Technical report

Volume 2 – Appendix A to D

Prepared for

National Blood Authority

Project

Update of Patient Blood Management Guideline for Adults with Critical Bleeding

The Commonwealth of Australia
as represented by the National Blood Authority

[redacted]

prepared by
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Note

This volume presents the literature search, screening results and critical appraisal (Appendix A to Appendix D) of studies included in the systematic literature review on Patient Blood Management in patients with critical bleeding. Volume 1 presents the main body of evidence and Volume 3 presents the data extraction forms that outline the study characteristics (Appendix E). These 3 volumes cover all research questions developed for this topic.

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Appendix A Literature search results

This appendix documents the literature search results for a systematic literature review on management of patients who are critically bleeding or at risk of critical bleeding. The search strategy was developed via Ovid for both Embase and MEDLINE.

A1 Question 1

A1.1 Embase

Table A1.1 Literature search results: Embase <1974 to 07 August 2019>

Search via Ovid for Level I, Level II, and Level III studies

#	Concept	Search string	Results 11 Aug 2018	Results 09 Aug 2019	Results 29 Sep 2021
1	Population (critical bleeding)	exp *hemorrhage/	259817	247926	316767
2		oral hemorrhage/ or postoperative hemorrhage/ or peptic ulcer hemorrhage/ or gastrointestinal hemorrhage/ or uterine hemorrhage/ or obstetric hemorrhage/ or antepartum hemorrhage/ or intrapartum hemorrhage/ or postpartum hemorrhage/	110293	114006	141169
3		*shock/ or hemorrhagic shock/ or hypovolemic shock/ or traumatic shock/ or exsanguination/ or hemorrhagic hypotension/	36605	31177	43503
4		((hemorrhag* or haemorrhag* or bleed* or bleeding or blood?loss* or 'blood-loss*' or bloodloss*) adj3 (critical or severe or massive or major or life threatening or 'life?threatening')).mp.	61622	65739	83563
5		((haemorrhagic or hemorrhagic or hypovolemic or hypovolaemic) adj shock).ti,ab.	14959	14648	18865
6		or/1-5	390621	383245	489030
7	Population (receiving transfusion)	exp *blood transfusion/ or Erythrocyte Transfusion/	74468	72393	87757
8		blood autotransfusion/ or blood component therapy/ or plasma transfusion/ or thrombocyte transfusion/ or Platelet Transfusion/ or Blood Component Transfusion/	30471	31763	37237
9		(blood component adj (transfus* or therapy)).ti,ab,kw.	995	1043	1074
10		or/7-9	89332	88205	106754
11	Combine population sets	6 or 10	466142	457123	578370
12	Population (trauma)	Multiple Trauma/	13168	13979	16062
13		trauma*.ab,ti,kw.	425499	444032	553681
14		(polytrauma* or poly?trauma* or 'poly trauma').ab,ti,kw.	5431	5931	7031
15		(multitrauma* or multi?trauma* or 'multi trauma').ab,ti,kw.	656	709	790
16		'multiple trauma*'.ab,ti,kw.	4420	4589	5137
17		blunt trauma/	17362	18332	21158
18		traumatic hematoma/	251	267	381
19		exp amputation, traumatic/	1967	1951	2346
20		or/12-19	436065	454898	566134
21	Population (wounds)	exp wounds, nonpenetrating/	24593	25853	29410
22		exp wounds, penetrating/	11345	11867	14126
23		surgical wound/	5896	6516	8324
24		wound hemorrhage/	206	218	264
25		or/21-24	39135	41380	48641
26	Population (injury)	*injury/	63412	59544	78858
27		exp blast injuries/	4121	4167	5098
28		exp abdominal injuries/	146075	149829	188227

#	Concept	Search string	Results 11 Aug 2018	Results 09 Aug 2019	Results 29 Sep 2021
29		exp thoracic injuries/	71818	73727	95598
30		exp war-related injuries/	4002	4285	5490
31		childhood injury/ or contusion/ or crush trauma/ or limb injury/	23216	24468	30675
32		organ injury/ or reperfusion injury/	54855	58827	64489
33		surgical injury/	4141	4402	5641
34		gunshot injury/	17147	16452	20854
35		accidental injury/	3145	3459	4260
36		battle injury/	4002	4285	5490
37		or/26-36	359476	366943	459124
38	Population (emergency)	*accidents/	10065	8490	13057
39		*emergency/	13784	13580	15727
40		((major* or life threatening or life?threatening or substantial* or multip* or severe* or serious* or catastrophic* or critical* or massive* or penetrating) adj3 (trauma* or injur* or emergenc* or accident*)).ti,ab.	121344	128104	154996
41		or/38-40	143506	148509	181621
42	Combine trauma/ emergency sets	20 or 25 or 37 or 41	795659	822998	1027508
43	Population (operative)	transplantation/	156865	148707	186111
44		emergency surgery/ or general surgery/ or major surgery/	40201	42693	55124
45		*surgery/ or abdominal surgery/ or cardiovascular surgery/ or thorax surgery/ or orthopedic surgery/	211594	199232	265866
46		pediatric surgery/ or obstetrics/ or obstetric care/	56718	57330	70545
47		(peri?operative or pre?operative or intra?operative or post?operative).ti,ab,kw.	846675	908000	1093613
48		(surg* or operat* or resect* or perioperat*).ab,ti,kw.	3279335	3434760	4254459
49		exp operative blood loss/	15899	19706	28478
50		peroperative care/	11777	12396	13795
51		peroperative complication/ or postoperative complication/ or preoperative complication/	343121	341349	417331
52		exp perioperative period/	41529	45985	57028
53		exp preoperative period/	275162	295862	364040
54		or/43-53	3830016	3968667	4916589
55	Combine population sets	42 or 54	4382387	4534835	5629461
56	Combine population sets (bleeding AND trauma/surgery or emergency)	11 and 55	164357	169773	208765
57	Prognostic factor (acid-base status)	acidosis/ or acidosis.ti,ab,kw.	52849	50778	66956
58		*alkalosis/	1986	1294	2252
59		blood pH/	5886	6109	7890
60		acid base balance/ or (acid base balance or acid?base balance).ti,ab,kw.	21790	17183	25890
61		base excess.ti,ab,kw.	3782	3958	4664
62		anion gap/ or urea blood level/ or uric acid blood level/	28335	31130	40143
63		bicarbonate blood level/	4108	4415	5741
64		lactate blood level/	16540	17933	22074
65		calcium blood level/ or calcium level?.ti,ab,kw.	40410	42366	51439
66		(ioni?ed calcium or hypocalc?emia or anion gap).ti,ab,kw.	22400	23481	28722
67		or/57-66	169459	169901	218326
68		exp Body Temperature/	56956	49076	68490
69		Body Temperature Regulation/	25110	22490	29312

#	Concept	Search string	Results 11 Aug 2018	Results 09 Aug 2019	Results 29 Sep 2021
70	Prognostic factor (temperature)	Hypothermia/	33359	32073	43789
71		(body temperatur$ or thermoregulat$ or hypothermi$).ab,ti,kw.	89522	88435	112069
72		or/68-71	138142	129127	169481
73	Prognostic factor (vital signs)	vital signs/ or vital sign*.ti,ab,kw.	28147	31110	39242
74		heart rate/ or ('heart rate*' or 'pulse rate*').ab,ti,kw.	286209	286594	348051
75		Respiratory Rate/ or ('respiratory rate*' or 'respiration rate*').ab,ti,kw.	41397	45159	59927
76		*Blood Pressure/	85114	76604	90077
77		systolic blood pressure/ or 'systolic blood pressure'.ab,ti,kw.	146914	160924	194778
78		shock index.ti,ab,kw.	831	985	1325
79		or/73-78	503725	513041	626558
80	Prognostic factor (INR/ APTT/ PTT)	international normalized ratio/	28782	32151	39447
81		activated partial thromboplastin time/	20384	3031	8083
82		partial thromboplastin time/	20917	21375	22568
83		prothrombin time/	27662	28139	37564
84		prothrombin time.ti,ab,kw.	15916	16719	20825
85		international normali?ed ratio.ti,ab,kw.	9674	10561	12196
86		partial thromboplastin time.ti,ab,kw.	12302	13121	15129
87		(PT?INR or INR).ti,ab,kw.	19907	21901	25933
88		(APTT or PTT).ti,ab,kw.	15601	17525	21380
89		or/80-88	77110	82450	102906
90	Prognostic factor (fibrinogen)	exp fibrinogen blood level/	8388	8900	11123
91		(fibrinogen adj3 level).ti,ab,kw.	3518	3686	4700
92	Prognostic factor (haemoglobin)	*hemoglobin/	32666	28406	38244
93		hemoglobin determination/	23986	21480	27502
94		hemoglobin blood level/	55679	62189	78269
95		(h?emoglobin adj3 level).ti,ab,kw.	17471	18975	23455
96		(blood adj2 marker?).ti,ab,kw.	5232	5800	6969
97	Prognostic factor (platelet count)	platelet count/	63569	11763	33281
98		"platelet count?".ti,ab,kw.	48406	52456	63927
99	Prognostic factor (haematocrit)	h?ematocrit.ti,ab,kw.	41537	43036	51774
100		"hematocrit"/	58893	56109	76984
101		or/90-100	253064	236629	309207
102	Combine prognostic factors	67 or 72 or 79 or 89 or 101	1065934	1056144	1326978
103	Combine population and prognostic factors	56 and 102	24692	26062	32065
104	Level I	exp meta analysis/ or meta analysis.mp. or exp systematic review/ or systematic review.mp. or pooled analysis.mp. or ((exp review/ or review.mp.) and (systemat* or pool*).mp.)	426010	487362	644343
105	Level II	exp comparative study/ or comparative study.mp. or exp clinical trial/ or clinical trial.mp. or randomized controlled trial.mp. or randomi?ed controlled trial.mp. or exp randomized controlled trial/ or exp randomization/ or randomization.mp. or randomi?ation.mp. or exp single blind procedure/ or single blind procedure.mp. or exp double blind procedure/ or double blind procedure.mp. or exp triple blind procedure/ or triple blind procedure.mp. or exp crossover procedure/ or crossover procedure.mp. or exp placebo/ or placebo*.mp. or random*.mp. or rct.mp. or single blind.mp. or single blinded.mp. or double blind.mp. or double blinded.mp. or treble blind.mp. or triple blind.mp. or triple blinded.mp. or exp prospective study/ or prospective study.mp.	4000544	4254668	2010112

#	Concept	Search string	Results 11 Aug 2018	Results 09 Aug 2019	Results 29 Sep 2021
106	Level III	exp clinical study/ or exp case control study/ or exp family study/ or exp longitudinal study/ or exp retrospective study/ or exp cohort analysis/ or (cohort adj1 stud*).mp. or (case control adj1 stud*).mp. or (exp prospective study/ not randomi?ed controlled trials.mp.) or (follow up adj1 stud*).mp. or (observational adj1 stud*).mp. or (epidemiologic* adj1 stud*).mp. or (cross sectional adj1 stud*).mp.	9081902	9676156	11450592
107	Level IV	case report/	2324356	2386781	2761122
108	Publication type	(editorial or letter or comment or historical article).pt.	1603355	1707119	1897012
109	Combine Level IV & publication type	107 or 108	3723885	3883039	4433250
110	nonhuman study*	(animals/ or nonhuman/) not humans/	6869279	6850515	6860196
111	Level I	(103 and 104) not (108 or 110)	599	676	895
112	Level II	(103 and 105) not (109 or 110 or 111)	5593	6051	7277
113	Level III	(103 and 106) not (109 or 110 or 111 or 112)	6314	6902	8563
114	Level III [2019 update]	limit 113 to yr="2018 -Current"	NA	993	NA
115	Level II [2019 update]	limit 112 to yr="2018 -Current"	NA	750	NA
116	Level I [2019 update]	limit 111 to yr="2018 -Current"	NA	119	NA
114	Level III [2021 update]	limit 113 to yr="2019 -Current"	NA	NA	1975
115	Level II [2021 update]	limit 112 to yr="2019 -Current"	NA	NA	1428
116	Level I [2021 update]	limit 111 to yr="2019 -Current"	NA	NA	239

NA, not applicable
*2018 search used (animals/ not humans/) or nonhuman/

A1.2 Medline

Table A1.2 Literature search results: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to August 2019

Search via Ovid for Level I, Level II, and Level III studies

#	Concept	Search string	Results 11 Aug 2018	Results 09 Aug 2019	Results 29 Sep 2021
1	Population (critical bleeding)	exp *hemorrhage/	197263	206629	222453
2		oral hemorrhage/ or postoperative hemorrhage/ or peptic ulcer hemorrhage/ or gastrointestinal hemorrhage/ or uterine hemorrhage/ or obstetric hemorrhage/ or antepartum hemorrhage/ or intrapartum hemorrhage/ or postpartum hemorrhage/	70613	72991	77959
3		*shock/ or hemorrhagic shock/ or hypovolemic shock/ or traumatic shock/ or exsanguination/ or hemorrhagic hypotension/	30459	31064	32457
4		((hemorrhag* or haemorrhag* or bleed* or bleeding or blood?loss* or 'blood-loss*' or bloodloss*) adj3 (critical or severe or massive or major or life threatening or 'life?threatening')).mp.	40296	42872	49602
5		((haemorrhagic or hemorrhagic or hypovolemic or hypovolaemic) adj shock).ti,ab.	11515	11993	13051
6		or/1-5	265810	278036	301760
7		exp *blood transfusion/ or Erythrocyte Transfusion/	49302	50882	54188

