before ICU admission was 88 +/- 468 mL
Outcome measures	30-day in hospital mortality Adverse events - Kidney events within 30 days ICU-free days
Number of participants	ICU only period:

	Balanced crystalloids: n=142 Saline: n=225 ED and ICU period: Balanced crystalloids: n=682 Saline: n=592
Duration of follow-up	Hospital discharge or 30-days after ICU admission
Loss to follow-up	n=0 - secondary analysis focused on people with Sepsis.
Methods of analysis	30-day in hospital mortality: Logistic regression model Other outcomes Mann- Whitney U test for continuous variables and the Pearson X2 test for categorical variables.

Study arms

Balanced crystalloids - ICU (N = 142)

Physician’s choice of lactated Ringer’s or Plasma-Lyte A. Fluids (Balanced crystalloids or Saline) administered in Emergency Department were not necessarily continued in ICU.

Saline - ICU (N = 225)

Fluids (Balanced crystalloids or Saline) administered in Emergency Department were not necessarily continued in ICU.

Balanced crystalloids - ICU and ED (N = 682)

Physician’s choice of lactated Ringer’s or Plasma-Lyte A. The choice between balanced crystalloids and saline was determined by the study beginning at the time of presentation to the ED and continued throughout the ICU admission

Saline - ICU and ED (N = 592)

The choice between balanced crystalloids and saline was determined by the study beginning at the time of presentation to the ED and continued throughout the ICU admission

Characteristics

Arm-level characteristics

Characteristic	Balanced crystalloids - ICU (N = 142)	Saline - ICU (N = 225)	Balanced crystalloids - ICU and ED (N = 682)	Saline - ICU and ED (N = 592)
% Female Nominal	31.1	49.3	46.3	43.6
Age (Years (IQR)) Median (IQR)	58 (45 to 70)	60 (48 to 68)	60 (49 to 69)	59 (46 to 69)
Ethnicity (White %) Nominal	76.1	75.1	74.6	75.8
Vasopressor (%) Receipt of vasopressors: continuous infusion of norepinephrine, epinephrine, phenylephrine, dopamine, or vasopressin in the 24 h before or after ICU admission. Nominal	42	42	42	40
Acute kidney injury (stage 2 >) (%) Nominal	23	29	26	24
30-day mortality Nominal	47	74	170	181
ICU-free days (days) Number of days on which a patient was alive and not in ICU in the first 28 days after enrolment Nominal	22	22	24	23
ICU-free days (days) Number of days on which a patient was alive and not in ICU in the first 28 days after enrolment Range	0 to 26	0 to 26	0 to 26	0 to 26

Characteristic	Balanced crystalloids - ICU (N = 142)	Saline - ICU (N = 225)	Balanced crystalloids - ICU and ED (N = 682)	Saline - ICU and ED (N = 592)
Balanced cystallloid received 24 hours before ICU admission (ml) Mean (SD)	492 (957)	523 (1063)	1109 (1682)	88 (468)
Saline received 24 hours before ICU admission (ml) Mean (SD)	560 (976)	613 (1015)	145 (532)	1135 (1524)
Ventilator free days (days) Number of days on which a patient was alive and not on a ventilator in the first 28 days after enrolment Nominal	28	24	27	27
Ventilator free days (days) Number of days on which a patient was alive and not on a ventilator in the first 28 days after enrolment Range	0 to 28	0 to 28	0.3 to 28	0 to 28
Vasopressor free days (days) Number of days on which a patient was alive and not requiring vasopressor in the first 28 days after enrolment Nominal	27	27	27	27
Vasopressor free days (days) Number of days on which a patient was alive and not requiring vasopressor in the first 28 days after enrolment Range	0 to 28	0 to 28	11 to 28	0 to 28
RRT-free days (days) Number of days on which a patient was alive and not receiving RRT the first 28 days after enrolment Nominal	28	28	28	28
RRT-free days (days) Number of days on which a patient	0 to 28	0 to 28	5 to 28	0 to 28

Characteristic	Balanced crystalloids - ICU (N = 142)	Saline - ICU (N = 225)	Balanced crystalloids - ICU and ED (N = 682)	Saline - ICU and ED (N = 592)
was alive and not receiving RRT the first 28 days after enrolment Range				
Major adverse kidney event within 30 days (Number of Events) A composite of death, receipt of new RRT, or final creatinine level that was at least 200% of the baseline level, with all events censored at hospital discharge or at 30 d after admission to the ICU, whichever occurred first. Nominal	56	95	236	233
Receipt of new RRT (Number of Events) Among patients with no prior RRT Nominal	7	25	47	50
Stage 2 or greater AKI developing after ICU admission (Number of Events) Among patients with no prior RRT Nominal	38	76	163	155

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Cluster trials

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(ROB from lack of proper randomisation is high - single ICU, alternation by month. This is more of a cohort study data, rather than cluster RCT. The overall negative impact probably lowered as all patients admitted into the ICU would be included. There is a lack of clarity in criteria for the selection of patients for this post-hoc analysis. This was mentioned as a subgroup in study protocol, but there were no analysis plans specified. There was no mention that the analysts are blinded to the allocation of the participants analysed. Note to AG - This is moderate to high,*

Section	Question	Answer
		depending on outcome but probably closer to high by study level, unless there are mitigative factors.)
Overall bias and Directness	Overall Directness	Directly applicable *(The main study included all patients admitted into the ICU. This study included 70% of all patients with sepsis from the main study.)*

Sivapalan, 2023

Bibliographic Reference	Sivapalan P; Ellekjaer KL; Jessen MK; Meyhoff TS; Cronhjort M; Hjortrup PB; Wetterslev J; Granholm A; Møller MH; Perner A; Lower vs Higher Fluid Volumes in Adult Patients With Sepsis: An Updated Systematic Review With Meta-Analysis and Trial Sequential Analysis.; Chest; 2023; vol. 164 (no. 4)

Study Characteristics

Study design	Systematic review
Study details	Dates searched The Cochrane Library (2022, Issue 9), MEDLINE (1946 onward), Embase (1974 onward), Science Citation Index Expanded and Conference Proceedings Citation Index (1990 onward), BIOSIS Previews (1969 onward), and Epistemonikos (no year-based restriction). Last search performed September 6, 2022. Ongoing trials in clinical trial registers (ie, ClinicalTrials.gov, EU Clinical Trials Register, World Health Organization International Clinical Trials Registry Platform search portal). Databases searched The Cochrane Library, MEDLINE, Embase, Science Citation Index Expanded and Conference Proceedings Citation Index, BIOSIS Previews, and Epistemonikos. Ongoing trials in clinical trial registers (ie, ClinicalTrials.gov, EU Clinical Trials Register, World Health Organization International Clinical Trials Registry Platform search portal). Sources of funding Author and institute support for research is outlined. Research Council of Rigshospitalet, Copenhagen, Denmark; and the Ehrenreich Foundation. Fresenius Kabi, Pfizer (CP231465), and Sygeforsikringen ‘danmark’ (2020-0320)
Inclusion criteria	XX

