Electronic Supplement Material

***Shankar-Hari M, Harrison D, Rowan K, Rubenfeld GD*. Estimating attributable fraction of sepsis to inform clinical trials.**

eMethods: Further description of study data source and methods

eTable-1: Operationalisation of Sepsis-3 Definitions

Table summarises the operationalisation of Sepsis-3 definitions. This has been recently reporting using the dataset used for this study.

Shankar-Hari M et al. *Epidemiology of sepsis and septic shock in critical care units: comparison between Sepsis-2 and Sepsis-3 populations using a national critical care database [21]*.

eTable-2: AFsepsis after excluding patients who had withdrawal of treatment within 12 hours

*AFsepsis and AFseptic shock were estimated using a posthoc sensitivity analysis after excluding patients with active treatment withdrawn 12 hours of ICU admission.

eTable-3: Summary of inclusion and exclusion criteria in the trials identified

eTable-4: Summary of sample size calculations in trials identified to compare with the AFsepsis model

The trials are listed by publication year starting with year 2015. The original reported sample size calculations were extracted and presented in Figure-2 and in this table. We did not use the reported adjustments during interim analyses. RRR was estimated using reported sample size calculations when not explicitly stated. *Lower limit of reported range was used to estimate RRR from 6% - 7% absolute risk reduction used in the trial to estimate sample size. Display code – identifies the trial in Figure-2. RRR = relative risk reduction; EGDT = Early goal directed therapy; Hb = Hemoglobin; Proportions were rounded to whole numbers without decimals.

eFigures:

eFIgure-1: Flow diagram for patients in the study

eFigure-2: Flow diagram for trial selection

eMethods: Further description of study data source and methods

For sepsis cases and non-septic critically ill controls, we used the consecutive admissions between January 2011 and December 2015 recorded in the Intensive Care National Audit & Research Centre (ICNARC) Case Mix Programme Database (CMPD) [22], The ICNARC-CMPD is the national clinical audit for adult general ICUs in England. For consecutive ICU admissions, trained data collectors collect sociodemographic, comorbidity, and physiologic data to precise rules and definitions, during the first 24 hours following admission to ICU. Diagnostic data are determined clinically and coded using the hierarchical ICNARC Coding Method with 5 tiers [22]. A code is automatically generated that represents a patient's clinical diagnosis route through this hierarchy. Collected data undergo extensive local and central validation prior to pooling into the CMPD. The CMPD has been independently assessed to be of high quality. Support for the collection and use of these data has been obtained under Section 251 of the National Health Service Act 2006 (PIAG 2–10(f)/2005).

Additional details of propensity models

We used nearest neighbour 1:1 greedy matching without replacement with caliper bandwidth specified as 0.1 standard deviation of the propensity score to generate a conditional probability of sepsis [23]. We checked balance of all the matched covariates using standardized differences of mean [23].

Rationale for sensitivity analysis

As a sensitivity analysis and to reflect frequent exclusion criteria in clinical trials, we ascertained AFsepsis and AFseptic shock in patients without severe comorbidities using propensity models with age, sex, and surgical status as covariates to confirm our assumption that comorbidity effect is accounted for by the main propensity model, by excluding all patients with comorbidities from the analysis set prior to deriving these models. We conducted a post hoc sensitivity analysis excluding patients who had withdrawal of treatment decision made within 12 hours of ICU admission. The rationale being that these patients would be excluded from sepsis and septic shock clinical trials.

eTable-1: Operationalisation of Sepsis-3 Definitions

Criteria	Sepsis-3
Infection	Reason for ICU admission
Organ dysfunction	SOFA score of 2 or more in any one organ system or SOFA score of one in two or more organ systems
Sepsis	Sepsis = Infection AND >=2 SOFA points
Septic shock	Infection AND cardiovascular SOFA>=2 AND serum lactate concentrations >2mmol/L

eTable-2: AFsepsis and AFseptic shock after excluding patients who had withdrawal of treatment within 12 hours