8	Population (receiving transfusion)	blood autotransfusion/ or blood component therapy/ or plasma transfusion/ or thrombocyte transfusion/ or Platelet Transfusion/ or Blood Component Transfusion/	9970	10357	11226
9		(blood component adj (transfus* or therapy)).ti,ab,kw.	543	563	634
10		or/7-9	52167	53877	57492
11	Combine population sets	6 or 10	311087	324653	351196
12	Population (trauma)	Multiple Trauma/	12039	12410	13031
13		trauma*.ab,ti,kw.	323363	343408	395691
14		(polytrauma* or poly?trauma* or 'poly trauma').ab,ti,kw.	3878	4180	4960
15		(multitrauma* or multi?trauma* or 'multi trauma').ab,ti,kw.	477	511	562
16		'multiple trauma*'.ab,ti,kw.	3360	3514	3907
17		blunt trauma/	0	0	0
18		traumatic hematoma/	0	0	0
19		exp amputation, traumatic/	4528	4646	4898
20		or/12-19	331788	352056	404771
21	Population (wounds)	exp wounds, nonpenetrating/	34304	35801	39630
22		exp wounds, penetrating/	34526	35441	37426
23		surgical wound/	337	636	1192
24		wound hemorrhage/	0	0	0
25		or/21-24	66074	68709	74929
26	Population (injury)	*injury/	54106	56051	60286
27		exp blast injuries/	3948	4126	4495
28		exp abdominal injuries/	19662	20064	20856
29		exp thoracic injuries/	25193	26152	28707
30		exp war-related injuries/	222	332	504
31		childhood injury/ or contusion/ or crush trauma/ or limb injury/	4705	4823	5053
32		organ injury/ or reperfusion injury/	24374	25710	29087
33		surgical injury/	30020	31038	32941
34		gunshot injury/	0	0	0
35		accidental injury/	0	0	151
36		battle injury/	0	0	0
37		or/26-36	155746	161647	175135
38	Population (emergency)	*accidents/	12902	13022	13244
39		*emergency/	12117	12513	13441
40		((major* or life threatening or life?threatening or substantial* or multip* or severe* or serious* or catastrophic* or critical* or massive* or penetrating) adj3 (trauma* or injur* or emergenc* or accident*)).ti,ab.	93030	98519	113072
41		or/38-40	116709	122676	138278
42	Combine trauma/ emergency sets	20 or 25 or 37 or 41	530367	558723	631184
43	Population (operative)	transplantation/	8815	8875	8985
44		emergency surgery/ or general surgery/ or major surgery/	37301	37970	39915
45		*surgery/ or abdominal surgery/ or cardiovascular surgery/ or thorax surgery/ or orthopedic surgery/	47146	48425	57544
46		pediatric surgery/ or obstetrics/ or obstetric care/	21311	21922	23535
47		(peri?operative or pre?operative or intra?operative or post?operative).ti,ab,kw.	626572	669009	777512
48		(surg* or operat* or resect* or perioperat*).ab,ti,kw.	2484488	2631882	3013591
49		exp operative blood loss/	0	0	0
50		peroperative care/	15856	16379	0
51		peroperative complication/ or postoperative complication/ or preoperative complication/	355193	370922	404865

52		exp perioperative period/	76487	83271	98007
53		exp preoperative period/	5337	6315	8888
54		or/43-53	2800446	2959596	3362538
55	Combine population sets	42 or 54	3161257	3339511	3792050
56	Combine population sets (bleeding AND trauma/surgery or emergency)	11 and 55	94470	99422	109244
57	Prognostic factor (acid-base status)	acidosis/ or acidosis.ti,ab,kw.	40540	41775	44732
58		*alkalosis/	2313	2331	2378
59		blood pH/	0	0	0
60		acid base balance/ or (acid base balance or acid?base balance).ti,ab,kw.	17672	17896	18383
61		base excess.ti,ab,kw.	2800	2905	3162
62		anion gap/ or urea blood level/ or uric acid blood level/	15663	15793	16076
63		bicarbonate blood level/	0	0	0
64		lactate blood level/	0	0	0
65		calcium blood level/ or calcium level?.ti,ab,kw.	12519	13032	14344
66		(ioni?ed calcium or hypocalc?emia or anion gap).ti,ab,kw.	15897	16731	18760
67		or/57-66	81329	83912	90196
68	Prognostic factor (temperature)	exp Body Temperature/	82606	84293	88246
69		Body Temperature Regulation/	22485	22901	23733
70		Hypothermia/	13291	13598	14293
71		(body temperatur$ or thermoregulat$ or hypothermi$).ab,ti,kw.	73945	76830	83739
72		or/68-71	129730	133626	142838
73	Prognostic factor (vital signs)	vital signs/ or vital sign*.ti,ab,kw.	12580	13863	17327
74		heart rate/ or ('heart rate*' or 'pulse rate*').ab,ti,kw.	230634	238241	257193
75		Respiratory Rate/ or ('respiratory rate*' or 'respiration rate*').ab,ti,kw.	19562	20704	24097
76		*Blood Pressure/	77692	79806	84456
77		systolic blood pressure/ or 'systolic blood pressure'.ab,ti,kw.	47592	50513	57284
78		shock index.ti,ab,kw.	460	533	766
79		or/73-78	341460	354610	387063
80	Prognostic factor (INR/ APTT/ PTT)	international normalized ratio/	4932	5246	5820
81		activated partial thromboplastin time/	6358	6560	7048
82		partial thromboplastin time/	6358	6560	7048
83		prothrombin time/	9557	9745	10153
84		prothrombin time.ti,ab,kw.	11563	12115	13480
85		international normali?ed ratio.ti,ab,kw.	7027	7583	8778
86		partial thromboplastin time.ti,ab,kw.	9163	9663	10813
87		(PT?INR or INR).ti,ab,kw.	8006	8614	10086
88		(APTT or PTT).ti,ab,kw.	8724	9541	11775
89		or/80-88	36504	38598	43867
90	Prognostic factor (fibrinogen)	exp fibrinogen blood level/	0	0	0
91		(fibrinogen adj3 level).ti,ab,kw.	2266	2355	2622
92	Prognostic factor (haemoglobin)	*hemoglobin/	28814	29361	30562
93		hemoglobin determination/	0	0	0
94		hemoglobin blood level/	0	0	0
95		(h?emoglobin adj3 level).ti,ab,kw.	11068	11891	13854
96		(blood adj2 marker?).ti,ab,kw.	3334	3671	4573
97	Prognostic factor (platelet count)	platelet count/	20182	20966	22796
98		"platelet count?".ti,ab,kw.	29062	30708	35248

99	Prognostic factor (haematocrit)	h?ematocrit.ti,ab,kw.	31327	32400	34861
100		"hematocrit"/	32576	32913	33529
101		or/90-100	128705	133353	144942
102	Combine prognostic factors	67 or 72 or 79 or 89 or 101	684228	709507	771620
103	Combine population & prognostic factors	56 and 102	9911	10449	11640
104	Level I	exp meta analysis/ or meta analysis.mp. or exp systematic review/ or systematic review.mp. or pooled analysis.mp. or ((exp review/ or review.mp.) and (systemat* or pool*).mp.)	279832	322123	432608
105	Level II	exp comparative study/ or comparative study.mp. or exp clinical trial/ or clinical trial.mp. or randomized controlled trial.mp. or randomi?ed controlled trial.mp. or exp randomized controlled trial/ or exp randomization/ or randomization.mp. or randomi?ation.mp. or exp single blind procedure/ or single blind procedure.mp. or exp double blind procedure/ or double blind procedure.mp. or exp triple blind procedure/ or triple blind procedure.mp. or exp crossover procedure/ or crossover procedure.mp. or exp placebo/ or placebo*.mp. or random*.mp. or rct.mp. or single blind.mp. or single blinded.mp. or double blind.mp. or double blinded.mp. or treble blind.mp. or triple blind.mp. or triple blinded.mp. or exp prospective study/ or prospective study.mp.	3482111	3631252	3995294
106	Level III	exp clinical study/ or exp case control study/ or exp family study/ or exp longitudinal study/ or exp retrospective study/ or exp cohort analysis/ or (cohort adj1 stud*).mp. or (case control adj1 stud*).mp. or (exp prospective study/ not randomi?ed controlled trials.mp.) or (follow up adj1 stud*).mp. or (observational adj1 stud*).mp. or (epidemiologic* adj1 stud*).mp. or (cross sectional adj1 stud*).mp.	2990924	3196726	3751241
107	Level IV	case report/	1888904	2036570	2213316
108	publication type	(editorial or letter or comment or historical article).pt.	1973542	2083054	2343470
109	Combine Level IV & publication type	107 or 108	3662305	3909974	4332658
110	nonhuman study	(animals/ not humans/) or nonhuman/	4447618	4573930	4857428
111	Level I	(103 and 104) not (108 or 110)	161	183	228
112	Level II	(103 and 105) not (109 or 110 or 111)	2846	2994	3309
113	Level III	(103 and 106) not (109 or 110 or 111 or 112)	1646	1825	2259
114	Level III [2019 update]	limit 113 to yr="2018 -Current"	NA	187	NA
115	Level II [2019 update]	limit 112 to yr="2018 -Current"	NA	138	NA
116	Level I [2019 update]	limit 111 to yr="2018 -Current"	NA	26	NA
114	Level III [2021 update]	limit 113 to yr="2019 -Current"	NA	NA	453
115	Level II [2021 update]	limit 112 to yr="2019 -Current"	NA	NA	322
116	Level I [2021 update]	limit 111 to yr="2019 -Current"	NA	NA	50

NA, not applicable

A1.3 EBM Reviews

EBM Reviews combines several resources into a single database and includes the following:

- Cochrane Database of Systematic Reviews (from 2005),
- ACP Journal Club (from 1991),

- Database of Abstracts of Reviews of Effects (from 1st Quarter 2016),
- Cochrane Clinical Answers (from July 2018),
- Cochrane Central Register of Controlled Trials (from June 2018),
- Cochrane Methodology Register (from 3rd Quarter 2012),
- Health Technology Assessment (from 4th Quarter 2016), and
- NHS Economic Evaluation Database (from 1st Quarter 2016)

Table A1.3 Literature search results: EBM Reviews

Search via Ovid for Level I, Level II, and Level III studies

#	Concept	Search string	Results 11 Aug 2018	Results 09 Aug 2019	Results 29 Sep 2021
1	Population (critical bleeding)	exp *hemorrhage/	5596	5874	6393
2		oral hemorrhage/ or postoperative hemorrhage/ or peptic ulcer hemorrhage/ or gastrointestinal hemorrhage/ or uterine hemorrhage/ or obstetric hemorrhage/ or antepartum hemorrhage/ or intrapartum hemorrhage/ or postpartum hemorrhage/	4093	4308	4772
3		*shock/ or hemorrhagic shock/ or hypovolemic shock/ or traumatic shock/ or exsanguination/ or hemorrhagic hypotension/	467	523	738
4		((hemorrhag* or haemorrhag* or bleed* or bleeding or blood?loss* or 'blood-loss*' or bloodloss*) adj3 (critical or severe or massive or major or life threatening or 'life?threatening')).mp.	7113	9170	11095
5		((haemorrhagic or hemorrhagic or hypovolemic or hypovolaemic) adj shock).ti,ab.	250	334	427
6		or/1-5	14067	16557	19403
7	Population (receiving transfusion)	exp *blood transfusion/ or Erythrocyte Transfusion/	1086	1134	1257
8		blood autotransfusion/ or blood component therapy/ or plasma transfusion/ or thrombocyte transfusion/ or Platelet Transfusion/ or Blood Component Transfusion/	429	447	504
9		(blood component adj (transfus* or therapy)).ti,ab,kw.	83	108	142
10		or/7-9	1412	1498	1679
11	Combine population sets	6 or 10	15179	17732	20711
12	Population (trauma)	Multiple Trauma/	216	220	238
13		trauma*.ab,ti,kw.	16456	22408	28485
14		(polytrauma* or poly?trauma* or 'poly trauma').ab,ti,kw.	145	187	224
15		(multitrauma* or multi?trauma* or 'multi trauma').ab,ti,kw.	18	29	38
16		'multiple trauma*'.ab,ti,kw.	287	409	480
17		blunt trauma/	0	0	0
18		traumatic hematoma/	0	0	0
19		exp amputation, traumatic/	44	47	59
20		or/12-19	16607	22575	28671
21	Population (wounds)	exp wounds, nonpenetrating/	592	639	806
22		exp wounds, penetrating/	346	356	34
23		surgical wound/	87	158	288
24		wound hemorrhage/	0	0	0
25		or/21-24	987	1113	1426
26	Population (injury)	*injury/	0	0	0
27		exp blast injuries/	20	20	21
28		exp abdominal injuries/	131	138	148
29		exp thoracic injuries/	347	389	542
30		exp war-related injuries/	0	0	0
31		childhood injury/ or contusion/ or crush trauma/ or limb injury/	109	112	128
32		organ injury/ or reperfusion injury/	474	503	597

#	Concept	Search string	Results 11 Aug 2018	Results 09 Aug 2019	Results 29 Sep 2021
33		surgical injury/	1587	1650	1785
34		gunshot injury/	0	0	0
35		accidental injury/	0	0	0
36		battle injury/	0	0	0
37		or/26-36	2642	2784	3192
38	Population (emergency)	*accidents/	2	0	0
39		*emergency/	0	0	0
40		((major* or life threatening or life?threatening or substantial* or multip* or severe* or serious* or catastrophic* or critical* or massive* or penetrating) adj3 (trauma* or injur* or emergenc* or accident*)).ti,ab.	5259	6848	8470
41		or/38-40	5261	6848	8470
42	Combine trauma/ emergency sets	20 or 25 or 37 or 41	21939	28817	36237
43	Population (operative)	transplantation/	45	44	44
44		emergency surgery/ or general surgery/ or major surgery/	366	377	407
45		*surgery/ or abdominal surgery/ or cardiovascular surgery/ or thorax surgery/ or orthopedic surgery/	362	376	401
46		pediatric surgery/ or obstetrics/ or obstetric care/	174	185	215
47		(peri?operative or pre?operative or intra?operative or post?operative).ti,ab,kw.	85052	110381	135015
48		(surg* or operat* or resect* or perioperat*).ab,ti,kw.	185786	253065	310941
49		exp operative blood loss/	0	0	0
50		peroperative care/	1501	1566	1689
51		peroperative complication/ or postoperative complication/ or preoperative complication/	774	17118	18715
52		exp perioperative period/	7495	8024	9031
53		exp preoperative period/	220	251	345
54		or/43-53	203716	276125	336969
55	Combine population sets	42 or 54	217925	294282	359909
56	Combine population sets (bleeding AND trauma/surgery or emergency)	11 and 55	5712	6888	8039
57	Prognostic factor (acid-base status)	acidosis/ or acidosis.ti,ab,kw.	1562	2156	2596
58		*alkalosis/	4	0	1
59		blood pH/	0	0	0
60		acid base balance/ or (acid base balance or acid?base balance).ti,ab,kw.	718	826	937
61		base excess.ti,ab,kw.	353	464	569
62		anion gap/ or urea blood level/ or uric acid blood level/	423	428	440
63		bicarbonate blood level/	0	0	0
64		lactate blood level/	0	0	0
65		calcium blood level/ or calcium level?.ti,ab,kw.	643	820	964
66		(ioni?ed calcium or hypocalc?emia or anion gap).ti,ab,kw.	960	1319	1608
67		or/57-66	3669	4881	5852
68	Prognostic factor (temperature)	exp Body Temperature/	3833	3953	4171
69		Body Temperature Regulation/	788	810	849
70		Hypothermia/	542	585	740
71		(body temperatur$ or thermoregulat$ or hypothermi$).ab,ti,kw.	5605	7673	9463
72		or/68-71	8143	10243	12150
73		vital signs/ or vital sign*.ti,ab,kw.	5406	11854	15864