	RCTs comparing different strategies intended to obtain a separation in IV fluid volumes in hospitalized adults with sepsis. No restrictions regarding language, publication source, or status. Adult patients with sepsis (as defined in original trials) independent of hospital setting. RCTs with a pre-planned strategy for separation of IV fluid volumes or balances regardless of whether a separation was obtained. Trials using hemodynamic parameters as triggers for IV fluid administration
Exclusion criteria	XX Quasi-randomized trials; Trials restricted to children; Trials with hemodynamic parameters as targets; Trials comparing different types of fluids and trials of resuscitation of severe blood loss and burns;
Number of studies included in the systematic review	Primary Outcomes: Mortality (13 RCTs reported on this outcome; n=3978); Serious and adverse events: (Six trials defined and reported on this outcome; n=3600); Health-related quality of life (0 trials reported on this outcome) Secondary outcomes: Duration of Mechanical Ventilation (Seven trials reported on this outcome but only six trials provided data that facilitated meta-analysis, n=3,481); Ventilator-free days (Ten trials reported on this outcome, data from eight trials was meta-analysed, n=3,476); Circulatory Support (Seven trials reported duration of vasopressor or inotropes, data from six trials allowed meta-analysis n=3,460), Vasopressor-free days (six trials reported this outcome, data from five trials allowed for meta-analysis, n=3,324); Renal replacement therapy (RRT) (nine trials reporting the use of RRT, n=3,645; three trials reported duration of RRT, n=1,753, Five trials reported RRT-free days, n=3,285); Acute kidney injury (AKI) (Three trials reported the incidence of AKI as part of SAEs, n1,754)
Additional comments	

Study arms

Lower fluid volumes (N = 2005)

Data collected from 13 RCTs. Six single-centre trials and seven trials multi-centre trials. Six trials reduced fluid volumes by assessing fluid responsiveness in combination with passive leg raise manoeuvres (n=4) echocardiography (n=1) and using fluid bolus tests (n=1). Fixed hemodynamic triggers were used in six trials of which four allowed additional hemodynamic assessment. In two trials, fluid volumes were reduced by using early intervention including vasopressors. Seven trials recommended crystalloids only as the fluid.

Higher fluid volumes (N = 1973)

Higher fluid volume was the control in the identified trials and were outlined as representing 'standard care' in eight trials; with seven trials recommended crystalloids only.

Critical appraisal - ROBIS checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	Low *(PRISMA checklist was available. The study protocol was pre-registered. There were very minor and justified deviations from the protocol.The data collection form was clear and appropriate, with a clear specification to prioritise collecting outcomes on an ITT basis, and on modified ITT defined by studies if not available.Although key criteria for ROB decisions were not pre-specified, this is unlikely to play a major role in affecting key findings of the review. The ROB of each outcome were available in the appendix and looked appropriate. Analysis plan was clear and appropriate.)*
Overall study ratings	Applicability as a source of data	Fully applicable

Annane, 2013

Bibliographic Reference	Annane, Djillali; Siami, Shidasp; Jaber, Samir; Martin, Claude; Elatrous, Souheil; Declère, Adrien Descorps; Preiser, Jean Charles; Outin, Hervé; Troché, Gilles; Charpentier, Claire; Trouillet, Jean Louis; Kimmoun, Antoine; Forceville, Xavier; Darmon, Michael; Lesur, Olivier; Reignier, Jean; Abroug, Fékri; Berger, Philippe; Clec'h, Christophe; Cousson, Joël; Thibault, Laure; Chevret, Sylvie; for the CRISTAL, Investigators; Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock: The CRISTAL Randomized Trial; JAMA; 2013; vol. 310 (no. 17); 1809-1817

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Sepsis patients are not a stratified group for randomisation and form only slightly over 54% of all participants. There is insufficient information to judge whether an open-label design*

Section	Question	Answer
		which allowed clinicians a choice of fluids from a class could pose a risk of bias.)
Overall bias and Directness	Overall Directness	Partially applicable *(patients were recruited from icu)*

Finfer, 2022

Bibliographic Reference	Finfer, Simon; Micallef, Sharon; Hammond, Naomi; Navarra, Leanlove; Bellomo, Rinaldo; Billot, Laurent; Delaney, Anthony; Gallagher, Martin; Gattas, David; Li, Qiang; Mackle, Diane; Mysore, Jayanthi; Saxena, Manoj; Taylor, Colman; Young, Paul; Myburgh, John; Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults; New England Journal of Medicine; 2022; vol. 386 (no. 9); 815-826

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(The risk for the overall study is low, but there is no stratification of sepsis at recruitment. therefore, using the subgroup data would break the randomisation process.)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(NOTE: Study recruited ICU patients requiring fluid resuscitation, in New Zealand and Australia. 2071 (42.3%) had sepsis. There was no stratification by diagnosis at recruitment.)*

Golla, 2022

Bibliographic Reference	Golla, R.; Kumar, S.; Dhibhar, D.P.; Bhalla, A.; Sharma, N.; 0.9% saline V/S Ringer's lactate for fluid resuscitation in adult sepsis patients in emergency medical services: An open-label randomized controlled trial; Hong Kong Journal of Emergency Medicine; 2022; vol. 29 (no. 5); 271-280

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Participants were "medical patients brought to emergency services of a large tertiary care center with an admission diagnosis of sepsis..." The setting is a non-OECD country (India))*

Pagano 2020

Bibliographic Reference	Pagano A, Porta G, Bosso G, Rosato V, Allegorico E, Serra C EA; Ringer lactate versus saline solution for resuscitation of sepsis and septic shock; 2020

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *The criteria for other concurrent management strategies was vague. The study was open-label, and other concurrent management strategies (especially vasopressors) were not balanced between groups. It is unclear if these differences are due to differences in response to the fluid or a different approach to managing by clinicians. It is unclear how this affects outcomes, especially outcomes related to other management (use of mechanical ventilation).)*
Overall bias and Directness	Overall Directness	Directly applicable *(The study recruited patients who had been admitted to the emergency department for sepsis or septic shock to receive either ringer lactate or normal saline)*

Semler, 2018

Bibliographic Reference	Semler MW; Self WH; Rice TW; Balanced Crystalloids versus Saline in Critically Ill Adults.; The New England journal of medicine; 2018; vol. 378 (no. 20)

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Cluster trials

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(There is a lack proper randomisation and concealment; ROB is high. In addition, there was sepsis patients not considered as a subgroup in the randomisation process. The data is more of a cohort study data than randomised study data.)*
Overall bias and Directness	Overall Directness	Partially applicable *(Patients were in the ICUs of a tertiary US centre. Applicability of findings to UK emergency department uncertain.)*