Parameter	**Sepsis N = 179,700**	**Non-sepsis N=179,702**	**Septic Shock N=36,832**	**Non-sepsis N=36,833**
Withdrawal of treatment N (%)	24,427 (13.6%)	19,963 (11.1%)	10,197 (27.7%)	4,034 (11.0%)
Time to withdrawal of treatment median (IQR) days	2.9 (1.0 – 7.8)	2.1 (0.8 – 4.9)	2.5 (1.0 -7.2)	2.5 (0.9 – 5.9)
Withdrawal of treatment within 12 hours of ICU admission N (%)	3,077 (1.7%)	2,923 (1.7%)	1,188 (3.2%)	563 (1.5%)
***RD (95% CI)** ***RR (95% CI)** ***AFsepsis or septic shock (%)** **P - value**	7.4% (6.7% – 8.1%) 1.21 (1.19 – 1.23) 17.2% (15.7% – 18.9%) <0.001		29.4% (27.9% – 31.0%) 1.80 (1.74 – 1.87) 44.5% (42.6% – 46.4%) <0.001	

eTable-3: Inclusion and exclusion criteria in the trials identified

N	Trial ID	Inclusion criteria	Exclusion criteria
1	Mouncey PR et al (2015)[8]	Adults (≥18 years of age) were eligible if within 6 hours after presentation to the emergency department they had a known or presumed infection, two or more criteria of the systemic inflammatory response syndrome, and either refractory hypotension (systolic blood pressure, <90 mm Hg; or mean arterial pressure, <65 mm Hg, despite resuscitation with at least 1 litre of intravenous fluids within 60 minutes) or hyperlactatemia (blood lactate level, ≥4mmol per litre)	Age less than 18 years; pregnancy; Primary diagnosis of: acute cerebral vascular event, acute coronary syndrome, acute pulmonary oedema; status asthmatics; major cardiac arrhythmia (as part of primary diagnosis); seizure; drug overdose; injury from burn or trauma; hemodynamic instability due to active gastrointestinal haemorrhage; Requirement for immediate surgery; Known history of AIDS; Do-not-Attempt-Resuscitation (DNAR) order; Advanced directives restricting implementation of the resuscitation protocol; Contradiction to: central venous catheterization or to blood transfusion; Attending clinician deems aggressive resuscitation unsuitable; Transferred from another in-hospital setting; Not able to commence resuscitation protocol within one hour of randomization or complete six hours of protocol treatment from commencement
2	Payen DM et al (2015)[3]	Patients with severe sepsis or septic shock and underwent emergency surgery to treat visually confirmed peritonitis. In order to distinguish between hypotension resulting from the effect of sedation, shock had to occur or persist within 10 h after surgical proce- dure with a duration of at least 2 h. Shock was classically defined as a hypotension resistant to fluid administration requiring norepinephrine or other vasopressor	Age < 18 years; protected adult under law; Pregnancy; Moribund status or life expectancy lower than 48h; Aplasia related to chemotherapy or malignancy; Non-surgically treated abdominal sepsis; Absence of intra-abdominal organ perforation ; A mesenteric ischemia without perforation; Trauma-induced gastro-intestinal perforation; Appendicle peritonitis; A cirrhosis Child C; A prolonged cardiac arrest within 72 hours before surgery; A contraindication to the use of heparin for hemoperfusion (risk of bleeding and / or history of heparin induced thrombocytopenia); Discovery of an advanced stage of cancer; Additionally, the patients who refused to participate even after inclusion by the emergency process and who refused to participate after recovery were excluded from the study analysis.
3	Yealy DM et al (2014)[11]	We recruited patients in the emergency department in whom sepsis was suspected according to the treating physician, who were at least 18 years of age, who met two or more criteria for systemic inflammatory response syndrome and who had refractory hypotension or a serum lactate level of 4 mmol per liter or higher.	Patients who had: a primary diagnosis of acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, major cardiac arrhythmia, active gastrointestinal hemorrhage, seizure, drug overdose, burn or trauma; a requirement for immediate surgery; a known CD4 count <50/mm2; an advance directive that would restrict protocol implementation; a contraindication to central venous catheterization; a high likelihood of refusing blood transfusion (e.g., Jehovah's Witness); a treating physician who deemed resuscitation to be futile; on-going participation in another interventional study; known pregnancy, or; been transferred from another hospital.
4	Peake SL et al (2014)[10]	Eligibility criteria were a suspected or confirmed infection, two or more criteria for a systemic inflammatory response and evidence of refractory hypotension or hypoperfusion. Refractory hypotension was defined as a systolic blood pressure of less than 90 mm Hg or a mean arterial pressure of less than 65 mm Hg after an intravenous fluid challenge of 1000 ml or more administered within a 60-minute period. Hypoperfusion was defined as a blood lactate level of 4.0 mmol per liter or more.	Patients were not eligible for enrolment if they met one or more of the following criteria: age < 18 years; contraindication to central venous catheter insertion in the superior vena cava; contraindication to receiving blood products; hemodynamic instability due to active bleeding; underlying disease process with a life expectancy < 90 days; death deemed imminent and inevitable; documented limitation of therapy order restricting implementation of the study protocol or aggressive care deemed unsuitable by the treating clinician; in-patient transfer from another acute health care facility; confirmed or suspected pregnancy; inability to commence EGDT within one hour of randomization or deliver EGDT for 6 hours
5	Holst LB et al (2014)[9]	(1) At least 2 SIRS criteria; **AND** (2) suspected focus of infection as either: An organism grown in blood or sterile site OR An abscess or infected tissue (e.g. pneumonia, peritonitis, urinary tract, vascular line infection, soft tissue, etc). **AND** (3) hypotension (Systolic blood pressure < 90 mmHg or mean arterial pressure < 70 mmHg) despite fluid therapy OR vasopressor/inotrope infusion to maintain blood pressure.	Documented wish against transfusion OR Previous serious adverse reaction with blood products, excl. transfusion-associated circulatory overload OR Presence of acute myocardial ischemia OR (defined as: patients diagnosed with *acute myocardial infarction (ST-elevation myocardial infarction or non-ST elevation myocardial infarction) or unstable angina pectoris* during current hospital admission, according to the criteria in the clinical setting in question (e.g. elevated biomarkers, ischemic signs on ECG, clinical presence) AND the patient has received treatment,