#	Concept	Search string	Results 11 Aug 2018	Results 09 Aug 2019	Results 29 Sep 2021
74	Prognostic factor (vital signs)	heart rate/ or ('heart rate*' or 'pulse rate*').ab,ti,kw.	44113	55319	64786
75		Respiratory Rate/ or ('respiratory rate*' or 'respiration rate*').ab,ti,kw.	3411	5305	7031
76		*Blood Pressure/	0	0	0
77		systolic blood pressure/ or 'systolic blood pressure'.ab,ti,kw.	13119	18811	23085
78		shock index.ti,ab,kw.	31	50	72
79		or/73-78	58069	78855	95106
80	Prognostic factor (INR/ APTT/ PTT)	international normalized ratio/	486	502	530
81		activated partial thromboplastin time/	487	495	509
82		partial thromboplastin time/	487	495	509
83		prothrombin time/	454	459	468
84		prothrombin time.ti,ab,kw.	1299	1793	2121
85		international normali?ed ratio.ti,ab,kw.	1593	2131	2578
86		partial thromboplastin time.ti,ab,kw.	1218	1581	1852
87		(PT?INR or INR).ti,ab,kw.	1482	2385	2954
88		(APTT or PTT).ti,ab,kw.	978	1507	1804
89		or/80-88	4407	6220	7394
90	Prognostic factor (fibrinogen)	exp fibrinogen blood level/	0	0	0
91		(fibrinogen adj3 level).ti,ab,kw.	413	549	632
92	Prognostic factor (haemoglobin)	*hemoglobin/	0	3	1
93		hemoglobin determination/	0	0	0
94		hemoglobin blood level/	1	1	1
95		(h?emoglobin adj3 level).ti,ab,kw.	3370	4987	6322
96		(blood adj2 marker?).ti,ab,kw.	953	1430	2070
97	Prognostic factor (platelet count)	platelet count/	1210	1236	1290
98		"platelet count?".ti,ab,kw.	3287	5868	7220
99	Prognostic factor (haematocrit)	h?ematocrit.ti,ab,kw.	3683	4840	5725
100		"hematocrit"/	1505	1518	1556
101	Combine prognostic factors	or/90-100	12098	17609	21653
102		67 or 72 or 79 or 89 or 101	82401	111720	134472
103	Combine population & prognostic factors	56 and 102	1136	1404	1647
104	Level I	exp meta analysis/ or meta analysis.mp. or exp systematic review/ or systematic review.mp. or pooled analysis.mp. or ((exp review/ or review.mp.) and (systemat* or pool*).mp.)	68287	85895	NA
105	Level II	exp comparative study/ or comparative study.mp. or exp clinical trial/ or clinical trial.mp. or randomized controlled trial.mp. or randomi?ed controlled trial.mp. or exp randomized controlled trial/ or exp randomization/ or randomization.mp. or randomi?ation.mp. or exp single blind procedure/ or single blind procedure.mp. or exp double blind procedure/ or double blind procedure.mp. or exp triple blind procedure/ or triple blind procedure.mp. or exp crossover procedure/ or crossover procedure.mp. or exp placebo/ or placebo*.mp. or random*.mp. or rct.mp. or single blind.mp. or single blinded.mp. or double blind.mp. or double blinded.mp. or treble blind.mp. or triple blind.mp. or triple blinded.mp. or exp prospective study/ or prospective study.mp.	954339	1200427	NA
106	Level III	exp clinical study/ or exp case control study/ or exp family study/ or exp longitudinal study/ or exp retrospective study/ or exp cohort analysis/ or (cohort adj1 stud*).mp. or (case control adj1 stud*).mp. or (exp prospective study/ not randomi?ed controlled trials.mp.) or (follow up adj1 stud*).mp. or (observational adj1 stud*).mp. or (epidemiologic* adj1 stud*).mp. or (cross sectional adj1 stud*).mp.	192541	208994	NA

#	Concept	Search string	Results 11 Aug 2018	Results 09 Aug 2019	Results 29 Sep 2021
107	Level IV	case report/	3	4	NA
108	publication type	(editorial or letter or comment or historical article).pt.	7477	8014	NA
109	Combine Level IV & publication type	107 or 108	7480	8018	NA
110	nonhuman study	(animals/ not humans/) or nonhuman/	25	27	NA
111	Level I	(103 and 104) not (108 or 110)	25	37	NA
112	Level II	(103 and 105) not (109 or 110 or 111)	1014	1239	NA
113	Level III	(103 and 106) not (109 or 110 or 111 or 112)	20	19	NA
114	Level I [2019 update]	limit 111 to yr="2018 -Current" [Limit not valid in DARE; records were retained]	NA	3	NA
115	Level II [2019 update]	limit 112 to yr="2018 -Current" [Limit not valid in DARE; records were retained]	NA	91	NA
116	Level III [2019 update]	limit 113 to yr="2018 -Current" [Limit not valid in DARE; records were retained]	NA	0	NA
114	Level I [2021 update]	limit 111 to yr="2019 -Current" [Limit not valid in DARE; records were retained]	NA	NA	NA
115	Level II [2021 update]	limit 112 to yr="2019 -Current" [Limit not valid in DARE; records were retained]	NA	NA	NA
116	Level III [2021 update]	limit 113 to yr="2019 -Current" [Limit not valid in DARE; records were retained]	NA	NA	NA

NA, not applicable

A1.4 PubMed

The PubMed search was restricted to records that are not indexed for MEDLINE (i.e. in-process citations and citations from journals (or parts of journals) that are not currently MEDLINE-indexed) and to records added to PubMed since January 2006. The search comprises free-text terms only and replicates the free-text sets in the Embase search (converted from the Ovid syntax).

Table A1.4 Literature search results: PubMed (in-process and citations not indexed in MEDLINE)

#	Concept	Search string	Results 11 Aug 2018	Results 09 Aug 2019	Results 29 Sep 2021
1	Population (critical bleeding)	(hemorrhag* [tiab] or haemorrhag*[tiab])	241643	253540	282605
2		((hemorrhag*[tiab] or haemorrhag*[tiab] or bleed*[tiab] or blood loss*[tiab] or blood-loss*[tiab] or bloodloss*[tiab]) AND (critical[tiab] or severe[tiab] or massive[tiab] or major[tiab] or life threatening[tiab] or serious[tiab] or significant[tiab] or substantial[tiab] or extreme[tiab] or catastrophic[tiab] or uncontrol*[tiab] or excess[tiab] or acute[tiab]))	210667	224755	260332
3		(#1 or #2)	336581	355647	402828
4	Population (blood transfusion)	(blood transfusion[tiab] or erythrocyte transfusion[tiab])	37024	38938	43511
5		(blood autotransfusion[tiab] or blood component therapy[tiab] or plasma transfusion[tiab] or thrombocyte transfusion[tiab] or platelet transfusion[tiab] or blood component transfusion[tiab] or blood component therapy[tiab])	3941	4218	5021
6		(#4 or #5)	40603	42760	48034
7	Combine population (critical bleeding requiring transfusion)	(#3 or #6)	369057	389613	440444

#	Concept	Search string	Results 11 Aug 2018	Results 09 Aug 2019	Results 29 Sep 2021
8	Population (trauma)	(trauma[tiab] or poly trauma[tiab] or polytrauma[tiab] or multitrauma[tiab] or multi trauma[tiab] or multiple trauma[tiab] or multiple wounds[tiab] or multiple wound[tiab] or multiple injuries[tiab] or multiple injury[tiab])	208879	222596	258022
9		blunt trauma[tiab]	8507	8895	9870
10		(traumatic[tiab] AND (hematoma[tiab] or haematoma[tiab] or shock[tiab] or amputation[tiab]))	10127	10704	12215
11		(#8 or #9 or #10)	215719	229772	266053
12	Population (injury)	((wounds[tiab] or wound[tiab]) AND (nonpenetrating[tiab] or penetrating[tiab] or surgical[tiab] or haemorrhage[tiab]))	40069	42749	49304
13		(injur*[tiab] AND (blast[tiab] or abdominal[tiab] or thorax[tiab] or thoracic[tiab] or war related[tiab] or childhood[tiab] or limb[tiab] or organ[tiab] or reperfusion[tiab] or surgical[tiab] or gunshot[tiab] or accidental[tiab] or battle[tiab]))	168019	179723	209878
14		((major[tiab] or life threatening[tiab] or substantial[tiab] or multiple[tiab] or severe[tiab] or serious[tiab] or catastrophic[tiab] or critical[tiab] or catastrophic[tiab] or massive[tiab] or penetrating[tiab]) AND (trauma[tiab] or traumatic[tiab] or injury[tiab] or injuries[tiab] or injured[tiab] or emergency[tiab] or emergencies[tiab] or accident[tiab]))	310545	334769	403486
15	Combine population (trauma and injury)	(#11 or #12 or #13 or #14)	575427	616844	728977
16	Population (surgery)	transplantation[tiab]	323592	340034	379116
17		(surgery[tiab] AND emergency[tiab] or general[tiab] or major[tiab])	2064741	2190063	2501722
18		(surgery[tiab] or abdominal surgery[tiab] or cardiovascular surgery[tiab] or thorax surgery[tiab] or (orthopaedic[tiab] or orthopedic[tiab] AND surgery[tiab]))	1094138	1162150	1334226
19		((pediatric[tiab] or paediatric[tiab] AND surgery[tiab]) or obstetrics[tiab] or maternity[tiab])	80495	86638	102062
20		((peroperative[tiab] or intraoperative[tiab] or intra operative[tiab] or postoperative[tiab] or post operative[tiab] or preoperative[tiab] or pre operative[tiab]) AND complication[tiab])	57438	62721	76407
21		perioperative[tiab]	78631	86169	111758
22		(#16 or #17 or #18 or #19 or #20 or #21)	3365441	3567502	4072467
23	Combine population (Trauma and injury and surgery)	(#15 or #22)	3748283	3976846	4554098
24	Combine population (critically bleeding with transfusion and trauma, injury, or surgery)	(#7 AND #23)	138385	148195	172976
25	Prognostic factor (acid-base status)	(acidosis[tiab] or acidoses[tiab] or ((acidosis[tiab] or acidoses[tiab]) AND (metabolic[tiab] or respiratory[tiab])))	34167	35407	38376
26		(alkalosis[tiab] or alkaloses[tiab] or ((alkalosis[tiab] or alkaloses[tiab]) AND (metabolic[tiab] or respiratory[tiab])))	5682	5819	6196
27		blood pH[tiab]	3620	3736	4049
28		((acid base[tiab] or acidbase[tiab]) AND (balance[tiab] or imbalance[tiab]))	5254	5410	5820
29		base excess[tiab]	2793	2901	3165

#	Concept	Search string	Results 11 Aug 2018	Results 09 Aug 2019	Results 29 Sep 2021
30		((blood levels[tiab] AND (bicarbonate[tiab] or lactate[tiab] or calcium[tiab])))	991	1037	1116
31	Prognostic factor (ionised calcium)	(ionised calcium[tiab] or ionized calcium[tiab] or hypocalcemia[tiab] or hypocalcaemia[tiab])	14234	14949	1672
32		anion gap[tiab]	1756	1885	2215
33	Combine prognostic factors (acid-base status and ionised calcium)	(#25 or #26 or #27 or #28 or #29 or #30 or #31 or #32)	60560	62918	68697
34	Prognostic factor (temperature)	(body temperature[tiab] or body temperature regulation[tiab])	29425	30681	33886
35		(hypothermi*[tiab] or thermoregulat*[tiab])	50357	52284	56798
36		(#34 or #35)	73007	75916	82937
37	Prognostic factor (vital signs)	vital sign*[tiab]	12147	13397	16887
38		(heart rate[tiab] or pulse rate[tiab])	149637	155905	171240
39		respiratory rate*[tiab]	13347	14067	16372
40		(blood pressure[tiab] or systolic blood pressure[tiab])	279734	291840	320935
41		shock index[tiab]	464	539	774
42		(#37 or #38 or #39 or #40 or #41)	390453	408370	452482
43	Prognostic factor (INR/ APTT/ PTT)	(international normalized ratio[tiab] or INR[tiab] or international normalised ratio[tiab])	11003	11883	13976
44		(activated partial thromboplastin time[tiab] or partial thromboplastin time[tiab])	9222	9730	10921
45		prothrombin time[tiab]	11760	12318	13725
46		(PTINR[tiab] or PT INR[tiab])	440	484	666
47		(#43 or #44 or #45 or #46)	25302	26800	30454
48	Prognostic factor (fibrinogen)	(fibrinogen blood level[tiab] or (fibrinogen[tiab] AND level[tiab]))	5938	6185	6983
49	Prognostic factor (haemoglobin)	(hemoglobin[tiab] or haemoglobin[tiab])	142934	150978	170828
50		((hemoglobin[tiab] or haemoglobin[tiab]) AND (determination[tiab] or blood level[tiab]))	4531	4629	4980
51		((hemoglobin[tiab] or haemoglobin[tiab]) AND level[tiab])	27634	29684	34611
52		(blood[tiab] AND marker[tiab])	43028	45640	52016
53	Prognostic factor (platelet count)	platelet count[tiab]	21224	22531	26165
54	Prognostic factor (haematocrit)	(hematocrit[tiab] or haematocrit[tiab] or PRBC[tiab] (packed[tiab] AND red[tiab] AND cell[tiab] AND volume[tiab]))	169	190	224
55	Combine prognostic factors	(#47 or #48 or #49 or #50 or #51 or #52 or #53 or #54)	783534	832006	274882
56		(#33 or #36 or #42 or #47 or #55)	1256525	1327453	840837
57	Combine population and prognostic factors	(#24 AND #56)	22376	24139	21270
58	Limit to publications not indexed in Medline	(#57 AND pubmednotmedline[sb])	1632	1933	2273
59	Date limit [2019 update]	Search ("2018/01/01"[Date - Entrez] : "3000"[Date - Entrez])	NA	1912188	NA
	Date limit [2021 update]	Search ("2019/01/01"[Date - Entrez] : "3000"[Date - Entrez])	NA	NA	3823374

#	Concept	Search string	Results 11 Aug 2018	Results 09 Aug 2019	Results 29 Sep 2021
60	Date limit [2019 update]	Search ((#58 AND #59))	NA	411	NA
	Date limit [2021 update]	Search ((#58 AND #59))	NA	NA	19