Semler, 2017

Bibliographic Reference	Semler MW; Wanderer JP; Ehrenfeld JM; Stollings JL; Self WH; Siew ED; Wang L; Byrne DW; Shaw AD; Bernard GR; Rice TW; ; ; Balanced Crystalloids versus Saline in the Intensive Care Unit. The SALT Randomized Trial.; American journal of respiratory and critical care medicine; 2017; vol. 195 (no. 10)

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Cluster trials

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(There is a lack of proper randomisation and concealment; ROB is high. In addition, the sepsis patients were not considered a subgroup in the randomisation process, only forming about 25% of the total population and slightly higher in one of the intervention arms. The data is more of a cohort study data than randomised study data)*
Overall bias and Directness	Overall Directness	Partially applicable *(Patients were in the ICUs of a tertiary US centre. The applicability of findings to UK emergency department is uncertain.)*

Young, 2015

Bibliographic Reference	Young P; Bailey M; Beasley R; Henderson S; Mackle D; McArthur C; McGuinness S; Mehrtens J; Myburgh J; Psirides A; Reddy S; Bellomo R; ; ; Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit: The SPLIT Randomized Clinical Trial.; JAMA; 2015; vol. 314 (no. 16)

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Cluster trials

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(The sepsis population forms only 4% of the study. There was an imbalance of missing participants between the intervention arms for morality that is sufficient to change conclusions.)*
Overall bias and Directness	Overall Directness	Partially applicable *(OECD country but ICU patients.)*

Zampieri, 2021

Bibliographic Reference	Zampieri FG; Machado FR; Biondi RS; Freitas FGR; Veiga VC; Figueiredo RC; Lovato WJ; Amêndola CP; Serpa-Neto A; Paranhos JLR; Guedes MAV; Lúcio EA; Oliveira-Júnior LC; Lisboa TC; Lacerda FH; Maia IS; Grion CMC; Assunção MSC; Manoel ALO; Silva-Junior JM; Duarte P; Soares RM; Miranda TA; de Lima LM; Gurgel RM; Paisani DM; Corrêa TD; Azevedo LCP; Kellum JA; Damiani LP; Brandão da Silva N; Cavalcanti AB; ; Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients: The BaSICS Randomized Clinical Trial.; JAMA; 2021; vol. 326 (no. 9)

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Although appropriate randomisation was carried out, the sepsis population formed less than 19% of the total participant group, and the randomisation effect is at risk of being broken. There is not baseline data or missing data information just for this subgroup.)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(ICU patients, non-OECD country.)*

Appendix E – Forest plots

Please see Beran 2022 for forest plots of RCT meta-analysis

Please see Sivapalan 2023 supplementary material for subgroup ‘early’ and ‘emergency department’ meta-analysis.

Appendix F – GRADE tables

Table 11: Balanced Crystalloid vs Normal Saline (evidence from Beran 2022 systematic review)

No of studies	Study design	Intervention group (BC) (events/total)	Comparator (NS) (events/total)	Effect size (Risk ratio / mean difference) (95% CI)	Absolute effect	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
Overall mortality										
8[1]	RCT	450 / 970	498 / 1017	RR 0.92 (0.82, 1.02)	39 fewer per 1000 (88 fewer to 10 more)	Very serious[6]	Serious[7]	Very serious[8]	Not serious	Very low
28 / 30 day-mortality										
4[4]	RCT	362 / 1414	569 / 1936	RR 0.87 (0.77, 0.97)	38 fewer per 1000 (68 fewer to 9 fewer)	Very serious[6]	Not serious	Very serious[8]	Serious[10]	Very low
Acute kidney injury										
2[2]	RCT	28 / 115	41 / 122	RR 0.71 (0.47, 1.06)	97 fewer per 1000 (178 fewer to 20 more)	Very serious[6]	Not serious	Serious[9]	Serious[10]	Very low

Need for RRT										
2[3]	RCT	12 / 115	18 / 129	RR 0.71 (0.36, 1.41)	41 fewer per 1000 (90 fewer to 57 more)	Very serious[6]	Not serious	Not serious	Very serious[11]	Very low

1. Annane 2013, Finfer 2022, Golla 2020, Pagano 2020, Semler 2017, Semler 2018, Young 2015, Zampieri 2021
2. Golla 2020, Young 2015
3. Golla 2020, Pagano 2020
4. Annane 2013, Golla 2020, Semler 2017, Semler 2018
5. Annane 2013, Finfer 2022, Young 2015, Zampieri 2021
6. 50% of studies assessed at high risk of bias
7. Rated down because $I^2 \geq 41\%$
8. Rated down due to majority of studies in analysis conducted in ICU settings
9. Rated down due to 50% of studies in ICU
10. Rated down due to confidence interval crossing one end of MID (0.8-1.25)
11. Rated down due to confidence interval crossing both ends of MID (0.8-1.25)
12. 50% of studies at moderate or high risk of bias

Table 12: Subgroup analysis of Semler 2018 trial (Jackson 2021 paper) – fluids started in emergency department

No of studies	Study design	Intervention group (BC) (events/total)	Comparator (NS) (events/total)	Effect size (odds ratio) (95% CI)	Absolute effect	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
30 day in-hospital mortality										

1[2]	Cluster RCT	170 / 682	181 / 592	OR 0.68 (0.52, 0.89)[1]	Not estimable[3]	Very serious[4]	Serious[5]	Not serious	Serious[6]	Very low
Major adverse kidney event within 30 days										
1[2]	Cluster RCT	236 / 682	233 / 592	OR 0.76 (0.59, 0.97)[1]	Not estimable[3]	Very serious[4]	Serious[5]	Not serious	Not serious	Very low
Receipt of new RRT										
1[2]	Cluster RCT	47 / 614	50 / 524	OR 0.79 (0.52, 1.19)[1]	Not estimable[3]	Very serious[4]	Serious[5]	Not serious	Serious[6]	Very low
Stage 2 or greater AKI developing after ICU admission										
1[2]	Cluster RCT	163 / 614	155 / 524	OR 0.86 (0.66, 1.12)[1]	Not estimable[3]	Very serious[4]	Serious[5]	Not serious	Serious[6]	Very low

1. OR's in this post-hoc analysis adjusted for covariates age, sex, race, source of admission, receipt of mechanical ventilation, and receipt of vasopressors
2. Jackson 2021
3. Adjusted effect as presented in OR not estimable
4. Risk of bias assessed as high
5. Single study analysis rated down once as per NICE methods
6. Confidence interval crosses one end of the MID (0.8 -1.25)

Table 13: 5% human albumin solution vs balanced crystalloid

No of studies	Study design	Intervention group (HAS) (events/total)	Comparator (BC) (events/total)	Effect size (risk ratio, odds ratio. Mean difference) (95% CI)	Absolute effect	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
30-day mortality										
1[1]	RCT	31 / 147	32 / 149	RR 1.43 (0.87, 2.35)[2]	92 more per 1000 (28 fewer to 290 more)	Very serious[3]	Serious[4]	Serious[5]	Serious[6]	Very low
In-hospital mortality										
1[1]	RCT	29 / 147	23 / 149	RR 1.28 (0.78, 2.10)	43 more per 1000 (34 fewer to 169 more)	Very serious[3]	Serious[4]	Serious[5]	Very serious[7]	Very low
RRT										