			initiated during current hospital admission, as a consequence of this (reperfusion strategies (PCI/thromobolysis) or initiation/increased antithrombotic treatment)). Life−threatening bleeding OR (defined as: (1) Presence of hemorrhagic shock, as judged by research or clinical staff. OR (2) the need for surgical procedure, incl. endoscopy to maintain hemoglobin levels); Red cell transfusion during current ICU admission OR Withdrawal from active therapy or brain death OR Acute burn injury - regardless of degree and burn surface area OR Lack of informed consent
6	Afzar P at al (2014)[13]	Presence of septic shock within less than 6 hours (onset defined by the time of introduction of catecholamines) A minimum vasopressor infusion rate of 0.1µg/Kg/min The criteria for septic shock were the official criteria of the American College of Chest Physicians / Society of Critical Care Medicine, i.e.: sepsis: patients with a systemic inflammatory response syndrome plus a suspected or Septic shock was defined as sepsis plus arterial hypotension (systolic blood pressure < 90 mm Hg) refractory to fluid resuscitation (minimum 30 mL/kg within 6 hours prior to the start of catecholamines) and requiring vasopressor support. The consent of the subject was obtained from the patient if his or her condition permitted, from family or person of trust if present. As last recourse, the procedure for inclusion in emergency situations was applied in the absence of the family or next of kin.	"Legally protected" adult patient., (i.e. These patients are protected by law and cannot be included in RCT e.g. patients who have no guardian, are convicted felons and in jail etc.; Person not affiliated with or non-beneficiary of a health care system.; Minors and pregnant women; Patient currently in an exclusion period following participation in another biomedical study; Participation in another interventional study with "28 day mortality" as primary endpoint or one of the secondary endpoints of SEPSISPAM; Decision. not to resuscitate.
7	Caironi O et al (2014)	Proved or suspected infection in at least one site: a) lung; b) abdomen; c) genito-urinary tract; d) other (blood, skin and soft tissue, central nervous system, bones and joints, cardiac system, catheter-related infection, other AND two or SIRS criteria AND Presence of at least a severe and acute sepsis-related organ dysfunction, as measured by the modified Sequential Organ Failure Assessment (SOFA) score of 1 or more on any one of the organ systems	Age below 18 years; Terminal state; Known adverse reaction to albumin administration; Severe sepsis or septic shock in patients after proved or suspected head injury, clinically Active; Congestive heart failure (New York Heart Association class of 3 or 4); Pathological conditions in which albumin administration is clinically indicated (hepatic cirrhosis with ascites, intestinal malabsorption syndrome, nephrotic syndrome, burns); More than 24 hours since inclusion criteria were met; Religious objection to the administration of human blood products; Inclusion in other experimental studies
8	Ranieri VM et al (2012)[17]	Inclusion criteria to obtain informed consent = 1. Aged C 18 years old; 2. Must have an infection requiring intravenous antimicrobial therapy; 3. Must meet at least two of the four systemic inflammatory response syndrome (SIRS) criteria. 4. Must have septic shock, defined as: (a) The patient must have received intravenous fluid resuscitation of C 30 mL/kg administered within the time period spanning the 4 hours before and 4 hours after initiation of vasopressor therapy. (b) The patient must have a continuous requirement for at least one of the vasopressors listed below at the dose shown below for at least four hours: Norepinephrine C 5 mcg/min Dopamine C 10 mcg/kg/min Phenylephrine C 25 mcg/min Epinephrine C 5 mcg/min Vasopressin C 0.03 units/min ; (c) The patient must meet at least 1 of the following criteria consistent with hypoperfusion during the 36 hours prior to study entry: Metabolic acidosis: base deficit C 5.0 mmol/L or venous bicarbonate \ 18 mmol/L or lactate C 2.5 mMol/L. Urine output \ 0.5 mL/kg h-1 for 1 hour or a 50% increase in creatinine from a known baseline level. Acute hepatic dysfunction: AST or ALT [500 IU/dL or bilirubin [2 g/dL. Inclusion criterion to proceed to randomisation 5. Patients must remain vasopressor dependent throughout the pretreatment period and through the time of randomisation with the goal of maintaining a systolic blood pressure of approximately 90 mm Hg or higher or a mean arterial pressure of 65 mm Hg or higher with reasonable attempts made to wean the patient from vasopressor support, if applicable. (Note: dopamine at doses \ 5 mcg/kg/min does not fulfil the criteria for vasopressor dependency.)	< 18 years of age; Does Not Have Evidence of Infection; Does Not Satisfy SIRS Criteria; Does Not Meet Septic Shock Criteria; Has Not Remained Vasopressor Dependant; Vasopressor Therapy for > 24 Hours; Sepsis Induced Organ Dysfunction > 36 Hours; Single Organ Dysfunction and Recent Surgery (within last 30 days); Post-op < 12 hours, Evidence of Bleeding, or Planned Surgery; Platelet Count < 30x 109/L; INR > 5.0; Active Internal Bleeding or Increased Risk for Bleeding; Receiving or Concurrent Need for Bleeding Risk Medications; Not Expected to Survive 28 Days due to Pre-existing Condition; Moribund & Death is Perceived to be Imminent; Not Committed to Aggressive Management; Received DrotAA within Last 30 Days; Pregnant or Lactating & the Milk is to be Ingested by the Newborn; Fail to Give Written Informed Consent; Participating in Competing Study of Investigational Drug; Incomplete Information available; Condition Improving; Second Sepsis Episode; Site On Hold; Pharmacy Issue; Not in ICU (Monitored Unit)
9	Huh JW et al (2011)[20]	Onset of septic shock within 6 h and relative adrenal insufficiency, defined as an increase in cortisol level of <9 mg/dL or a basal cortisol level of <25 mg/dL.	Advanced cancer, immunosuppression, previous treatment with corticosteroids, refusal of the attending staff or patient family and absence of adrenal insufficiency