A2 Questions 2, 3, 4, & 6

A2.1 Embase

Table A2.1 Literature search results: Embase <1974 to August, 2019>

Search via Ovid for Level I, Level II, and Level III studies

#	Concept	Searches	Results 07 Aug 2018	Results 05 Aug 2019	Results 29 Sep 2021
1	Population (critical bleeding)	exp *hemorrhage/	264457	247796	316767
2		oral hemorrhage/ or postoperative hemorrhage/ or peptic ulcer hemorrhage/ or gastrointestinal hemorrhage/ or uterine hemorrhage/ or obstetric hemorrhage/ or antepartum hemorrhage/ or intrapartum hemorrhage/ or postpartum hemorrhage/	105730	113963	141169
3		*shock/ or hemorrhagic shock/ or hypovolemic shock/ or traumatic shock/ or exsanguination/	37198	30797	43020
4		((hemorrhag* or haemorrhag* or bleed* or bleeding or blood?loss* or 'blood-loss*' or bloodloss*) adj3 (critical or severe or massive or major or life threatening or life?threatening or serious* or significant* or substantial* or extreme or catastrophic or uncontroll* or excessive* or acute*)).ti,ab.	110082	114148	143033
5		((haemorrhagic or hemorrhagic or hypovolemic or hypovolaemic) adj shock).ti,ab.	15760	14639	18865
6		1 or 2 or 3 or 4 or 5	417363	409235	521482
7	Population (receiving transfusion)	exp *blood transfusion/ or erythrocyte transfusion/	72777	72374	87757
8		blood autotransfusion/ or blood component therapy/ or plasma transfusion/ or thrombocyte transfusion/ or Platelet Transfusion/ or Blood Component Transfusion/	29285	31754	37237
9		(blood component adj (transfus* or therapy)).ti,ab,kw.	961	1043	1074
10		or/7-9	87183	88181	106754
11	Combine population sets	6 or 10	490993	482130	609692
12	Population (trauma)	multiple trauma/	12980	13976	16062
13		trauma*.ab,ti,kw.	439540	443788	553681
14		(polytrauma* or poly?trauma* or 'poly trauma').ab,ti,kw.	5185	5928	7031
15		(multitrauma* or multi?trauma* or 'multi trauma').ab,ti,kw.	631	708	790
16		'multiple trauma*'.ab,ti,kw.	4320	4589	5137
17		blunt trauma/	16900	18324	21158
18		traumatic hematoma/	284	267	381
19		exp amputation, traumatic/	1995	1951	2346
20		Or/12-19	449851	454651	566134
21	Population (wounds)	exp wounds, nonpenetrating/	23980	25843	29410
22		exp wounds, penetrating/	11518	11865	14126
23		surgical wound/	5870	6516	8324
24		wound hemorrhage/	178	218	264
25		Or/21-24	38878	41368	48641
26	Population (injury)	*injury/	69500	59507	78858
27		exp blast injuries/	4021	4167	5098
28		exp abdominal injuries/	147300	149779	188227

#	Concept	Searches	Results 07 Aug 2018	Results 05 Aug 2019	Results 29 Sep 2021
29		exp thoracic injuries/	73827	73681	95598
30		exp war-related injuries/	4435	4285	5490
31		childhood injury/ or contusion/ or crush trauma/ or limb injury/	22988	24456	30675
32		organ injury/ or reperfusion injury/	52068	58786	64489
33		surgical injury/	4740	4401	5641
34		gunshot injury/	17223	16448	20854
35		accidental injury/	2772	3458	4260
36		battle injury/	4435	4285	5490
37		or/26-36	366858	366762	459124
38	Population (emergency)	*accidents/	12166	8481	13057
39		*emergency/	15014	13564	15727
40		((major* or life threatening or life?threatening or substantial* or multip* or severe* or serious* or catastrophic* or critical* or massive* or penetrating) adj3 (trauma* or injur* or emergenc* or accident*)).ti,ab.	121434	128045	154996
41		Or/38-40	146638	148426	181621
42	Combine trauma/ emergency sets	20 or 25 or 37 or 41	817012	822552	1027508
43	Population (operative)	transplantation/	172910	148673	186111
44		emergency surgery/ or general surgery/ or major surgery/	39266	42675	55124
45		*surgery/ or abdominal surgery/ or cardiovascular surgery/ or thorax surgery/ or orthopedic surgery/	237341	199212	265866
46		pediatric surgery/ or obstetrics/ or obstetric care/	57815	57298	70545
47		(peri?operative or pre?operative or intra?operative or post?operative).ti,ab,kw.	839491	907486	1093613
48		(surg* or operat* or resect* or perioperat*).ab,ti,kw.	3369061	3432946	4254459
49		exp operative blood loss/	11239	19689	28478
50		peroperative care/	10759	12395	13795
51		peroperative complication/ or postoperative complication/ or preoperative complication/	322591	341263	417331
52		exp perioperative period/	36409	45972	57028
53		exp preoperative period/	258060	295673	364040
54		Or/43-53	3925690	3966686	4916589
55	Combine population sets	42 or 54	4492341	4532517	5627461
56	Combine population sets (bleeding AND trauma/surgery or emergency)	11 and 55	175318	183357	225425
57	Intervention (MHP)	(massive transfusion$ or blood transfusion$ or blood component$ or blood component transfusion).ti,ab,kw.	76345	76272	95628
58		(massive transfusion adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	571	722	931
59		(massive h?emorrhage adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	57	70	97
60		(massive bleed$ adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	5	5	9

#	Concept	Searches	Results 07 Aug 2018	Results 05 Aug 2019	Results 29 Sep 2021
61		(major h?emorrhage adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	72	91	119
62		(major transfusion adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	4	4	5
63		(major bleed$ adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	5	5	7
64		(critical bleed$ adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	3	3	9
65		(critical h?emorrhage adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	0	0	0
66		((erythrocyte* or red blood cell* or rbc or red cell* or packed cell? or prbc) adj5 transfus*).mp.	33615	38684	46929
67		(MTP? or MHP?).ti,ab,kw.	8203	9130	10499
68		Or/57-67	110367	115333	142410
69	Intervention (RBC transfusion)	blood transfusion/ or erythrocyte transfusion/	135171	136410	171827
70		((erythrocyte* or red blood cell* or rbc or red cell* or packed cell? or prbc) adj5 transfus*).ti,ab,kw.	21187	23427	28569
71	Intervention (blood component)	blood component therapy/ or plasma transfusion/ or thrombocyte transfusion/ or Platelet Transfusion/ or Blood Component Transfusion/	21169	23527	28355
72		((blood component or blood product) adj3 (therap* or transfus*)).ti,ab,kw.	2866	3271	3806
73		Or/69-72	157206	160147	200621
74		fresh frozen plasma/	13459	16158	18871
75		((plasma adj1 (fresh or frozen or thawed or liquid)) or ffp).ti,ab,kw.	12834	13890	16186
76		Cryoprecipitate/	3737	4247	5246
77		(cryoprecipitate or cryo?precipitate or cryo precipitate).ti,ab,kw.	3323	3458	4213
78		*fibrinogen/ad, tu, dt, iv	423	381	457
79		fibrinogen concentrate/	624	894	1143
80		(fibrinogen adj (concentrate or infusion)).ti,ab,kw.	647	803	1001
81		(clotting adj ('Factor 1' or 'Factor I')).ti,ab,kw.	2	2	2
82		(RiaSTAP or Clottagen* or Fibrorass* or Haemocomplettan).mp.	213	256	294
83		((platelet* or thrombocyt*) adj3 (infus* or therap* or transfus*)).ti,ab,kw.	17897	19388	23210
84		(plasma adj2 (infusion or transfusion)).ti,ab,kw.	5091	4960	6014
85		Or/74-84	43840	48051	57070
86	Intervention (PCC)	activated prothrombin complex concentrate/	1896	2181	2479
87		prothrombin complex/	3617	4136	5086
88		*prothrombin/ad, tu, dt, th	68	52	72
89		(activated prothrombin or APCC or coagulation factor concentrate).ti,ab,kw.	1207	1398	1626
90		('prothrombin complex concentrate' or PCC).ti,ab,kw.	11759	13564	16076
91		(Beriplex* or Octaplex* or Cofact or Prothrombinex* or Proplex* or Prothroraas* or Haemosolvex* or Profiline* or Prothromplex* or Bebulin* or "HT Defix" or Facnyne* or "PPSB-Human" or "UMAN Complex" or Kaskadil*).mp.	845	937	992
92		37224-63-8.rn.	2579	3341	4048
93		Or/86-92	15763	18089	21499

#	Concept	Searches	Results 07 Aug 2018	Results 05 Aug 2019	Results 29 Sep 2021
94	Population AND MHP	56 and 68	23436	26798	32155
95	Population AND RBC or blood component transfusion	56 and (73 or 85)	34534	39031	46927
96	Population AND PCC	56 and 93	1464	1794	2199
97	Level I	exp meta analysis/ or meta analysis.mp. or exp systematic review/ or systematic review.mp. or pooled analysis.mp. or ((exp review/ or review.mp.) and (systemat* or pool*).mp.)	383415	486774	644343
98	Level II	exp comparative study/ or comparative study.mp. or exp clinical trial/ or clinical trial.mp. or randomized controlled trial.mp. or randomi?ed controlled trial.mp. or exp randomized controlled trial/ or exp randomization/ or randomization.mp. or randomi?ation.mp. or exp single blind procedure/ or single blind procedure.mp. or exp double blind procedure/ or double blind procedure.mp. or exp triple blind procedure/ or triple blind procedure.mp. or exp crossover procedure/ or crossover procedure.mp. or exp placebo/ or placebo*.mp. or random*.mp. or rct.mp. or single blind.mp. or single blinded.mp. or double blind.mp. or double blinded.mp. or treble blind.mp. or triple blind.mp. or triple blinded.mp. or exp prospective study/ or prospective study.mp.	3810895	4252502	5010112
99	Level III	exp clinical study/ or exp case control study/ or exp family study/ or exp longitudinal study/ or exp retrospective study/ or exp cohort analysis/ or (cohort adj1 stud*).mp. or (case control adj1 stud*).mp. or (exp prospective study/ not randomi?ed controlled trials.mp.) or (follow up adj1 stud*).mp. or (observational adj1 stud*).mp. or (epidemiologic* adj1 stud*).mp. or (cross sectional adj1 stud*).mp.	8710809	9670551	11450592
100	Level IV	case report/	2266240	2385838	2761122
101	Publication type	(editorial or letter or comment or historical article).pt.	1498639	1706347	1897012
102		100 or 101	3577425	3881337	4433250
103	Not animals	(animals/ or nonhuman/) not humans/	5827837	6154954	6860196
104	Level I (MHP)	(94 and 97) not (101 or 103)	802	1043	1368
105	Level II	(94 and 98) not (102 or 103 or 104)	5335	6364	7397
106	Level III	(94 and 99) not (102 or 103 or 104 or 105)	6666	8157	9946
107	Level I (RBC and blood components)	(95 and 97) not (101 or 103)	1127	1480	1917
108	Level II	(95 and 98) not (102 or 103 or 104)	7713 [a]	9058	10552
109	Level III	(95 and 99) not (102 or 103 or 104 or 105)	10945	13329	16152
110	Level I (PCC)	(96 and 97) not (101 or 103)	55	77	104
111	Level II	(96 and 98) not (102 or 103 or 104)	370	458	551
112	Level III	(96 and 99) not (102 or 103 or 104 or 105)	435	542	736
113	Level I (MHP) [2019 update]	limit 104 to yr="2018 -Current"	NA	181	NA
114	Level II [2019 update]	limit 105 to yr="2018 -Current"	NA	769	NA
115	Level III [2019 update]	limit 106 to yr="2018 -Current"	NA	1160	NA
116	Level I (RBC and blood component transfusion) [2019 update]	limit 107 to yr="2018 -Current"	NA	238	NA

#	Concept	Searches	Results 07 Aug 2018	Results 05 Aug 2019	Results 29 Sep 2021
117	Level II [2019 update]	limit 108 to yr="2018 -Current"	NA	1041	NA
118	Level III [2019 update]	limit 109 to yr="2018 -Current"	NA	1709	NA
119	Level I (PCC) [2019 update]	limit 110 to yr="2018 -Current"	NA	13	NA
120	Level II [2019 update]	limit 111 to yr="2018 -Current"	NA	49	NA
121	Level III [2019 update]	limit 112 to yr="2018 -Current"	NA	81	NA
	Level I (MHP) [2021 update]	limit 104 to yr="2019 -Current"	NA	NA	398
	Level II [2021 update]	limit 105 to yr="2019 -Current"	NA	NA	1351
	Level III [2021 update]	limit 106 to yr="2019 -Current"	NA	NA	2250
	Level I (RBC and blood component transfusion) [2021 update]	limit 107 to yr="2019 -Current"	NA	NA	524
	Level II [2021 update]	limit 108 to yr="2019 -Current"	NA	NA	1883
	Level III [2021 update]	limit 109 to yr="2019 -Current"	NA	NA	3448
	Level I (PCC) [2021 update]	limit 110 to yr="2019 -Current"	NA	NA	32
	Level II [2021 update]	limit 111 to yr="2019 -Current"	NA	NA	106
	Level III [2021 update]	limit 112 to yr="2019 -Current"	NA	NA	215

a. Due to a technical error in exporting citations from Embase via OVID, the literature search for Level II evidence of RBC and blood component transfusion was repeated on 16 Oct 2018.