1[1]	RCT	1/147	2/149	RR 0.51 (0.05, 5.53)	6 fewer per 1000 (12 fewer to 59 more)	Very serious[3]	Serious[4]	Serious[5]	Very serious[7]	Very low
AKI										
1[1]	RCT	36/147	30/149	RR 1.29 (0.74, 2.23)	58 more per 1000 (52 fewer to 247 more)	Very serious[3]	Serious[4]	Serious[5]	Very serious[7]	Very low

1. Gray 2024
2. Authors present as an adjusted odds ratio of 1.54 (0.84–2.83)
3. Risk of bias assessed as high
4. Rated down for single study data as per agreed NICE methods
5. Assessed as partially applicable as 801/1303 participants did not meet study enrolment criteria
6. Confidence interval crosses one side of the default MID (0.8-1.25)
7. Confidence interval crosses both sides of the default MID (0.8-1.25)

Table 14: Lower vs Higher fluid volumes - evidence from Sivapalan SR subgroup 'early phase' of sepsis fluid resuscitation

No of studies	Study design	Lower fluid volume (events/total)	Higher fluid volume (events/total)	Effect size (risk ratio, odds ratio. mean difference) (97 or 99% CI)	Absolute effect	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty

All -cause mortality										
7[1]	RCT	235 / 1064	221 / 1012	RR 1.02 (97% CI 0.85, 1.22)	4 more per 1000 (33 fewer to 48 more)	Not serious	Not serious	Serious[17]	Not serious	Moderate
Serious adverse events[2]										
4[3]	RCT	52 / 991	48 / 937	RR 0.95 (97% CI 0.64, 1.42)	3 fewer per 1000 (18 fewer to 21 more)	Serious[11]	Not serious	Serious[12]	Very serious[13]	Very low
Duration of mechanical ventilation[5]										
4[4]	RCT	n=921	n=878	MD -1.14 (99% CI -3.25, 0.97)	N/A	Serious[11]	Very serious[15]	Seroius[17]	Serious[14]	Very low
Duration of vasopressor or inotropes[6]										
4[4]	RCT	n=958	n=918	MD 2.22 (99% CI -6.48, 10.92)	N/A	Serious[11]	Serious[16]	Seroius[17]	Not serious	Very low
Use of renal replacement therapy										

5[7]	RCT	33 / 976	37 / 942	RR 0.72 (99% CI 0.30, 1.73)	11 fewer per 1000 (27 fewer to 28 more)	Not serious	Not serious	Serious[17]	Very serious[13]	Very low
Incidence of AKI										
2[8]	RCT	10 / 116	11 / 116	RR 0.92 (99% CI 0.32, 2.61)	8 fewer per 1000 (65 fewer to 153 more)	Serious[11]	Not serious	Not serious	Very serious[13]	Very low
ICU length of stay										
4[9]	RCT	N= 202	N = 158	MD -1.29 (97% CI -3.20, 0.62)	N/A	Not serious	Not serious	Serious[17]	Not serious	Moderate
Hospital length of stay										
4[10]	RCT	n=268	n=214	MD 0.60 (97% CI -0.80, 1.99)	N/A	Serious[11]	Not serious	Serious[17]	Not serious	Moderate

1. Jessen 2022, Douglas 2020, Corl 2019, Shapiro 2023, Van Genderen 2015, MacDonald 2018, Lanspa 2018
2. 'As defined in the original trials or any untoward medical occurrence that fulfils the International Council on Harmonization Guideline for Good Clinical Practice's definition'
3. Douglas 2020, Jessen 2022, Macdonald 2018, Shapiro 2023
4. Corl 2019, Douglas 2020, Shapiro 2023, MacDonald 2018
5. Unit of measurement = days

6. Unit of measurement = hours
7. Douglas 2020, Jessen 2022, Macdonald 2018, Shapiro 2023, Corl 2019
8. Jessen 2022, Corl 2019
9. Lanspa 2018, Douglas 2020, Corl 2019, Macdonald 2018
10. Douglas 2020, Corl 2019, Macdonald 2018, Jessen 2022
11. ≥ 50% of studies rated as 'some concern' for risk of bias for this outcome
12. Review authors rate this as indirect due to SAE 'not defined or reported in all trials and the definitions varied across the trials'
13. Confidence intervals cross both sides of the default MIDs 0.8-1.25
14. Confidence interval crosses one end of the calculated MID 2.33 (0.5 x median SD in control arm)
15. I^2 >60%
16. I^2 > 40%
17. >50% of primary studies partially applicable as they contain interventions other than fluids

Table 15: Lower vs Higher fluid volumes - subgroup analysis of sepsis only (not septic shock) ED population