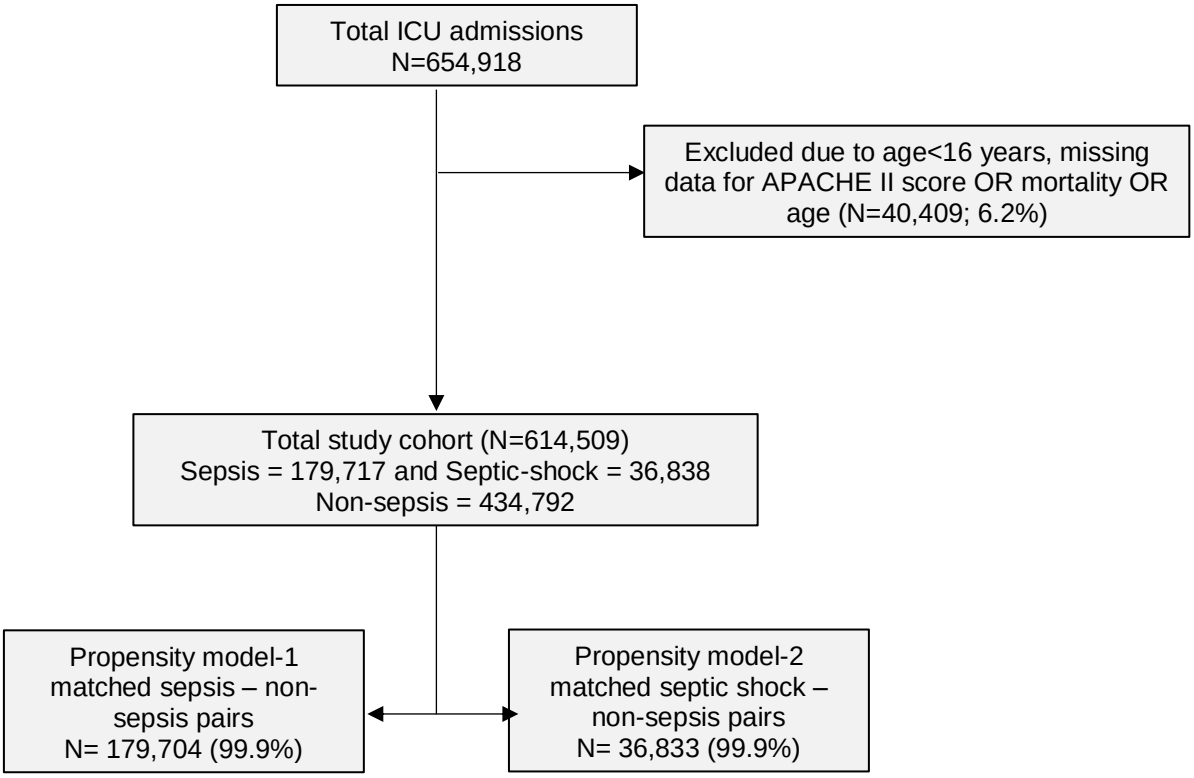
10	De Backer D et al (2010)[19]	All patients 18 years of age or older in whom a vasopressor agent was required for the treatment of shock were included in the study.	Patients were excluded if they were younger than 18 years of age; had already received a vasopressor agent (dopamine, norepinephrine, epinephrine, or phenylephrine) for more than 4 hours during the current episode of shock; had a serious arrhythmia, such as rapid atrial fibrillation (>160 beats per minute) or ventricular tachycardia; or had been declared brain-dead.
11	Patel GP et al (2010)[4]	Eligible patients had to be in shock (MAP <60 mmHg and/or systolic blood pressure <90 mmHg) after adequate fluid resuscitation, as determined by a CVP greater than 8 mmHg for non-mechanically ventilated patients (12 to 15 mmHg for patients requiring mechanical ventilation) and require the administration of a vasopressor for management.	Patients were excluded from the study if they were found to have alternative causes of their shock (i.e., hypovolemic, haemorrhagic, cardiogenic, anaphylactic, and/or obstructive shock) or another cause of their SIRS. Patients who were allergic to DA or NE were excluded, as were patients who were on vasopressors for more than 6 h before enrolment
12	Palizas F et al (2009)[5]	All adult patients fulfilling criteria for septic shock according to the ACCP/SCCM Consensus Conference within 48 hours of ICU admission were considered and selected if they were in a 12-hour time window.	Exclusion criteria were: terminal illness with the patient expected to die within 28 days, irreversible neurologic impairment, and contraindication for nasogastric tube placement.
13	Stephens DP et al (2008)[6]	Septic shock was defined according to the ACCP/SCCM Consensus Conference criteria and included the presence of sepsis, shock, and evidence of at least one other organ dysfunction. The inclusion criteria were adult patients (18 yrs of age) admitted to the ICU that met these criteria for septic shock who were assessed for eligibility within 24 hrs of meeting these criteria. The time from screening to consent and study drug administration was limited to 36 hrs.	Patients with culture-confirmed melioidosis, hematologic malignancy, febrile neutropenia, myelodysplasia or congenital neutropenia, splenomegaly, acute myocardial infarction in the previous 24 hrs, pregnancy, known hypersensitivity to G-CSF, known objection to participation, previous transplantation, active orders limiting treatment, and patients with an expected survival of 24 hrs, patients previously enrolled or who had received G-CSF within the previous month
14	Sprung CL et al (2008)[15]		
15	Russell JA et al (2008)[12]	Patients older than 16 years of age who had septic shock that was resistant to fluids (as defined by lack of response to 500 ml of normal saline or a requirement for vasopressors) and low-dose norepinephrine were considered for enrolment.	