A2.2 Medline

Table A2.2 Literature search results: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to August, 2019

Search via Ovid for Level I, Level II, and Level III studies

#	Concept	Searches	Results 07 Aug 2018	Results 05 Aug 2019	Results 29 Sep 2021
1	Population (critical bleeding)	exp *hemorrhage/	197317	206514	222453
2		oral hemorrhage/ or postoperative hemorrhage/ or peptic ulcer hemorrhage/ or gastrointestinal hemorrhage/ or uterine hemorrhage/ or obstetric hemorrhage/ or antepartum hemorrhage/ or intrapartum hemorrhage/ or postpartum hemorrhage/	70627	72945	77959
3		*shock/ or hemorrhagic shock/ or hypovolemic shock/ or traumatic shock/ or exsanguination/	30463	31054	32457
4		((hemorrhag* or haemorrhag* or bleed* or bleeding or blood?loss* or 'blood-loss*' or bloodloss*) adj3 (critical or severe or massive or major or life threatening or life?threatening or serious* or significant* or substantial* or extreme or catastrophic or uncontroll* or excessive* or acute*)).ti,ab.	72182	76508	87383
5		((haemorrhagic or hemorrhagic or hypovolemic or hypovolaemic) adj shock).ti,ab.	11517	11988	13051
6		1 or 2 or 3 or 4 or 5	283562	296538	323109

#	Concept	Searches	Results 07 Aug 2018	Results 05 Aug 2019	Results 29 Sep 2021
7	Population (receiving transfusion)	exp *blood transfusion/ or erythrocyte transfusion/	49321	50863	54188
8		blood autotransfusion/ or blood component therapy/ or plasma transfusion/ or thrombocyte transfusion/ or Platelet Transfusion/ or Blood Component Transfusion/	9971	10352	11226
9		(blood component adj (transfus* or therapy)).ti,ab,kw.	542	563	634
10		7 or 8 or 9	52186	53856	57492
11	Combine population sets	6 or 10	328502	342779	372136
12	Population (trauma)	multiple trauma/	12039	12407	13031
13		trauma*.ab,ti,kw.	323568	343560	395691
14		(polytrauma* or poly?trauma* or 'poly trauma').ab,ti,kw.	3881	4177	4960
15		(multitrauma* or multi?trauma* or 'multi trauma').ab,ti,kw.	478	512	562
16		'multiple trauma*'.ab,ti,kw.	3360	3513	3907
17		blunt trauma/	0	0	0
18		traumatic hematoma/	0	0	0
19		exp amputation, traumatic/	4528	4645	4898
20		12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	331994	352205	404771
21	Population (wounds)	exp wounds, nonpenetrating/	34311	35783	39630
22		exp wounds, penetrating/	34530	35434	37426
23		surgical wound/	339	634	1192
24		wound hemorrhage/	0	0	0
25		21 or 22 or 23 or 24	66087	68683	74929
26	Population (injury)	*injury/	54111	56034	60286
27		exp blast injuries/	3948	4125	4495
28		exp abdominal injuries/	19662	20060	20856
29		exp thoracic injuries/	25200	26143	28707
30		exp war-related injuries/	222	327	504
31		childhood injury/ or contusion/ or crush trauma/ or limb injury/	4706	4822	5053
32		organ injury/ or reperfusion injury/	24384	25703	29087
33		surgical injury/	30031	31024	32941
34		gunshot injury/	0	0	0
35		accidental injury/	0	0	151
36		battle injury/	0	0	0
37		26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	155779	161590	175135
38	Population (emergency)	*accidents/	12902	13018	13244
39		*emergency/	12118	12508	13441
40		((major* or life threatening or life?threatening or substantial* or multip* or severe* or serious* or catastrophic* or critical* or massive* or penetrating) adj3 (trauma* or injur* or emergenc* or accident*)).ti,ab.	93075	98565	113072
41		38 or 39 or 40	116755	122715	138278
42	Combine trauma/ emergency sets	20 or 25 or 37 or 41	530618	558846	63184
43	Population (operative)	transplantation/	8815	8873	8985
44		emergency surgery/ or general surgery/ or major surgery/	37302	37968	39915
45		*surgery/ or abdominal surgery/ or cardiovascular surgery/ or thorax surgery/ or orthopedic surgery/	47148	48418	57544
46		pediatric surgery/ or obstetrics/ or obstetric care/	21312	21915	23535
47		(peri?operative or pre?operative or intra?operative or post?operative).ti,ab,kw.	626988	669390	777512
48		(surg* or operat* or resect* or perioperat*).ab,ti,kw.	2485886	2632936	3013591
49		exp operative blood loss/	0	0	0
50		peroperative care/	15858	16364	0

#	Concept	Searches	Results 07 Aug 2018	Results 05 Aug 2019	Results 29 Sep 2021
51		peroperative complication/ or postoperative complication/ or preoperative complication/	355274	370687	404865
52		exp perioperative period/	76525	83182	98007
53		exp preoperative period/	5341	6302	8888
54		43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53	2801924	2960694	3362538
55	Combine population sets	42 or 54	3162893	3340691	3792050
56	Combine population sets (bleeding AND trauma/surgery or emergency)	11 and 55	103100	108528	119841
57	Intervention (MHP)	(massive transfusion$ or blood transfusion$ or blood component$ or blood component transfusion).ti,ab,kw.	51687	54156	60034
58		(massive transfusion adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	283	325	425
59		(massive h?emorrhage adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	12	17	26
60		(massive bleed$ adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	2	3	5
61		(major h?emorrhage adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	13	14	22
62		(major transfusion adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	1	1	1
63		(major bleed$ adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	4	4	5
64		(critical bleed$ adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	1	1	2
65		(critical h?emorrhage adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	0	0	0
66		((erythrocyte* or red blood cell* or rbc or red cell* or packed cell? or prbc) adj5 transfus*).mp.	16572	17630	19871
67		(MTP? or MHP?).ti,ab,kw.	6185	6539	7475
68		57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67	70166	73728	82098
69	Intervention (RBC transfusion)	blood transfusion/ or erythrocyte transfusion/	54429	56248	60241
70		((erythrocyte* or red blood cell* or rbc or red cell* or packed cell? or prbc) adj5 transfus*).ti,ab,kw.	11772	12669	14537
71	Intervention (blood component)	blood component therapy/ or plasma transfusion/ or thrombocyte transfusion/ or Platelet Transfusion/ or Blood Component Transfusion/	9971	10352	11226
72		((blood component or blood product) adj3 (therap* or transfus*)).ti,ab,kw.	1694	1818	2142
73		69 or 70 or 71 or 72	67221	69796	75437
74		fresh frozen plasma/	20921	21584	23760
75		((plasma adj1 (fresh or frozen or thawed or liquid)) or ffp).ti,ab,kw.	7206	7594	8598
76		Cryoprecipitate/	0	0	0
77		(cryoprecipitate or cryo?precipitate or cryo precipitate).ti,ab,kw.	1910	1974	2182
78		*fibrinogen/ad, tu, dt, iv	0	0	1045
79		fibrinogen concentrate/	0	0	0
80		(fibrinogen adj (concentrate or infusion)).ti,ab,kw.	356	400	498
81		(clotting adj ('Factor 1' or 'Factor I')).ti,ab,kw.	0	0	0
82		(RiaSTAP or Clottagen* or Fibrorass* or Haemocomplettan).mp.	22	24	31
83		((platelet* or thrombocyt*) adj3 (infus* or therap* or transfus*)).ti,ab,kw.	10401	10968	12416
84		(plasma adj2 (infusion or transfusion)).ti,ab,kw.	3575	3674	4055
85		74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84	40108	41688	47053
86	Intervention (PCC)	activated prothrombin complex concentrate/	0	0	0
87		prothrombin complex/	0	0	0
88		*prothrombin/ad, tu, dt, th	135	138	143

#	Concept	Searches	Results 07 Aug 2018	Results 05 Aug 2019	Results 29 Sep 2021
89		(activated prothrombin or APCC or coagulation factor concentrate).ti,ab,kw.	610	661	70
90		('prothrombin complex concentrate' or PCC).ti,ab,kw.	9172	9947	11818
91		(Beriplex* or Octaplex* or Cofact or Prothrombinex* or Proplex* or Prothroraas* or Haemosolvex* or Profiline* or Prothromplex* or Bebulin* or "HT Defix" or Facnyne* or "PPSB-Human" or "UMAN Complex" or Kaskadil*).mp.	171	176	184
92		37224-63-8.rn.	936	1009	1189
93		86 or 87 or 88 or 89 or 90 or 91 or 92	9998	10820	12791
94	Population AND MHP	56 and 68	12087	12905	14610
95	Population AND RBC or blood component transfusion	56 and (73 or 85)	14200	15087	17093
96	Population AND PCC	56 and 93	414	448	559
97	Level I	exp meta analysis/ or meta analysis.mp. or exp systematic review/ or systematic review.mp. or pooled analysis.mp. or ((exp review/ or review.mp.) and (systemat* or pool*).mp.)	280162	322370	432608
98	Level II	exp comparative study/ or comparative study.mp. or exp clinical trial/ or clinical trial.mp. or randomized controlled trial.mp. or randomi?ed controlled trial.mp. or exp randomized controlled trial/ or exp randomization/ or randomization.mp. or randomi?ation.mp. or exp single blind procedure/ or single blind procedure.mp. or exp double blind procedure/ or double blind procedure.mp. or exp triple blind procedure/ or triple blind procedure.mp. or exp crossover procedure/ or crossover procedure.mp. or exp placebo/ or placebo*.mp. or random*.mp. or rct.mp. or single blind.mp. or single blinded.mp. or double blind.mp. or double blinded.mp. or treble blind.mp. or triple blind.mp. or triple blinded.mp. or exp prospective study/ or prospective study.mp.	3483178	3631107	3995294
99	Level III	exp clinical study/ or exp case control study/ or exp family study/ or exp longitudinal study/ or exp retrospective study/ or exp cohort analysis/ or (cohort adj1 stud*).mp. or (case control adj1 stud*).mp. or (exp prospective study/ not randomi?ed controlled trials.mp.) or (follow up adj1 stud*).mp. or (observational adj1 stud*).mp. or (epidemiologic* adj1 stud*).mp. or (cross sectional adj1 stud*).mp.	2992198	3195048	3751241
100	Level IV	case report/	1889194	2035776	2213316
101	Publication type	(editorial or letter or comment or historical article).pt.	1975176	2084799	2343470
102		100 or 101	3664177	3910990	4332658
103	Not animals	(animals/ or nonhuman/) not humans/	4448309	4572156	4857428
104	Level I (MHP)	(94 and 97) not (101 or 103)	443	520	675
105	Level II	(94 and 98) not (102 or 103 or 104)	3528	3729	4157
106	Level III	(94 and 99) not (102 or 103 or 104 or 105)	2400	2663	3265
107	Level I (RBC and blood component transfusion)	(95 and 97) not (101 or 103)	477	557	734
108	Level II	(95 and 98) not (102 or 103 or 104)	3924	4163	4707
109	Level III	(95 and 99) not (102 or 103 or 104 or 105)	3471	3808	4608
110	Level I (PCC)	(96 and 97) not (101 or 103)	16	19	24
111	Level II	(96 and 98) not (102 or 103 or 104)	75	81	104
112	Level III	(96 and 99) not (102 or 103 or 104 or 105)	102	115	154
113	Level I (MHP) [2019 update]	limit 104 to yr="2018 -Current"	NA	79	NA
114	Level II [2019 update]	limit 105 to yr="2018 -Current"	NA	232	NA
115	Level III [2019 update]	limit 106 to yr="2018 -Current"	NA	266	NA
116	Level I (RBC and blood component)	limit 107 to yr="2018 -Current"	NA	82	NA

#	Concept	Searches	Results 07 Aug 2018	Results 05 Aug 2019	Results 29 Sep 2021
	[2019 update]				
117	Level II [2019 update]	limit 108 to yr="2018 -Current"	NA	254	NA
118	Level III [2019 update]	limit 109 to yr="2018 -Current"	NA	329	NA
119	Level I (PCC) [2019 update]	limit 110 to yr="2018 -Current"	NA	4	NA
120	Level II [2019 update]	limit 111 to yr="2018 -Current"	NA	9	NA
121	Level III [2019 update]	limit 112 to yr="2018 -Current"	NA	14	NA
	Level I (MHP) [2021 update]	limit 104 to yr="2019 -Current"	NA	NA	185
	Level II [2021 update]	limit 105 to yr="2019 -Current"	NA	NA	456
	Level III [2021 update]	limit 106 to yr="2019 -Current"	NA	NA	631
	Level I (RBC and blood component) [2021 update]	limit 107 to yr="2019 -Current"	NA	NA	191
	Level II [2021 update]	limit 108 to yr="2019 -Current"	NA	NA	539
	Level III [2021 update]	limit 109 to yr="2019 -Current"	NA	NA	781
	Level I (PCC) [2021 update]	limit 110 to yr="2019 -Current"	NA	NA	6
	Level II [2021 update]	limit 111 to yr="2019 -Current"	NA	NA	23
	Level III [2021 update]	limit 112 to yr="2019 -Current"	NA	NA	35

A2.3 EBM Reviews

EBM Reviews combines several resources into a single database and includes the following:

- Cochrane Database of Systematic Reviews (from 2005),
- ACP Journal Club (from 1991),
- Database of Abstracts of Reviews of Effects (from 1st Quarter 2016),
- Cochrane Clinical Answers (from July 2018),
- Cochrane Central Register of Controlled Trials (from June 2018),
- Cochrane Methodology Register (from 3rd Quarter 2012),
- Health Technology Assessment (from 4th Quarter 2016), and
- NHS Economic Evaluation Database (from 1st Quarter 2016)

Table A2.3 Literature search results: EBM Reviews

Search via Ovid for Level I, Level II, and Level III studies

#	Concept	Searches	Results 07 Aug 2018	Results 05 Aug 2019	Results 29 Sep 2021
1	Population (critical bleeding)	exp *hemorrhage/	5624	5851	6393
2		oral hemorrhage/ or postoperative hemorrhage/ or peptic ulcer hemorrhage/ or gastrointestinal hemorrhage/ or uterine hemorrhage/ or obstetric hemorrhage/ or antepartum hemorrhage/ or intrapartum hemorrhage/ or postpartum hemorrhage/	4108	4299	4772