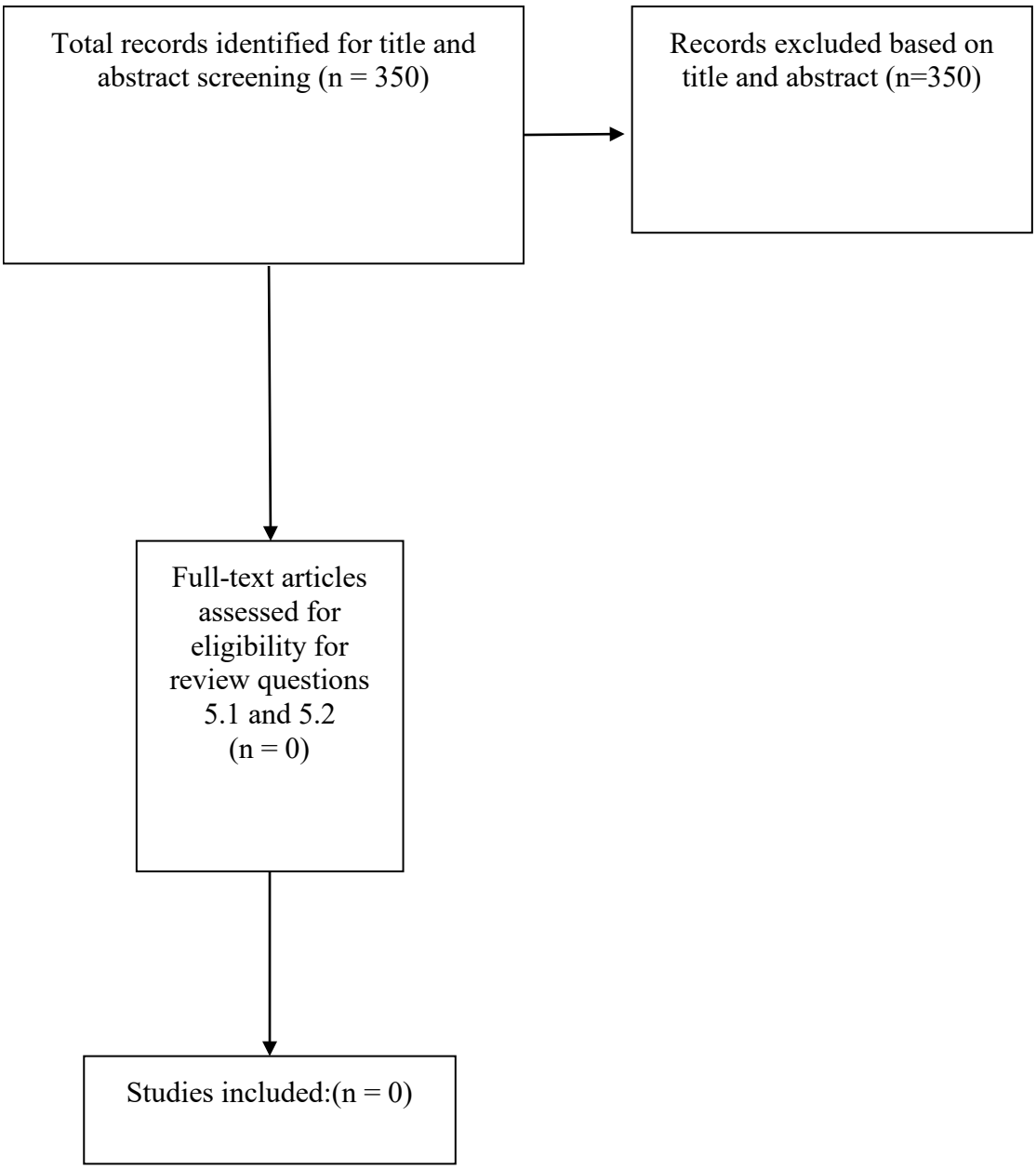
No of studies	Study design	Lower fluid volume (events/total)	Higher fluid volume (events/total)	Effect size (risk ratio, odds ratio. mean difference) (97 or 99% CI)	Absolute effect	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
All -cause mortality										
3[1]	RCT	188 / 877	187 / 880	RR 1.01 (97% CI 0.83, 1.23)	2 more per 1000 (36 fewer to 49 more)	Not serious	Not serious	Serious[10]	Not serious	Moderate

Serious adverse events[2]										
3[1]	RCT	42 / 893	19 / 892	RR 1.02 (97% CI 0.66, 1.58)	0 more per 1000 (7 fewer to 12 more)	Serious[6]	Not serious	Serious[8]	Serious[9]	Very low
Duration of mechanical ventilation[5]										
2[2]	RCT	n=823	n=820	MD -0.08 (99% CI -0.52, 0.35)	N/A	Not serious	Not serious	Serious[10]	Not serious	Moderate
Duration of vasopressor or inotropes[6]										
2[2]	RCT	n=828	n=827	MD 0.00 (99% CI -0.33, 0.34)	N/A	Not serious	Not serious	Serious[10]	Not serious	Moderate
Use of renal replacement therapy										
3[1]	RCT	28 / 849	28 / 849	RR 1.00 (99% CI 0.51, 1.96)	0 more per 1000 (16 fewer to 32 more)	Not serious	Not serious	Serious[10]	Not serious	Moderate
Incidence of AKI										

1[3]	RCT	9 / 61	10 / 62	RR 0.91 (99% CI 0.31. 2.72)	14 fewer per 1000 (111 fewer to 277 more)	Not serious	Serious[7]	Serious[10]	Serious[7]	Very low
ICU length of stay										
1[4]	RCT	n= 50	n=49	MD 0.10 (97% CI -0.90, 1.10)	N/A	Not serious	Serious[7]	Serious[10]	Serious[7]	Very low
Hospital length of stay										
2[5]	RCT	n = 111	n= 112	MD 1.18 (97% CI -0.72, 3.08)	N/A	Not serious	Not serious	Serious[10]	Not serious	Moderate

1. Jessen 2022, Shapiro 2023, MacDonald 2018
2. Shapiro 2023, MacDonald 2018
3. Jessen 2022
4. MacDonald 2018
5. MacDonald 2018, Jessen 2022
6. ≥ 50% of studies rated as 'some concern' for risk of bias for this outcome
7. Rated down for single study data as per agreed NICE methods
8. Review authors rate this as indirect due to SAE 'not defined or reported in all trials and the definitions varied across the trials'
9. Confidence intervals cross both sides of the default MIDs 0.8-1.25
10. >50% of primary studies partially applicable as they contain interventions other than fluids

Appendix G – Economic evidence study selection



Appendix H – Excluded studies

Study	Reason for exclusion
Abedi, Farshad; Zarei, Batool; Elyasi, Sepideh (2024) Albumin: a comprehensive	- Not a relevant study design

Study	Reason for exclusion
review and practical guideline for clinical use. European journal of clinical pharmacology 80(8): 1151-1169	
Akbar, R., George, Y., Madjid, A.S. et al. (2021) Early administration of norepinephrine prevents the occurrence of fluid overload in the resuscitation of septic shock patients. Critical Care and Shock september2021: 257-268	- Study does not contain a relevant intervention
Allen, John M, Feild, Carinda, Shoulders, Bethany R et al. (2019) Recent Updates in the Pharmacological Management of Sepsis and Septic Shock: A Systematic Review Focused on Fluid Resuscitation, Vasopressors, and Corticosteroids. The Annals of pharmacotherapy 53(4): 385-395	- Not a relevant study design *Narrative review*
Asfar, Pierre, Schortgen, Frederique, Boisrame-Helms, Julie et al. (2017) Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S): a two-by-two factorial, multicentre, randomised, clinical trial. The Lancet. Respiratory medicine 5(3): 180-190	- Study does not contain a relevant intervention
Barlow, Brooke and Bissell, Brittany D (2021) Evaluation of Evidence, Pharmacology, and Interplay of Fluid Resuscitation and Vasoactive Therapy in Sepsis and Septic Shock. Shock (Augusta, Ga.) 56(4): 484-492	- Not a relevant study design
Bartoli, Arianna, D'Angelo, Andrea, Ippolito, Domenico et al. (2023) The Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) randomized clinical trial. Internal and emergency medicine 18(8): 2419-2421	- Not a relevant study design *Summary abstract of included trial*
Bjerregaard, Mads Rye; Hjortrup, Peter Buhl; Perner, Anders (2019) Indications for fluid resuscitation in patients with septic shock: Post-hoc analyses of the CLASSIC trial. Acta anaesthesiologica Scandinavica 63(3): 337-343	- Wrong population *Post-hoc analysis of trial of 'later' fluid resuscitation >6hours*
Brown, R.M., Wang, L., Coston, T.D. et al. (2019) Balanced Crystalloids versus Saline in Sepsis: A secondary analysis of the SMART clinical trial. American Journal of Respiratory and Critical Care Medicine 200(12): 1487-1495	- Study already in an included systematic review