unstable coronary syndrome (acute myocardial infarction during this episode of shock based on the combination of history, electrocardiogram, and enzyme changes (as defined by investigator); greater than 24 hours had elapsed since the patient met entry criteria; use of open-label vasopressin for blood pressure support during the current hospital admission; malignancy or other irreversible disease or condition for which six-month mortality was estimated to be ≥ 50%; acute mesenteric ischemia either proven or suspected. A patient could be excluded by the investigator if, in their judgment, the condition was strongly suspected but not proven by conventional criteria or the attending physician had initiated presumptive therapy, death anticipated within 12 hours; underlying chronic heart disease (NYHA class III or IV) and shock; physician and team were not committed to aggressive care; severe hyponatremia (serum sodium < 130 mmol/L); traumatic brain injury(GCS<8prior to onset of sepsis); Raynaud's phenomenon, systemic sclerosis or vasospastic diathesis, pregnancy(positiveserumβ-HCG).
16	Werdan K et al (2007)[14]	Four of nine positive sepsis criteria: Temperature; White blood cell count 12 G/L or 3.5 G/L Heart rate>100 beats/min; Respiratory rate>28 breaths/min or FIO2>0.21; Mean arterial pressure<75 mm Hg; In case of invasive hemodynamic moni- toring (not obligatory for study partici- pation), cardiac index 4.5 L/min/m2 or systemic vascular resistance 800 dyne/ sec/cm5 Platelets<100 G/L; Positive blood cultures; Clinical evidence of sepsis (surgical or invasive procedure during the preceding 48 hrs or presence of an obvious septic focus); A sepsis score of 12–27, rating several variables categorized into four classes according to Elebute and Stoner: local signs of infection, pyrexia, organ failure, and labo- ratory values 3. An APACHE II score of 20 –35 as a measure of the degree of disease severity	Not provided with the main paper. Readers are referred to a previous publication 10 years ago – by Pilz G, Fateh-Moghadam S, Viell B, et al: Supplemental immunoglobulin therapy in sepsis and septic shock—Comparison of mortality under treatment with polyvalent i.v. immunoglobulin versus placebo. Proto- col of a multicenter, randomized, prospec- tive, double-blind trial. Theor Surg 1993; 8:61– 83
17	Annane D et al (2007)[16]	evidence of infection; at least two of the four criteria for systemic inflammatory response syndrome (temperature above 38°C or below 36°C, heart rate above 90 bpm, respiratory rate above 20 cycles per min and arterial CO2 tension below 32 mm Hg or need for mechanical ventilation, polymorphonuclear neutrophil count above 12×10^9 cells per L or below 4×10^9 cells per L); and at least two signs of tissue hypoperfusion or organ dysfunction. These signs were defined as a ratio of arterial oxygen tension over inspired fraction of oxygen of less than 280 mm Hg (if patient was mechanically ventilated), urinary output below 0·5 mL per kg of bodyweight per h or below 30 mL/h (for at least 1 h), or arterial lactate concentration above 2 mmol/L, platelet count below 100×10^9 cells per L. Additionally, patients had to meet the three following criteria for less than 24 h: systolic blood pressure below 90 mm Hg or mean blood pressure below 70 mm	Reasons for exclusion were pregnancy; evidence of obstructive cardiomyopathy, acute myocardial ischaemia, or pulmonary embolism; advanced stage cancer, haematological malignancy, or AIDS with a decision to withhold or withdraw aggressive therapies; persistent (longer than a week) polymorphonuclear neutrophil count of less than $0{\cdot}5\times10^9$ cells per L; and inclusion in another clinical trial.