#	Concept	Searches	Results 07 Aug 2018	Results 05 Aug 2019	Results 29 Sep 2021
3		*shock/ or hemorrhagic shock/ or hypovolemic shock/ or traumatic shock/ or exsanguination/	469	517	738
4		((hemorrhag* or haemorrhag* or bleed* or bleeding or blood?loss* or 'blood-loss*' or bloodloss*) adj3 (critical or severe or massive or major or life threatening or life?threatening or serious* or significant* or substantial* or extreme or catastrophic or uncontroll* or excessive* or acute*)).ti,ab.	8623	11039	13467
5		((haemorrhagic or hemorrhagic or hypovolemic or hypovolaemic) adj shock).ti,ab.	259	331	427
6		1 or 2 or 3 or 4 or 5	14977	17732	21031
7	Population (receiving transfusion)	exp *blood transfusion/ or erythrocyte transfusion/	1091	1127	1257
8		blood autotransfusion/ or blood component therapy/ or plasma transfusion/ or thrombocyte transfusion/ or Platelet Transfusion/ or Blood Component Transfusion/	430	444	504
9		(blood component adj (transfus* or therapy)).ti,ab,kw.	84	108	142
10		7 or 8 or 9	1418	1488	1679
11	Combine population sets	6 or 10	16086	18891	22329
12	Population (trauma)	multiple trauma/	216	220	238
13		trauma*.ab,ti,kw.	17202	22220	28485
14		(polytrauma* or poly?trauma* or 'poly trauma').ab,ti,kw.	157	186	224
15		(multitrauma* or multi?trauma* or 'multi trauma').ab,ti,kw.	17	29	38
16		'multiple trauma*'.ab,ti,kw.	293	407	480
17		blunt trauma/	0	0	0
18		traumatic hematoma/	0	0	0
19		exp amputation, traumatic/	45	47	59
20		12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	17357	22386	28671
21	Population (wounds)	exp wounds, nonpenetrating/	600	635	806
22		exp wounds, penetrating/	347	355	374
23		surgical wound/	91	149	288
24		wound hemorrhage/	0	0	0
25		21 or 22 or 23 or 24	1000	1099	1426
26	Population (injury)	*injury/	0	0	0
27		exp blast injuries/	20	20	21
28		exp abdominal injuries/	131	137	148
29		exp thoracic injuries/	350	386	542
30		exp war-related injuries/	0	0	0
31		childhood injury/ or contusion/ or crush trauma/ or limb injury/	109	112	128
32		organ injury/ or reperfusion injury/	474	501	597
33		surgical injury/	1594	1649	1785
34		gunshot injury/	0	0	0
35		accidental injury/	0	0	0
36		battle injury/	0	0	0
37		26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	2652	2778	3192
38	Population (emergency)	*accidents/	1	0	0
39		*emergency/	0	0	0
40		((major* or life threatening or life?threatening or substantial* or multip* or severe* or serious* or catastrophic* or critical* or massive* or penetrating) adj3 (trauma* or injur* or emergenc* or accident*)).ti,ab.	5516	6801	8470
41		38 or 39 or 40	5517	6801	8470
42	Combine trauma/ emergency sets	20 or 25 or 37 or 41	22798	28592	36237
43	Population (operative)	transplantation/	45	44	44
44		emergency surgery/ or general surgery/ or major surgery/	367	377	407

#	Concept	Searches	Results 07 Aug 2018	Results 05 Aug 2019	Results 29 Sep 2021
45		*surgery/ or abdominal surgery/ or cardiovascular surgery/ or thorax surgery/ or orthopedic surgery/	362	376	401
46		pediatric surgery/ or obstetrics/ or obstetric care/	175	185	214
47		(peri?operative or pre?operative or intra?operative or post?operative).ti,ab,kw.	86942	109658	135015
48		(surg* or operat* or resect* or perioperat*).ab,ti,kw.	190371	251390	310941
49		exp operative blood loss/	0	0	0
50		peroperative care/	1505	1564	1698
51		peroperative complication/ or postoperative complication/ or preoperative complication/	774	17071	18715
52		exp perioperative period/	7547	7986	9031
53		exp preoperative period/	223	250	345
54		43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53	208206	274331	336969
55	Combine population sets	42 or 54	222785	292339	359909
56	Combine population sets (bleeding AND trauma/surgery or emergency)	11 and 55	6051	7323	8671
57	Intervention (MHP)	(massive transfusion$ or blood transfusion$ or blood component$ or blood component transfusion).ti,ab,kw.	5555	7435	8977
58		(massive transfusion adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	24	28	45
59		(massive h?emorrhage adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	2	5	10
60		(massive bleed$ adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	1	1	1
61		(major h?emorrhage adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	7	10	16
62		(major transfusion adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	0	0	0
63		(major bleed$ adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	3	4	4
64		(critical bleed$ adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	0	0	0
65		(critical h?emorrhage adj (protocol$ or guid$ or algorith$ or polic$ or strateg$ or practice$)).ti,ab,kw.	0	0	0
66		((erythrocyte* or red blood cell* or rbc or red cell* or packed cell? or prbc) adj5 transfus*).mp.	2978	3676	4364
67		(MTP? or MHP?).ti,ab,kw.	536	665	791
68		57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67	8204	10724	12868
69	Intervention (RBC transfusion)	blood transfusion/ or erythrocyte transfusion/	2417	2492	2697
70		((erythrocyte* or red blood cell* or rbc or red cell* or packed cell? or prbc) adj5 transfus*).ti,ab,kw.	2342	3071	3733
71	Intervention (blood component)	blood component therapy/ or plasma transfusion/ or thrombocyte transfusion/ or Platelet Transfusion/ or Blood Component Transfusion/	430	444	504
72		((blood component or blood product) adj3 (therap* or transfus*)).ti,ab,kw.	257	332	440
73		69 or 70 or 71 or 72	4579	5422	6340
74		fresh frozen plasma/	477	496	571
75		((plasma adj1 (fresh or frozen or thawed or liquid)) or ffp).ti,ab,kw.	856	1089	1316
76		Cryoprecipitate/	0	0	0
77		(cryoprecipitate or cryo?precipitate or cryo precipitate).ti,ab,kw.	142	209	265
78		*fibrinogen/ad, tu, dt, iv	0	0	2
79		fibrinogen concentrate/	0	0	0
80		(fibrinogen adj (concentrate or infusion)).ti,ab,kw.	113	170	215
81		(clotting adj ('Factor 1' or 'Factor I')).ti,ab,kw.	0	0	0

#	Concept	Searches	Results 07 Aug 2018	Results 05 Aug 2019	Results 29 Sep 2021
82		(RiaSTAP or Clottagen* or Fibrorass* or Haemocomplettan).mp.	19	42	55
83		((platelet* or thrombocyt*) adj3 (infus* or therap* or transfus*)).ti,ab,kw.	2616	3748	4459
84		(plasma adj2 (infusion or transfusion)).ti,ab,kw.	924	1024	1178
85		74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84	4635	6075	7187
86	Intervention (PCC)	activated prothrombin complex concentrate/	0	0	0
87		prothrombin complex/	0	0	0
88		*prothrombin/ad, tu, dt, th	0	0	0
89		(activated prothrombin or APCC or coagulation factor concentrate).ti,ab,kw.	67	76	90
90		('prothrombin complex concentrate' or PCC).ti,ab,kw.	404	493	673
91		(Beriplex* or Octaplex* or Cofact or Prothrombinex* or Proplex* or Prothroraas* or Haemosolvex* or Profiline* or Prothromplex* or Bebulin* or "HT Defix" or Facnyne* or "PPSB-Human" or "UMAN Complex" or Kaskadil*).mp.	38	59	71
92		37224-63-8.rn.	0	0	0
93		86 or 87 or 88 or 89 or 90 or 91 or 92	457	558	754
94	Population AND MHP	56 and 68	1477	1725	2046
95	Population AND RBC or blood component transfusion	56 and (73 or 85)	1406	1601	1868
96	Population AND PCC	56 and 93	27	41	57
97	Level I	exp meta analysis/ or meta analysis.mp. or exp systematic review/ or systematic review.mp. or pooled analysis.mp. or ((exp review/ or review.mp.) and (systemat* or pool*).mp.)	68951	85855	NA
98	Level II	exp comparative study/ or comparative study.mp. or exp clinical trial/ or clinical trial.mp. or randomized controlled trial.mp. or randomi?ed controlled trial.mp. or exp randomized controlled trial/ or exp randomization/ or randomization.mp. or randomi?ation.mp. or exp single blind procedure/ or single blind procedure.mp. or exp double blind procedure/ or double blind procedure.mp. or exp triple blind procedure/ or triple blind procedure.mp. or exp crossover procedure/ or crossover procedure.mp. or exp placebo/ or placebo*.mp. or random*.mp. or rct.mp. or single blind.mp. or single blinded.mp. or double blind.mp. or double blinded.mp. or treble blind.mp. or triple blind.mp. or triple blinded.mp. or exp prospective study/ or prospective study.mp.	973159	1195761	NA
99	Level III	exp clinical study/ or exp case control study/ or exp family study/ or exp longitudinal study/ or exp retrospective study/ or exp cohort analysis/ or (cohort adj1 stud*).mp. or (case control adj1 stud*).mp. or (exp prospective study/ not randomi?ed controlled trials.mp.) or (follow up adj1 stud*).mp. or (observational adj1 stud*).mp. or (epidemiologic* adj1 stud*).mp. or (cross sectional adj1 stud*).mp.	194352	208414	NA
100	Level IV	case report/	3	4	NA
101	Publication type	(editorial or letter or comment or historical article).pt.	7523	7977	NA
102		100 or 101	7526	7981	NA
103	Not animals	(animals/ or nonhuman/) not humans/	25	26	NA
104	Level I (MHP)	(94 and 97) not (101 or 103)	56	82	NA
105	Level II	(94 and 98) not (102 or 103 or 104)	1312	1515	NA
106	Level III	(94 and 99) not (102 or 103 or 104 or 105)	21	21	NA
107	Level I (RBC and blood component transfusion)	(95 and 97) not (101 or 103)	39	55	NA
108	Level II	(95 and 98) not (102 or 103 or 104)	1257	1435	NA
109	Level III	(95 and 99) not (102 or 103 or 104 or 105)	219	230	NA
110	Level I (PCC)	(96 and 97) not (101 or 103)	1	1	NA
111	Level II	(96 and 98) not (102 or 103 or 104)	25	36	NA
112	Level III	(96 and 99) not (102 or 103 or 104 or 105)	4	5	NA

#	Concept	Searches	Results 07 Aug 2018	Results 05 Aug 2019	Results 29 Sep 2021
113	Level I (MHP) [2019 update]	limit 104 to yr="2018 -Current"	NA	17	NA
114	Level II [2019 update]	limit 105 to yr="2018 -Current"	NA	110	NA
115	Level III [2019 update]	limit 106 to yr="2018 -Current"	NA	0	NA
116	Level I (RBC and blood component) [2019 update]	limit 107 to yr="2018 -Current"	NA	10	NA
117	Level II [2019 update]	limit 108 to yr="2018 -Current"	NA	90	NA
118	Level III [2019 update]	limit 109 to yr="2018 -Current"	NA	5	NA
119	Level I (PCC) [2019 update]	limit 110 to yr="2018 -Current"	NA	0	NA
120	Level II [2019 update]	limit 111 to yr="2018 -Current"	NA	5	NA
121	Level III [2019 update]	limit 112 to yr="2018 -Current"	NA	1	NA

A2.4 PubMed

The PubMed search was restricted to records that are not indexed for MEDLINE (i.e. in-process citations and citations from journals (or parts of journals) that are not currently MEDLINE-indexed) and to records added to PubMed since January 2006. The search comprises free-text terms only and replicates the free-text sets in the Embase search (converted from the Ovid syntax).

Table A2.4 Literature search results: PubMed (in-process and citations not indexed in MEDLINE): Question 2 (MHP and RBC transfusion)

#	Concept	Searches	Results 07 Aug 2018	Results 06 Aug 2019	Results 29 Sep 2021
1	Population (critical bleeding)	Search (hemorrhag* [tiab] or haemorrhag*[tiab])	241742	253453	282605
2		Search ((hemorrhag*[tiab] or haemorrhag*[tiab] or bleed*[tiab] or blood loss*[tiab] or blood-loss*[tiab] or bloodloss*[tiab]) AND (critical[tiab] or severe[tiab] or massive[tiab] or major[tiab] or life threatening[tiab] or serious[tiab] or significant[tiab] or substantial[tiab] or extreme[tiab] or catastrophic[tiab] or uncontrol*[tiab] or excess[tiab] or acute[tiab]))	210795	224654	260332
3		Search (#1 or #2)	336749	355506	402828
4	Population (receiving transfusion)	Search (blood transfusion[tiab] or erythrocyte transfusion[tiab])	37042	38925	43511
5		Search (blood autotransfusion[tiab] or blood component therapy[tiab] or plasma transfusion[tiab] or thrombocyte transfusion[tiab] or platelet transfusion[tiab] or blood component transfusion[tiab] or blood component therapy[tiab])	3945	4215	5021
6		Search (#4 or #5)	40624	42744	48034
7	Combine population sets	Search (#3 or #6)	369240	389459	440444
8	Population (trauma)	Search (trauma[tiab] or poly trauma[tiab] or polytrauma[tiab] or multitrauma[tiab] or multi trauma[tiab] or multiple trauma[tiab] or multiple wounds[tiab] or multiple wound[tiab] or multiple injuries[tiab] or multiple injury[tiab])	208976	222481	258022
9		Search blunt trauma[tiab]	8512	8890	9870
10		Search (traumatic[tiab] AND (hematoma[tiab] or haematoma[tiab] or shock[tiab] or amputation[tiab]))	10132	10696	12215