Study	Reason for exclusion
Castro, Ricardo, Kattan, Eduardo, Ferri, Giorgio et al. (2020) Effects of capillary refill time-vs. lactate-targeted fluid resuscitation on regional, microcirculatory and hypoxia-related perfusion parameters in septic shock: a randomized controlled trial. Annals of intensive care 10(1): 150	- Study does not contain a relevant intervention
Chen, Yi and Gao, Yongli (2023) Comparison of Balanced Crystalloids versus Normal Saline in Critically Ill Patients: A Systematic Review with Meta-Analysis and Trial Sequential Analysis of Randomized Controlled Trials. Therapeutics and clinical risk management 19: 783-799	- Wrong population *Although subgroup sepsis population no detail provided on primary studies in meta-analysis*
Chua, J.R.; Benedicto, J.P.; Chiu, H.H.C. (2019) Balanced crystalloids versus normal saline as intravenous fluid therapy among critically ill patients: A meta-analysis of randomized controlled trials. Phillippine Journal of Internal Medicine 57(2): 115-119	- Wrong population *Not sepsis specific*
Corl, Keith A, Prodromou, Michael, Merchant, Roland C et al. (2019) The Restrictive IV Fluid Trial in Severe Sepsis and Septic Shock (RIFTS): A Randomized Pilot Study. Critical care medicine 47(7): 951-959	- Study already in an included systematic review
Douglas, Ivor S, Alapat, Philip M, Corl, Keith A et al. (2020) Fluid Response Evaluation in Sepsis Hypotension and Shock: A Randomized Clinical Trial. Chest 158(4): 1431-1445	- Study already in an included systematic review
Drew, D.; Hendin, A.; Eagles, D. (2023) Which crystalloid should we be using for the resuscitation of septic patients?. Canadian Journal of Emergency Medicine 25(1): 20-21	- Not a relevant study design *Abstract from included SR*
Ehrman, Robert R, Gallien, John Z, Smith, Reid K et al. (2019) Resuscitation Guided by Volume Responsiveness Does Not Reduce Mortality in Sepsis: A Meta-Analysis. Critical care explorations 1(5): e0015	- More recent systematic review included that covers the same topic *Intervention also focused on volume responsiveness*
Elsayed, A.A.; Elhamid Ahmed, R.A.; Beshey, B.N. (2022) Early goal directed therapy versus a protocolized resuscitation care in early management of septic shock. Egyptian Journal of Anaesthesia 38(1): 58-63	- Study does not contain a relevant intervention

Study	Reason for exclusion
Geng, Li, Tian, Xiaoxue, Gao, Zifeng et al. (2023) Different Concentrations of Albumin Versus Crystalloid in Patients with Sepsis and Septic Shock: A Meta-Analysis of Randomized Clinical Trials. Journal of intensive care medicine 38(8): 679-689	- Wrong population *Some studies in analysis dating back to 1980s -sepsis definition and systems irrelevant*
Golla, R., Kumar, S., Dhibhar, D.P. et al. (2022) 0.9% saline V/S Ringer's lactate for fluid resuscitation in adult sepsis patients in emergency medical services: An open-label randomized controlled trial. Hong Kong Journal of Emergency Medicine 29(5): 271-280	- Study already in an included systematic review
Golla, R, Kumar, S, Dhibhar, DP et al. (2022) 0.9% saline V/S Ringer's lactate for fluid resuscitation in adult sepsis patients in emergency medical services: an open-label randomized controlled trial. Hong kong journal of emergency medicine 29(5): 271-280	- Study already in an included systematic review
Gottlieb, M. (2017) Early goal-directed therapy versus usual care in the management of septic shock. Canadian Journal of Emergency Medicine 19(1): 65-67	- Study does not contain a relevant intervention
Hammond, Drayton A, Lam, Simon W, Rech, Megan A et al. (2020) Balanced Crystalloids Versus Saline in Critically Ill Adults: A Systematic Review and Meta-analysis. The Annals of pharmacotherapy 54(1): 5-13	- More recent systematic review included that covers the same topic *Unable to tell which 5 studies makes up sepsis subgroup analysis*
Hernandez, Glenn, Cavalcanti, Alexandre Biasi, Ospina-Tascon, Gustavo et al. (2018) Early goal-directed therapy using a physiological holistic view: the ANDROMEDA-SHOCK-a randomized controlled trial. Annals of intensive care 8(1): 52	- Study does not contain a relevant intervention
Hernandez, Glenn, Ospina-Tascon, Gustavo A, Damiani, Lucas Petri et al. (2019) Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. JAMA 321(7): 654-664	- Study does not contain a relevant intervention *Intervention peripheral perfusion vs lactate guided*
Hjortrup, P B, Haase, N, Wetterslev, J et al. (2017) Effects of fluid restriction on	- Wrong population

Study	Reason for exclusion
measures of circulatory efficacy in adults with septic shock. Acta anaesthesiologica Scandinavica 61(4): 390-398	*Study forms part of included SR but analysis not included in authors definition of 'early' fluid resuscitation or ED subgroup analysis*
Hjortrup, Peter B, Haase, Nicolai, Bundgaard, Helle et al. (2016) Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Intensive care medicine 42(11): 1695-1705	- Duplicate reference
Hou, Peter C, Filbin, Michael R, Napoli, Anthony et al. (2016) Cardiac Output Monitoring Managing Intravenous Therapy (COMMIT) to Treat Emergency Department Patients with Sepsis. Shock (Augusta, Ga.) 46(2): 132-8	- Study does not contain a relevant intervention
Jiang, Shuaiyu, Wu, Mengmeng, Lu, Xiaoguang et al. (2021) Is restrictive fluid resuscitation beneficial not only for hemorrhagic shock but also for septic shock?: A meta-analysis. Medicine 100(12): e25143	- More recent systematic review included that covers the same topic *And majority of studies included non-OECD*
Jorda, Anselm, Douglas, Ivor S, Staudinger, Thomas et al. (2024) Fluid management for sepsis-induced hypotension in patients with advanced chronic kidney disease: a secondary analysis of the CLOVERS trial. Critical care (London, England) 28(1): 231	- Secondary publication of an included study that does not provide any additional relevant information
Kabil, Gladis, Frost, Steven A, Hatcher, Deborah et al. (2022) Early fluid bolus in adults with sepsis in the emergency department: a systematic review, meta-analysis and narrative synthesis. BMC emergency medicine 22(1): 3	- Study does not contain a relevant intervention
Kellum, John A, Chawla, Lakhmir S, Keener, Christopher et al. (2016) The Effects of Alternative Resuscitation Strategies on Acute Kidney Injury in Patients with Septic Shock. American journal of respiratory and critical care medicine 193(3): 281-7	- Study does not contain a relevant intervention *and data from a pre-2016 study*
Khattar, Georges, El Gharib, Khalil, Pokima, Ngowari et al. (2024) Fluid Resuscitation Dilemma in End-stage Renal Disease Patients Presenting with Sepsis: A Systematic Review and Meta-analysis.	- Not a relevant study design *Cohort studies in analysis*