		Hg; administration of fluid bolus of at least 1000 mL or capillary wedge pressure between 12 and 18 mm Hg; and need for more than 15 μg per kg of bodyweight per min of dopamine or any dose of epinephrine or norepinephrine.	
18	Angstwurm MWA et al (2007)[7]	Males and females>18yrs with an Acute Physiology and Chronic Health Evaluation (APACHE) III score (22) 70 and at least two of the following criteria (23): Rectal body temperature >38°C or hypothermia <36°C; Heart rate>90 beats/min; Respiratory frequency >20 and PaCO2 mm Hg >4.3 kPa; Leukocytes 12,000/ L or 4 000/ L or 10% immature leukocytes; Decrease of platelet count 50% within the first 24 hrs or platelets 150,000/ L at admission; Admission into the study after diagnosis within 24 hrs; Beginning of treatment within 1 hr after inclusion; Informed consent either from the patient or the relative/close friend	Pregnancy; Missing informed consent of the patient or the relative/intimate friend of the patient; Withdrawal of informed consent by patient or next of kin after inclusion into the study; Participation in any other clinical trial cur- rently or within the last 30 days; Prior participation in this clinical trial; Cerebral injury due to hypoxia after cardio- pulmonary resuscitation; Primary concomitant disease with an ex- pected high mortality within 2 months; Do-not-resuscitate code; Malignant primary disease as the cause of SIRS or sepsis, for example, agranulocytosis as a result of chemotherapy or idiopathic bone marrow aplasia; Hemorrhagic-necrotizing pancreatitis with- out infectious complications