#	Concept	Searches	Results 07 Aug 2018	Results 06 Aug 2019	Results 29 Sep 2021
11		Search (#8 or #9 or #10)	215818	229653	266053
12	Population (wounds)	Search ((wounds[tiab] or wound[tiab]) AND (nonpenetrating[tiab] or penetrating[tiab] or surgical[tiab] or haemorrhage[tiab]))	40092	42729	49304
13	Population (injury)	Search (injur*[tiab] AND (blast[tiab] or abdominal[tiab] or thorax[tiab] or thoracic[tiab] or war related[tiab] or childhood[tiab] or limb[tiab] or organ[tiab] or reperfusion[tiab] or surgical[tiab] or gunshot[tiab] or accidental[tiab] or battle[tiab]))	168127	179610	209878
14	Population (emergency)	Search ((major[tiab] or life threatening[tiab] or substantial[tiab] or multiple[tiab] or severe[tiab] or serious[tiab] or catastrophic[tiab] or critical[tiab] or catastrophic[tiab] or massive[tiab] or penetrating[tiab]) AND (trauma[tiab] or traumatic[tiab] or injury[tiab] or injuries[tiab] or injured[tiab] or emergency[tiab] or emergencies[tiab] or accident[tiab]))	310755	334519	403486
15	Combine trauma/ wounds/ injury sets	Search (#11 or #12 or #13 or #14)	575778	616444	728977
16	Population (operative)	Search transplantation[tiab]	323709	339871	379116
17		Search (surgery[tiab] AND emergency[tiab] or general[tiab] or major[tiab])	2065829	2188892	2501722
18		Search (surgery[tiab] or abdominal surgery[tiab] or cardiovascular surgery[tiab] or thorax surgery[tiab] or (orthopaedic[tiab] or orthopedic[tiab] AND surgery[tiab]))	1094754	1161528	1334226
19		Search ((pediatric[tiab] or paediatric[tiab] AND surgery[tiab]) or obstetrics[tiab] or maternity[tiab])	80546	86590	102062
20		Search ((peroperative[tiab] or intraoperative[tiab] or intra operative[tiab] or postoperative[tiab] or post operative[tiab] or preoperative[tiab] or pre operative[tiab]) AND complication[tiab])	57486	62673	76407
21		Search perioperative[tiab]	78714	86101	111758
22		Search (#16 or #17 or #18 or #19 or #20 or #21)	3367176	3565631	4072467
23	Combine population sets	Search (#15 or #22)	3750237	3974710	4554098
24	Combine Population sets (bleeding AND trauma/surgery or emergency)	Search (#7 AND #23)	138479	148124	172976
25	Intervention (MHP)	Search (massive transfusion*[tiab] or blood transfusion*[tiab] or blood component*[tiab] or blood component transfusion[tiab])	51791	54348	60666
26		Search (massive transfusion[tiab] AND (protocol*[tiab] or guid*[tiab] or algorithm*[tiab] or policy[tiab] or policies[tiab] or strategy[tiab] or strategies[tiab] or practice*[tiab]))	629	715	884
27		Search ((massive haemorrhage[tiab] or massive hemorrhage[tiab]) AND (protocol*[tiab] or guid*[tiab] or algorithm*[tiab] or policy[tiab] or policies[tiab] or strategy[tiab] or strategies[tiab] or practice*[tiab]))	305	332	415
28		Search (massive bleed*[tiab] AND (protocol*[tiab] or guid*[tiab] or algorithm*[tiab] or policy[tiab] or policies[tiab] or strategy[tiab] or strategies[tiab] or practice*[tiab]))	277	307	386
29		Search ((major hemmorhage[tiab] or major haemorrhage[tiab]) AND (protocol*[tiab] or guid*[tiab] or algorithm*[tiab] or policy[tiab] or policies[tiab] or strategy[tiab] or strategies[tiab] or practice*[tiab]))	104	113	142
30		Search (major transfusion[tiab] AND (protocol*[tiab] or guid*[tiab] or algorithm*[tiab] or policy[tiab] or policies[tiab] or strategy[tiab] or strategies[tiab] or practice*[tiab]))	17	20	23
31		Search (major bleed*[tiab] AND (protocol*[tiab] or guid*[tiab] or algorithm*[tiab] or policy[tiab] or policies[tiab] or strategy[tiab] or strategies[tiab] or practice*[tiab]))	2568	2920	3931
32		Search (critical bleed*[tiab] AND (protocol*[tiab] or guid*[tiab] or algorithm*[tiab] or policy[tiab] or policies[tiab] or strategy[tiab] or strategies[tiab] or practice*[tiab]))	53	57	71

#	Concept	Searches	Results 07 Aug 2018	Results 06 Aug 2019	Results 29 Sep 2021
33		Search ((critical hemmorhage[tiab] or critical haemorrhage[tiab]) AND (protocol*[tiab] or guid*[tiab] or algorithm*[tiab] or policy[tiab] or policies[tiab] or strategy[tiab] or strategies[tiab] or practice*[tiab]))	4	4	6
34		Search (transfus*[tiab] AND (erythrocyte*[tiab] or red blood cell*[tiab] or rbc[tiab] or red cell*[tiab] or packed cell[tiab] or prbc[tiab]))	19638	20923	23790
35		Search (#25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34)	67914	71676	80947
36	Population AND MHP	Search (#24 AND #35)	21704	23501	28112
37	Exclude studies from Medline	Search (#36 AND pubmednotmedline[sb])	1581	1910	2842
38	Date limit [2019 update]	Search (("2018/01/01"[Date - Entrez] : "3000"[Date - Entrez])) AND #37	NA	421	NA
	Date limit [2021 update]	Search (("2019/01/01"[Date - Entrez] : "3000"[Date - Entrez])) AND #37	NA	NA	1025

Table A2.5 Literature search results: PubMed (in-process and citations not indexed in MEDLINE): Questions 3 and 6 (RBC transfusion and blood cell components)

#	Concept	Searches	Results 07 Aug 2018	Results 06 Aug 2019	Results 29 Sep 2021
1	Population (critical bleeding)	Search (hemorrhag* [tiab] or haemorrhag*[tiab])	241742	3974710	282605
2		Search ((hemorrhag*[tiab] or haemorrhag*[tiab] or bleed*[tiab] or blood loss*[tiab] or blood-loss*[tiab] or bloodloss*[tiab]) AND (critical[tiab] or severe[tiab] or massive[tiab] or major[tiab] or life threatening[tiab] or serious[tiab] or significant[tiab] or substantial[tiab] or extreme[tiab] or catastrophic[tiab] or uncontrol*[tiab] or excess[tiab] or acute[tiab]))	210795	3565631	260332
3		Search (#1 or #2)	336749	2188892	402828
4	Population (receiving transfusion)	Search (blood transfusion[tiab] or erythrocyte transfusion[tiab])	37042	1161528	43511
5		Search (blood autotransfusion[tiab] or blood component therapy[tiab] or plasma transfusion[tiab] or thrombocyte transfusion[tiab] or platelet transfusion[tiab] or blood component transfusion[tiab] or blood component therapy[tiab])	3945	616444	5021
6		Search (#4 or #5)	40624	389459	48034
7	Combine population sets	Search (#3 or #6)	369240	355506	440444
8	Population (trauma)	Search (trauma[tiab] or poly trauma[tiab] or polytrauma[tiab] or multitrauma[tiab] or multi trauma[tiab] or multiple trauma[tiab] or multiple wounds[tiab] or multiple wound[tiab] or multiple injuries[tiab] or multiple injury[tiab])	208976	339871	258022
9		Search blunt trauma[tiab]	8512	334519	9870
10		Search (traumatic[tiab] AND (hematoma[tiab] or haematoma[tiab] or shock[tiab] or amputation[tiab]))	10132	328993	12215
11		Search (#8 or #9 or #10)	215818	253453	266053
12	Population (wounds)	Search ((wounds[tiab] or wound[tiab]) AND (nonpenetrating[tiab] or penetrating[tiab] or surgical[tiab] or haemorrhage[tiab]))	40092	229653	49304
13	Population (injury)	Search (injur*[tiab] AND (blast[tiab] or abdominal[tiab] or thorax[tiab] or thoracic[tiab] or war related[tiab] or childhood[tiab] or limb[tiab] or organ[tiab] or reperfusion[tiab] or surgical[tiab] or gunshot[tiab] or accidental[tiab] or battle[tiab]))	168127	224654	209878
14	Population (emergency)	Search ((major[tiab] or life threatening[tiab] or substantial[tiab] or multiple[tiab] or severe[tiab] or serious[tiab] or catastrophic[tiab] or critical[tiab] or catastrophic[tiab] or massive[tiab] or penetrating[tiab]) AND (trauma[tiab] or traumatic[tiab] or injury[tiab] or injuries[tiab] or injured[tiab] or emergency[tiab] or emergencies[tiab] or accident[tiab]))	310755	222481	403486

#	Concept	Searches	Results 07 Aug 2018	Results 06 Aug 2019	Results 29 Sep 2021
15	Combine trauma/ wounds/ injury sets	Search (#11 or #12 or #13 or #14)	575778	201676	728977
16	Population (operative)	Search transplantation[tiab]	323709	192107	379116
17		Search (surgery[tiab] AND emergency[tiab] or general[tiab] or major[tiab])	2065829	179610	2501722
18		Search (surgery[tiab] or abdominal surgery[tiab] or cardiovascular surgery[tiab] or thorax surgery[tiab] or (orthopaedic[tiab] or orthopedic[tiab] AND surgery[tiab]))	1094754	155621	1334226
19		Search ((pediatric[tiab] or paediatric[tiab] AND surgery[tiab]) or obstetrics[tiab] or maternity[tiab])	80546	148124	102062
20		Search ((peroperative[tiab] or intraoperative[tiab] or intra operative[tiab] or postoperative[tiab] or post operative[tiab] or preoperative[tiab] or pre operative[tiab]) AND complication[tiab])	57486	86590	76407
21		Search perioperative[tiab]	78714	86101	111758
22		Search (#16 or #17 or #18 or #19 or #20 or #21)	3367176	62673	4072467
23	Combine population sets	Search (#15 or #22)	3750237	56148	4554098
24	Combine Population sets (bleeding AND trauma/surgery or emergency)	Search (#7 AND #23)	138479	54417	172976
25	Intervention (RBC or blood component transfusion)	Search (blood transfusion[tiab] or erythrocyte transfusion[tiab] or blood component transfusion[tiab])	37186	49652	43697
26		Search (transfus*[tiab] AND (erythrocyte*[tiab] or red blood cell*[tiab] or rbc[tiab] or red cell*[tiab] or packed cell*[tiab] or prbc[tiab]))	19772	45512	23940
27		Search ((Blood component[tiab] or plasma[tiab] or thrombocyte[tiab] or platelet[tiab] or blood component[tiab] or blood product[tiab]) AND (transfus*[tiab] or therap*[tiab]))	147291	42744	178393
28		Search (#25 or #26 or #27)	190987	42729	229835
29		Search (fresh frozen plasma[tiab] or (plasma[tiab] AND (fresh[tiab] or frozen[tiab] or thawed[tiab] or liquid[tiab])))	53269	39078	63149
30		Search (cryoprecipitate[tiab] or cryo precipitate[tiab])	1910	38925	2193
31		Search fibrinogen[tiab]	44205	26200	49707
32		Search (fibrinogen[tiab] AND (concentrate[tiab] or infusion[tiab]))	1903	21065	2169
33		Search (clotting[tiab] AND (factor 1[tiab] or factor1[tiab] or factor I[tiab]))	43	10696	52
34		Search (RiaSTAP[tiab] or Clottagen*[tiab] or Fibrorass*[tiab] or Haemocomplettan[tiab] or hemocomplettan[tiab])	24	8890	33
35		Search ((platelet*[tiab] or thrombocyte*[tiab]) AND (infus*[tiab] or therap*[tiab] or transfus*[tiab]))	51566	4215	62017
36		Search (plasma[tiab] AND (infusion[tiab] or transfusion[tiab]))	48608	2017	52476
37		Search (#29 or #30 or #31 or #32 or #33 or #34 or #35 or #36)	184652	1977	212082
38		Search (#28 or #37)	314329	1970	367538
39	Population AND RBC or blood component transfusion	Search (#24 AND #38)	24440	420	30684
40	Exclude studies from Medline	Search (#39 AND pubmednotmedline[sb])	1697	44	2939
41	Date limit [2019 update]	Search (("2018/01/01"[Date - Entrez] : "3000"[Date - Entrez]) AND #40)	NA	26	NA
	Date limit [2021 update]	Search (("2019/01/01"[Date - Entrez] : "3000"[Date - Entrez]) AND #40)	NA	NA	993

Table A2.6 Literature search results: PubMed (in-process and citations not indexed in MEDLINE): Question 6 (prothrombin complex concentrate)

#	Concept	Searches	Results 07 Aug 2018	Results 06 Aug 2019	Results 29 Sep 2021
1	Population (critical bleeding)	Search (hemorrhag* [tiab] or haemorrhag*[tiab])	241742	3974710	282605
2		Search ((hemorrhag*[tiab] or haemorrhag*[tiab] or bleed*[tiab] or blood loss*[tiab] or blood-loss*[tiab] or bloodloss*[tiab]) AND (critical[tiab] or severe[tiab] or massive[tiab] or major[tiab] or life threatening[tiab] or serious[tiab] or significant[tiab] or substantial[tiab] or extreme[tiab] or catastrophic[tiab] or uncontrol*[tiab] or excess[tiab] or acute[tiab]))	210795	3565631	260332
3		Search (#1 or #2)	336749	2188892	402828
4	Population (receiving transfusion)	Search (blood transfusion[tiab] or erythrocyte transfusion[tiab])	37042	1161528	43511
5		Search (blood autotransfusion[tiab] or blood component therapy[tiab] or plasma transfusion[tiab] or thrombocyte transfusion[tiab] or platelet transfusion[tiab] or blood component transfusion[tiab] or blood component therapy[tiab])	3945	616444	5021
6		Search (#4 or #5)	40624	389459	48034
7	Combine population sets	Search (#3 or #6)	369240	355506	440444
8	Population (trauma)	Search (trauma[tiab] or poly trauma[tiab] or polytrauma[tiab] or multitrauma[tiab] or multi trauma[tiab] or multiple trauma[tiab] or multiple wounds[tiab] or multiple wound[tiab] or multiple injuries[tiab] or multiple injury[tiab])	208976	339871	258022
9		Search blunt trauma[tiab]	8512	334519	9870
10		Search (traumatic[tiab] AND (hematoma[tiab] or haematoma[tiab] or shock[tiab] or amputation[tiab]))	10132	253453	12215
11		Search (#8 or #9 or #10)	215818	229653	266053
12	Population (wounds)	Search ((wounds[tiab] or wound[tiab]) AND (nonpenetrating[tiab] or penetrating[tiab] or surgical[tiab] or haemorrhage[tiab]))	40092	224654	49304
13	Population (injury)	Search (injur*[tiab] AND (blast[tiab] or abdominal[tiab] or thorax[tiab] or thoracic[tiab] or war related[tiab] or childhood[tiab] or limb[tiab] or organ[tiab] or reperfusion[tiab] or surgical[tiab] or gunshot[tiab] or accidental[tiab] or battle[tiab]))	168127	222481	209878
14	Population (emergency)	Search ((major[tiab] or life threatening[tiab] or substantial[tiab] or multiple[tiab] or severe[tiab] or serious[tiab] or catastrophic[tiab] or critical[tiab] or catastrophic[tiab] or massive[tiab] or penetrating[tiab]) AND (trauma[tiab] or traumatic[tiab] or injury[tiab] or injuries[tiab] or injured[tiab] or emergency[tiab] or emergencies[tiab] or accident[tiab]))	310755	179610	403486
15	Combine trauma/ wounds/ injury sets	Search (#11 or #12 or #13 or #14)	575778	148124	728977
16	Population (operative)	Search transplantation[tiab]	323709	86590	379116
17		Search (surgery[tiab] AND emergency[tiab] or general[tiab] or major[tiab])	2065829	86101	2501722
18		Search (surgery[tiab] or abdominal surgery[tiab] or cardiovascular surgery[tiab] or thorax surgery[tiab] or (orthopaedic[tiab] or orthopedic[tiab] AND surgery[tiab]))	1094754	62673	1334226
19		Search ((pediatric[tiab] or paediatric[tiab] AND surgery[tiab]) or obstetrics[tiab] or maternity[tiab])	80546	42744	102062
20		Search ((peroperative[tiab] or intraoperative[tiab] or intra operative[tiab] or postoperative[tiab] or post operative[tiab] or preoperative[tiab] or pre operative[tiab]) AND complication[tiab])	57486	42729	76407
21		Search perioperative[tiab]	78714	38925	111758
22		Search (#16 or #17 or #18 or #19 or #20 or #21)	3367176	10696	4072467
23	Combine population sets	Search (#15 or #22)	3750237	8890	4554098