Study	Reason for exclusion
Journal of intensive care medicine: 8850666241261673	
Khatua, B., Yaron, J.R., El-Kurdi, B. et al. (2020) Ringer's lactate prevents early organ failure by providing extracellular calcium. Journal of Clinical Medicine 9(1): 263	- Wrong population
Kumar, Susheel, Golla, Rithvik, Bhalla, Ashish et al. (2020) 0.9% Saline v/s Ringer's Lactate for fl uid resuscitation in adult sepsis patients in emergency medical services: An open label Randomized Controlled trial. The Journal of the Association of Physicians of India 68(1): 87	- Non-OECD country
Lanspa, Michael J, Burk, Rebecca E, Wilson, Emily L et al. (2018) Echocardiogram-guided resuscitation versus early goal-directed therapy in the treatment of septic shock: a randomized, controlled, feasibility trial. Journal of intensive care 6: 50	- Study already in an included systematic review *Although and indirect match, SR authors have reviewed fluid volumes given in each arm and included for lower vs higher volumes*
Lewis, Sharon R, Pritchard, Michael W, Evans, David Jw et al. (2018) Colloids versus crystalloids for fluid resuscitation in critically ill people. The Cochrane database of systematic reviews 8: cd000567	- Wrong population *Critically ill - and sepsis specific studies all pre-2016*
Li, Binghu, Zhao, Hongliang, Zhang, Jie et al. (2020) Resuscitation Fluids in Septic Shock: A Network Meta-Analysis of Randomized Controlled Trials. Shock (Augusta, Ga.) 53(6): 679-685	- More recent systematic review included that covers the same topic *Only post-2016 relevant study already in included SR*
Linden, Anja, Spangfors, M, Olsen, M H et al. (2024) Protocolized reduction of non-resuscitation fluids versus usual care in septic shock patients (REDUSE): a randomized multicentre feasibility trial. Critical care (London, England) 28(1): 166	- Study does not contain a relevant intervention
Liu, B.; Ding, X.; Yang, J. (2016) Effect of early goal directed therapy in the treatment of severe sepsis and/or septic shock. Current Medical Research and Opinion 32(11): 1773-1782	- Study does not contain a relevant intervention
Lu, Yao, Zhang, Han, Teng, Fang et al. (2018) Early Goal-Directed Therapy in Severe Sepsis and Septic Shock: A Meta-Analysis and Trial Sequential Analysis of Randomized Controlled Trials. Journal of intensive care medicine 33(5): 296-309	- Study does not contain a relevant intervention

Study	Reason for exclusion
Macdonald, Stephen P J, Keijzers, Gerben, Taylor, David McD et al. (2018) Restricted fluid resuscitation in suspected sepsis associated hypotension (REFRESH): a pilot randomised controlled trial. Intensive care medicine 44(12): 2070-2078	- Study already in an included systematic review
Macdonald, Stephen, Bosio, Erika, Keijzers, Gerben et al. (2023) Effect of intravenous fluid volume on biomarkers of endothelial glycocalyx shedding and inflammation during initial resuscitation of sepsis. Intensive care medicine experimental 11(1): 21	- Secondary publication of an included study that does not provide any additional relevant information
Maiwall, Rakhi, Kumar, Abhinav, Pasupuleti, Samba Siva Rao et al. (2022) A randomized-controlled trial comparing 20% albumin to plasmalyte in patients with cirrhosis and sepsis-induced hypotension [ALPS trial]. Journal of hepatology 77(3): 670-682	- Non-OECD country
Martensson, J and Bellomo, R (2017) Does fluid management affect the occurrence of acute kidney injury?. Current opinion in anaesthesiology 30(1): 84-91	- Not a relevant study design
Martin, Greg S and Bassett, Paul (2019) Crystalloids vs. colloids for fluid resuscitation in the Intensive Care Unit: A systematic review and meta-analysis. Journal of critical care 50: 144-154	- Wrong population *critically ill - not sepsis specific*
Meyer, J and Shankar-Hari, M (2017) Protocolised early goal-directed therapy in patients with sepsis/septic shock does not result in improved survival compared with usual care with less invasive resuscitation strategies. Evidence-based medicine 22(6): 223	- Study does not contain a relevant intervention
Min, Y, He, Y, Tuo, L et al. (2023) Application of a combination of lactated Ringer's solution and ulinastatin for early resuscitation in sepsis. Tropical journal of pharmaceutical research 22(12): 2525-2530	- Non-OECD country
Ounhasuttiyanon, A., Vareesangthip, K., Chanchairujira, T. et al. (2024) Balanced Crystalloid Solution or Normal Saline in Fluid Resuscitation in Critically Ill Patients: A Meta-Analysis and Trial Sequential Analysis of Randomized Controlled Trials.	- Wrong population *Critically ill not sepsis specific*

Study	Reason for exclusion
Journal of the Medical Association of Thailand 107(3): 177-184	
Pannu, Ashok Kumar (2023) Circulatory shock in adults in emergency department. Turkish journal of emergency medicine 23(3): 139-148	- Not a relevant study design *Narrative review of care processes*
Park, Clarice Hyesuk Lee, de Almeida, Juliano Pinheiro, de Oliveira, Gisele Queiroz et al. (2019) Lactated Ringer's Versus 4% Albumin on Lactated Ringer's in Early Sepsis Therapy in Cancer Patients: A Pilot Single-Center Randomized Trial. Critical care medicine 47(10): e798-e805	- Non-OECD country
Pence, Madeline, Tran, Quincy K, Shesser, Robert et al. (2022) Outcomes of CMS-mandated fluid administration among fluid-overloaded patients with sepsis: A systematic review and meta-analysis. The American journal of emergency medicine 55: 157-166	- Not a relevant study design *SR of observational studies*
Philips, Cyriac Abby, Maiwall, Rakhi, Sharma, Manoj Kumar et al. (2021) Comparison of 5% human albumin and normal saline for fluid resuscitation in sepsis induced hypotension among patients with cirrhosis (FRISC study): a randomized controlled trial. Hepatology international 15(4): 983-994	- Outcome does not match that specified in protocol
Qayyum, Shahid and Shahid, Kamran (2023) Fluid Resuscitation in Septic Patients. Cureus 15(8): e44317	- Not a relevant study design *Narrative review*
Ramasco, F, Aguilar, G, Aldecoa, C et al. (2024) Towards the personalization of septic shock resuscitation: the fundamentals of ANDROMEDA-SHOCK-2 trial. Revista espanola de anestesiologia y reanimacion 71(2): 112-124	- Not a relevant study design
Reynolds, Paul M; Stefanos, Sylvia; MacLaren, Robert (2023) Restrictive resuscitation in patients with sepsis and mortality: A systematic review and meta-analysis with trial sequential analysis. Pharmacotherapy 43(2): 104-114	- More recent systematic review included that covers the same topic *Included SR contains more primary papers*
Reynolds, Paul M, Wells, Lauren, MacLaren, Robert et al. (2020) Establishing the Therapeutic Index of Fluid Resuscitation in the Septic Patient: A Narrative Review	- More recent systematic review included that covers the same topic