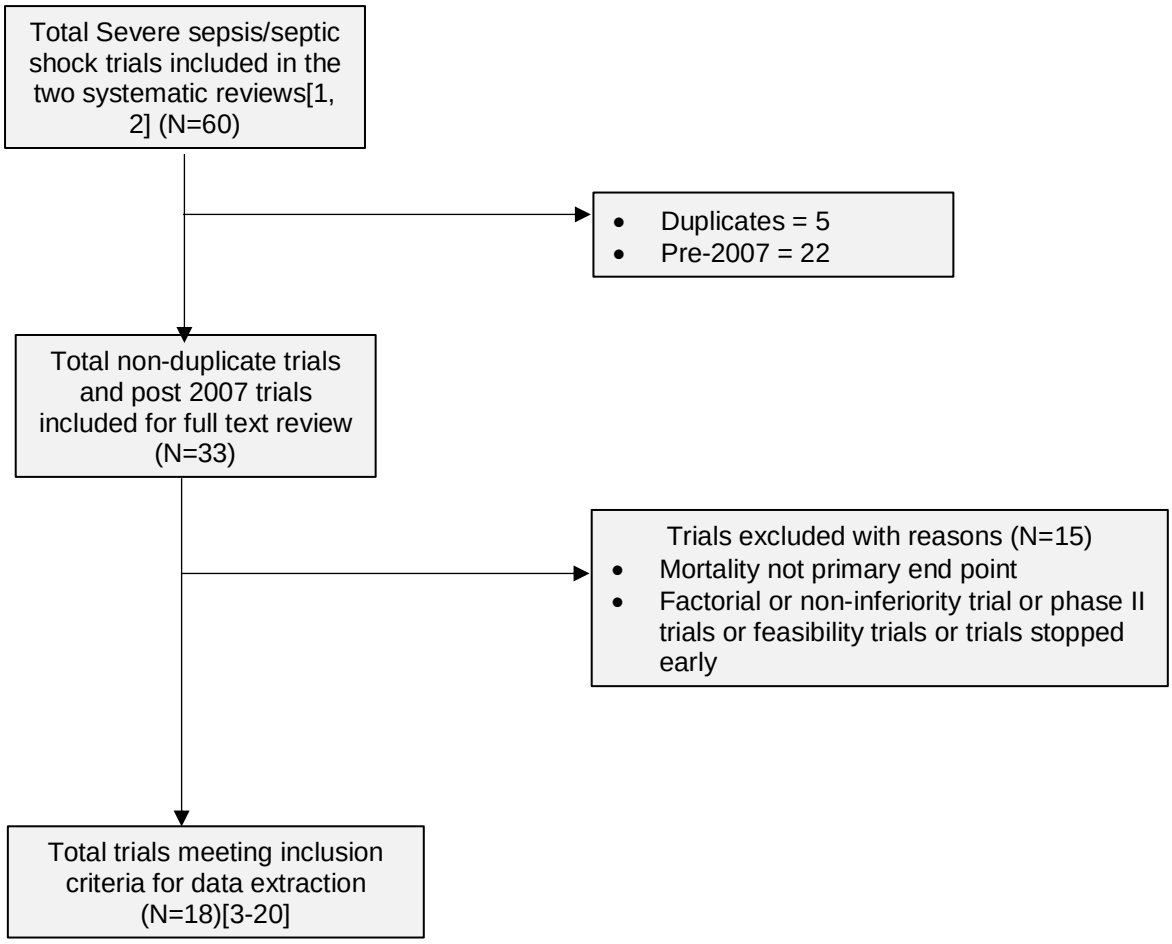
eTable-4: Trials identified to illustrate the AFsepsis model