Study	Reason for exclusion
and Meta-Analysis. Pharmacotherapy 40(3): 256-269	
Rowan, Kathryn M, Angus, Derek C, Bailey, Michael et al. (2017) Early, Goal-Directed Therapy for Septic Shock - A Patient-Level Meta-Analysis. The New England journal of medicine 376(23): 2223-2234	- Study does not contain a relevant intervention
Saoraya, Jutamas, Wongsamita, Lipda, Srisawat, Nattachai et al. (2021) The effects of a limited infusion rate of fluid in the early resuscitation of sepsis on glycocalyx shedding measured by plasma syndecan-1: a randomized controlled trial. Journal of intensive care 9(1): 1	- Non-OECD country
Self, Wesley H, Semler, Matthew W, Bellomo, Rinaldo et al. (2018) Liberal Versus Restrictive Intravenous Fluid Therapy for Early Septic Shock: Rationale for a Randomized Trial. Annals of emergency medicine 72(4): 457-466	- Not a relevant study design
Semler, Matthew W, Janz, David R, Casey, Jonathan D et al. (2020) Conservative Fluid Management After Sepsis Resuscitation: A Pilot Randomized Trial. Journal of intensive care medicine 35(12): 1374-1382	- Study already in an included systematic review *Although included in SR analysis from this paper excluded as does not form part of the author's definition of 'early' fluids for resuscitation or subgroup ED analysis*
Shahnoor, Husna, Divi, Rachana, Addi Palle, Lokeshwar Raaju et al. (2023) The Effects of Restrictive Fluid Resuscitation on the Clinical Outcomes in Patients with Sepsis or Septic Shock: A Meta-Analysis of Randomized-Controlled Trials. Cureus 15(9): e45620	- More recent systematic review included that covers the same topic
Shapiro, Nathan I, Douglas, Ivor S, Brower, Roy G et al. (2023) Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension. The New England journal of medicine 388(6): 499-510	- Study already in an included systematic review
Silversides, J.A., McMullan, R., Emerson, L.M. et al. (2022) Feasibility of conservative fluid administration and deresuscitation compared with usual care in critical illness: the Role of Active Deresuscitation After Resuscitation-2 (RADAR-2) randomised clinical trial. Intensive Care Medicine 48(2): 190-200	- Wrong population

Study	Reason for exclusion
Silversides, Jonathan A, Major, Emmet, Ferguson, Andrew J et al. (2017) Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. Intensive care medicine 43(2): 155-170	- More recent systematic review included that covers the same topic *Primary papers all pre-2016 cut off*
Smart, Lisa, Macdonald, Stephen P J, Bosio, Erika et al. (2019) Bolus therapy with 3% hypertonic saline or 0.9% saline in emergency department patients with suspected sepsis: A pilot randomised controlled trial. Journal of critical care 52: 33-39	- Comparator in study does not match that specified in protocol
Tseng, C-H, Chen, T-T, Chan, M-C et al. (2021) Impact of Comorbidities on Beneficial Effect of Lactated Ringers vs. Saline in Sepsis Patients. Frontiers in medicine 8	- Not a relevant study design
Tseng, Chien-Hua, Chen, Tzu-Tao, Wu, Mei-Yi et al. (2020) Resuscitation fluid types in sepsis, surgical, and trauma patients: a systematic review and sequential network meta-analyses. Critical care (London, England) 24(1): 693	- More recent systematic review included that covers the same topic *Majority of studies pre-2016 and go too far back for relevant sepsis definition*
Vaeli Zadeh, Ali, Wong, Alan, Crawford, Andrew Carl et al. (2023) Guideline-based and restricted fluid resuscitation strategy in sepsis patients with heart failure: A systematic review and meta-analysis. The American journal of emergency medicine 73: 34-39	- Not a relevant study design *SR of observational studies*
Vargas, M., Marra, A., Buonano, P. et al. (2020) Randomized Controlled Trials on Lower vs Higher Fluid Volumes During Initial Management of Sepsis Are Very Fragile. Chest 158(1): 427-428	- Not a relevant study design
Wang, X, Yuan, Z, Chen, Q et al. (2018) Effect of different crystalloids on internal environment in patients with septic shock receiving early fluid resuscitation: a prospective randomized controlled trial. Zhonghua wei zhong bing ji jiu yi xue 30(9): 824-829	- Non-OECD country
Ward, M.A., Kuttab, H.I., Tuck, N. et al. (2022) The Effect of Fluid Initiation Timing	- Not a relevant study design

Study	Reason for exclusion
on Sepsis Mortality: A Meta-Analysis. Journal of Intensive Care Medicine 37(11): 1504-1511	*retrospective observational studies in analysis*
Zampieri, Fernando G; Bagshaw, Sean M; Semler, Matthew W (2023) Fluid Therapy for Critically Ill Adults With Sepsis: A Review. JAMA 329(22): 1967-1980	- Not a relevant study design *Not a systematic review with meta-analysis*
Zampieri, Fernando G, Machado, Flavia R, Biondi, Rodrigo S et al. (2022) Association between Type of Fluid Received Prior to Enrollment, Type of Admission, and Effect of Balanced Crystalloid in Critically Ill Adults: A Secondary Exploratory Analysis of the BaSICS Clinical Trial. American journal of respiratory and critical care medicine 205(12): 1419-1428	- Study already in an included systematic review
Zhang, Jing, Liu, Fang, Wu, Ziyi et al. (2024) ACETATE RINGER'S SOLUTION VERSUS NORMAL SALINE SOLUTION IN SEPSIS: A RANDOMIZED, CONTROLLED TRIAL. Shock (Augusta, Ga.) 61(4): 520-526	- Non-OECD country
Zhang, Z., Hong, Y., Smischney, N.J. et al. (2017) Early management of sepsis with emphasis on early goal directed therapy: AME evidence series 002. Journal of Thoracic Disease 9(2): 392-405	- Study does not contain a relevant intervention
Zhao, C.-C., Ye, Y., Li, Z.-Q. et al. (2022) Effect of goal-directed fluid therapy on renal function in critically ill patients: a systematic review and meta-analysis. Renal Failure 44(1): 777-789	- Study does not contain a relevant intervention
Zitek, Tony, Skaggs, Zachary D, Rahbar, Aryan et al. (2018) Does Intravenous Lactated Ringer's Solution Raise Serum Lactate?. The Journal of emergency medicine 55(3): 313-318	- Not a relevant study design *Abstract only*
Zou, Yan, Ma, Ke, Xiong, Ji-Bin et al. (2018) Comparison of the effects of albumin and crystalloid on mortality among patients with septic shock: systematic review with meta-analysis and trial sequential analysis. Sao Paulo medical journal = Revista paulista de medicina 136(5): 421-432	- More recent systematic review included that covers the same topic *Included studies all pre-2016 cut off*