N	Trial ID	Control group	Intervention group	Code	Mortality time point	Control group mortality	RRR	Power	Alpha	Sample size per group
1	Mouncey PR et al (2015)[8]	Standard care	EGDT	A	90-day	40%	20%	80%	5%	630
2	Payen DM et al (2015)[3]	Standard care	Polymyxin B hemoperfusion	B	28-day	37%	54%	94%	4.5%	120
3	Yealy DM et al (2014)[11]	Standard care*	EGDT	C	60-day	30% - 46%*	20%	80%	5%	650
4	Peake SL et al (2014)[10]	Standard care	EGDT	D	90-day	38%	20%	85% - 90%	5%	800
5	Holst LB et al (2014)[9]	>7g/L Hb target	>9g/L Hb target	E	90-day	45%	20%	80%	5%	500
6	Afzar P at al (2014)[13]	65 – 70mmHg MAP target	80 – 85mmHg MAP target	F	28-day	45%	22%	80%	5%	400
7	Caironi O et al (2014)	Standard care	Albumin>30g/L	G	28-day	45%	17%	80%	5%	675
8	Ranieri VM et al (2012)[17]	Placebo	Activated protein C	H	28-day	35%	20%	80%	5%	750
9	Huh JW et al (2011)[20]	3-day hydrocortisone	7-day hydrocortisone	I	28-day	35%	50%	80%	5%	136
10	De Backer D et al (2010)[19]	Dopamine	Nor-epinephrine	J	28-day	43%	15%	80%	5%	765
11	Patel GP et al (2010)[4]	Dopamine	Norepinephrine	K	28-day	60%	33%	80%	5%	120
12	Palizas F et al (2009)[5]	CI>3.0L/min/m2	Intramucosal pH>7.32	L	28-day	40%	50%	80%	5%	64
13	Stephens DP et al (2008)[6]	Placebo	G-CSF	M	Hospital	60%	38%	80%	5%	82
14	Sprung CL et al (2008)[15]	Placebo	Hydrocortisone	N	28-day	50%	20%	80%	5%	400
15	Russell JA et al (2008)[12]	Nor-epinephrine	Vasopressin	O	28-day	60%	17%	80%	5%	388
16	Werdan K et al (2007)[14]	Placebo	IVIg	P	28-day	30%	33%	90%	5%	400
17	Annane D et al (2007)[16]	Epinephrine	Nor-epinephrine + Dobutamine	Q	28-day	60%	33%	95%	5%	170
18	Angstwurm MWA et al (2007)[7]	Standard care	Selenium	R	28-day	50%	40%	80%	5%	119
	Summary statistics	-	-	-	-	44% (37% - 50%)	20% (20% - 38%)	-	-	-

eFIgure-1: Flow diagram for patients in the study



eFigure-2: Flow diagram for trial selection



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