#	Concept	Searches	Results 07 Aug 2018	Results 06 Aug 2019	Results 29 Sep 2021
24	Combine Population sets (bleeding AND trauma/surgery or emergency)	Search (#7 AND #23)	138479	4215	172976
25	Intervention (PCC)	Search (activated prothrombin[tiab] or activated prothrombin complex concentrate[tiab] or prothrombin complex[tiab] or coagulation factor concentrate[tiab])	2150	2619	2639
26		Search 37224-63-8[rn]	936	2304	1190
27		Search (Beriplex*[tiab] or Octaplex*[tiab] or Cofact[tiab] or Prothrombinex*[tiab] or Proplex*[tiab] or Prothroraas*[tiab] or Haemosolvex*[tiab] or Profiline*[tiab] or Prothromplex*[tiab] or Bebulin*[tiab] or HT Defix[tiab] or Facnyne*[tiab] or PPSB-Human[tiab] or UMAN Complex[tiab] or Kaskadil*[tiab])	171	1009	191
28		Search (#25 or #26 or #27)	2457	684	2988
29	Population AND PCC	Search (#24 AND #28)	627	177	839
30	Exclude studies from Medline	Search (#29 AND pubmednotmedline[sb])	47	50	74
31	Date limit [2019 update]	Search (("2018/01/01"[Date - Entrez] : "3000"[Date - Entrez]) AND #30)	NA	8	NA
	Date limit [2021 update]	Search (("2019/01/01"[Date - Entrez] : "3000"[Date - Entrez]) AND #30)	NA	NA	23

A3 Questions 5,7,8 & 9

A3.1 Embase

Table A3.1 Literature search results: Embase <1974 to 07 August 09, 2019>

Search via Ovid for Level I, Level II, and Level III studies

#	Concept	Search string	Results 06 Aug 2018	Results [a] 12 Aug 2019	Results 29 Sep 2021
1	Population (critical bleeding)	exp *hemorrhage/	259851	847600	316767
2		oral hemorrhage/ or postoperative hemorrhage/ or peptic ulcer hemorrhage/ or gastrointestinal hemorrhage/ or uterine hemorrhage/ or obstetric hemorrhage/ or antepartum hemorrhage/ or intrapartum hemorrhage/ or postpartum hemorrhage/	110391	114080	141169
3		*shock/ or hemorrhagic shock/ or hypovolemic shock/ or traumatic shock/ or exsanguination/ or hemorrhagic hypotension/	36615	31187	43503
4		((hemorrhag* or haemorrhag* or bleed* or bleeding or blood?loss* or 'blood-loss*' or bloodloss*) adj3 (critical or severe or massive or major or life threatening or 'life?threatening')).mp.	61652	65945	83563
5		((haemorrhagic or hemorrhagic or hypovolemic or hypovolaemic) adj shock).ti,ab.	14962	14656	18865
6		or/1-5	390769	873742	489030
7	Population (requiring transfusion)	exp *blood transfusion/ or Erythrocyte Transfusion/	74515	72432	87757
8		blood autotransfusion/ or blood component therapy/ or plasma transfusion/ or thrombocyte transfusion/ or Platelet Transfusion/ or Blood Component Transfusion/	30494	31803	37237
9		(blood component adj (transfus* or therapy)).ti,ab,kw.	995	1045	1074
10		or/7-9	89391	88277	106754
11	Population (critical bleeding requiring transfusion)	6 or 10	466337	937380	578370
12	Population (Trauma)	Multiple Trauma/	13176	13990	16062
13		trauma*.ab,ti,kw.	425647	444363	553681

#	Concept	Search string	Results 06 Aug 2018	Results [a] 12 Aug 2019	Results 29 Sep 2021
14		(polytrauma* or poly?trauma* or 'poly trauma').ab,ti,kw.	5434	5935	7031
15		(multitrauma* or multi?trauma* or 'multi trauma').ab,ti,kw.	656	710	790
16		'multiple trauma*'.ab,ti,kw.	4421	4591	5137
17		blunt trauma/	17375	18339	21158
18		traumatic hematoma/	251	268	381
19		exp amputation, traumatic/	1967	1949	2346
20		or/12-19	436221	455238	566134
21		exp wounds, nonpenetrating/	24609	25861	29410
22		exp wounds, penetrating/	11353	11869	14126
23		surgical wound/	5902	6526	8324
24		wound hemorrhage/	206	218	264
25		or/21-24	39161	41399	48641
26	Population (injury)	*injury/	63401	59519	78858
27		exp blast injuries/	4121	4176	5098
28		exp abdominal injuries/	146172	149868	188227
29		exp thoracic injuries/	71854	73761	95598
30		exp war-related injuries/	4007	4285	5490
31		childhood injury/ or contusion/ or crush trauma/ or limb injury/	23235	24514	30675
32		organ injury/ or reperfusion injury/	54857	58915	64489
33		surgical injury/	4145	4404	5641
34		gunshot injury/	17157	16457	20854
35		accidental injury/	3150	3463	4260
36		battle injury/	4007	4285	5490
37		or/26-36	359626	367123	459124
38		*accidents/	10065	8490	13057
39		*emergency/	13781	13564	15727
40		((major* or life threatening or life?threatening or substantial* or multip* or severe* or serious* or catastrophic* or critical* or massive* or penetrating) adj3 (trauma* or injur* or emergenc* or accident*)).ti,ab.	121394	128165	154996
41	Population (emergency)	or/38-40	143555	148554	181621
42	combine trauma and emergency	20 or 25 or 37 or 41	795964	823503	1027508
43	Population (operative)	transplantation/	156867	148698	186111
44		emergency surgery/ or general surgery/ or major surgery/	40248	42718	55124
45		*surgery/ or abdominal surgery/ or cardiovascular surgery/ or thorax surgery/ or orthopedic surgery/	211686	199336	265866
46		pediatric surgery/ or obstetrics/ or obstetric care/	56749	57348	0545
47		(peri?operative or pre?operative or intra?operative or post?operative).ti,ab,kw.	847011	908549	1093613
48		(surg* or operat* or resect* or perioperat*).ab,ti,kw.	3280513	3436828	4254459
49		exp operative blood loss/	15965	19768	28478
50		peroperative care/	11791	12410	13795
51		peroperative complication/ or postoperative complication/ or preoperative complication/	343395	341609	417331
52		exp perioperative period/	41616	46075	57028
53		exp preoperative period/	275439	296050	364040
54		or/43-53	3831483	3970932	4916589
55	combine population sets (trauma, emergency, operative)	42 or 54	4384064	4537469	5627461

#	Concept	Search string	Results 06 Aug 2018	Results [a] 12 Aug 2019	Results 29 Sep 2021
56	Combine trauma, emergency, and operative with bleeding	11 and 55	164460	387360	208765
57	Intervention (factor VII)	exp Factor VIIa/ or exp recombinant blood clotting factor 7a/	9289	9724	10391
58		(recombinant f*VIIa or activated factor seven).ti,ab,kw.	460	502	914
59		(recombinant activated factor VII or recombinant activated VIIa).mp.	1670	1752	1843
60		((recombinant adj4 VIIa) or (recombinant adj4 FVIIa) or (recombinant adj4 VII) or (recombinant adj4 FVII)).mp.	4745	4975	5327
61		((recombinant adj3 factor 7) or (recombinant adj3 factor 7a)).mp.	6606	6972	7520
62		(fVIIa or 'f VIIa' or f7a or 'f 7a' or rfVIIa or 'r fVIIa' or 'r f VIIa' or rf7a or 'r f7a' or 'r f 7a').mp.	4743	5075	5479
63		or/57-62	11471	12058	1289
64		eptacog*.mp.	73	89	118
65		feiba.mp.	1193	1269	1389
66		niastase.mp.	35	38	41
67		(novoseven* or 'novo seven*').mp.	2366	2440	2538
68		(novo7 or 'novo 7').mp.	44	57	57
69		('nn 1731' or nn1731).mp.	47	47	47
70		'102786-61-8'.rn.	0	0	0
71		proconvertin.mp.	99	73	397
72		or/64-71	3345	3471	3996
73		63 or 72	12102	12718	13934
74	Intervention (antifibrinolytics)	exp Antifibrinolytic Agents/	30766	30149	38324
75		exp Fibrinolytic Agents/	126847	128592	158566
76		exp Fibrinolysis/dt	3	2	2
77		(antifibrinoly* or 'anti fibrinoly*').ab,ti,kw.	4174	4254	5551
78		(antiplasmin* or 'anti plasmin*').ab,ti,kw.	3521	3546	4042
79		(fibrinolysis inhibitor* or 'plasmin inhibitor*').ab,ti,kw.	2873	2933	3247
80		or/74-79	155749	157101	194142
81	Intervention (TXA)	exp Tranexamic Acid/	10982	12245	15399
82		'tranexamic acid'.ab,ti,kw,rn.	11319	12592	15825
83		cyklokapron.ab,ti,kw.	48	43	53
84		TXA.ab,ti,kw.	1355	1705	2475
85		Lysteda.ab,ti,kw.	14	14	17
86		('1197-18-8' or '701-54-2').rn.	9790	10972	13824
87		or/81-86	11722	13018	16337
88	Intervention (aprotinin)	exp APROTININ/	12826	11906	13948
89		Aprotinin.ab,ti,kw,rn.	13768	12838	14563
90		Transylol.ab,ti,kw.	0	0	0
91		'9087-70-1'.rn.	12449	11514	13189
92		exp Aminocaproic Acid/	5869	5879	7286
93		'Aminocaproic Acid'.ab,ti,kw,rn.	6668	6352	7813
94		Amicar.ab,ti,kw.	113	117	137
95		('1319-82-0' or '60-32-2').rn.	5590	5587	6326
96		or/88-95	19363	18145	21813
97	Intervention (EACA)	('epsilon aminocapr$' or 'epsilon?aminocapr$' or 'aminomethylbenz$').ab,ti,kw.	1999	1667	2485
98		EACA.ab,ti,kw.	736	687	1036
99		56-91-7.rn.	229	225	263
100		('4?aminomethylbenz$' or '4 aminomethylbenz$').ab,ti,kw.	36	34	40
101		('p?aminomethylbenz$' or 'p aminomethylbenz$').ab,ti,kw.	54	29	92
102		PAMBA.ab,ti,kw.	100	61	178

#	Concept	Search string	Results 06 Aug 2018	Results [a] 12 Aug 2019	Results 29 Sep 2021
103		or/97-102	2535	2140	3244
104		80 or 87 or 96 or 103	158097	159177	196712
105	Intervention (TEG/ROTEM)	exp Thrombelastography/	7488	7260	10912
106		goal directed therapy/	74	77	90
107		(thromb?elastograph* or thromb?elastomet*).mp.	9769	10031	14023
108		viscoelast*.mp.	18104	19752	24110
109		(TEG or ROTEG or ROTEM).mp.	5139	5988	7504
110		(h?emoscope* or H?emonet*).mp.	1554	1680	1888
111		'activat* clot* time*'.mp.	2199	2340	2621
112		or/105-111	31200	33243	41880
113	Intervention (Cell Salvage)	exp Blood Transfusion, Autologous/	8546	8603	9277
114		'cell salvage'.mp.	1025	1131	1295
115		'blood salvage'.mp.	1120	1258	1458
116		('autologous adj5 transfusion*').mp.	3156	3244	3472
117		'blood conserv*'.mp.	1563	1665	1880
118		'cell saver''.mp.	1058	1142	1242
119		('autotransfusion' or 'auto transfusion').mp.	9035	9091	9828
120		'salvage therap*'.mp.	22481	24283	28640
121		'erythrocyte salvage'.mp.	7	7	9
122		or/113-121	35021	37127	42779
123	Population and rFVIIa	56 and 73	2785	3800	3158
124	Population AND antifibrinolytics	56 and 104	8626	14351	11427
125	Population & TEG/ROTEM	56 and 112	2486	3857	3347
126	Population & Cell salvage	56 and 122	7007	8447	7759
127	Level I	exp meta analysis/ or meta analysis.mp. or exp systematic review/ or systematic review.mp. or pooled analysis.mp. or ((exp review/ or review.mp.) and (systemat* or pool*).mp.)	426339	487879	644343
128	Level II	exp comparative study/ or comparative study.mp. or exp clinical trial/ or clinical trial.mp. or randomized controlled trial.mp. or randomi?ed controlled trial.mp. or exp randomized controlled trial/ or exp randomization/ or randomization.mp. or randomi?ation.mp. or exp single blind procedure/ or single blind procedure.mp. or exp double blind procedure/ or double blind procedure.mp. or exp triple blind procedure/ or triple blind procedure.mp. or exp crossover procedure/ or crossover procedure.mp. or exp placebo/ or placebo*.mp. or random*.mp. or rct.mp. or single blind.mp. or single blinded.mp. or double blind.mp. or double blinded.mp. or treble blind.mp. or triple blind.mp. or triple blinded.mp. or exp prospective study/ or prospective study.mp.	4002529	4258375	5010112
129	Level III	exp clinical study/ or exp case control study/ or exp family study/ or exp longitudinal study/ or exp retrospective study/ or exp cohort analysis/ or (cohort adj1 stud*).mp. or (case control adj1 stud*).mp. or (exp prospective study/ not randomi?ed controlled trials.mp.) or (follow up adj1 stud*).mp. or (observational adj1 stud*).mp. or (epidemiologic* adj1 stud*).mp. or (cross sectional adj1 stud*).mp.	9085841	9684506	11450592
130	Publication type filters	case report/	2325194	2388237	2761122
131		(editorial or letter or comment or historical article).pt.	1604135	1707606	1897012
132		130 or 131	3725293	3884759	4433250
133	nonhuman study	(animals/ or nonhuman/) not humans/	6872862	6853002	6860196
134	rFVIIa Level I	(123 and 127) not (131 or 133)	147	192	193
135	rFVIIa Level II	(123 and 128) not (132 or 133 or 134)	586	760	686
136	rFVIIa Level III	(123 and 129) not (132 or 133 or 134 or 135)	414	530	498
137	TXA Level I	(124 and 127) not (131 or 133)	553	899	808
138	TXA Level II	(124 and 128) not (132 or 133 or 137)	2535	4015	3353

#	Concept	Search string	Results 06 Aug 2018	Results [a] 12 Aug 2019	Results 29 Sep 2021
139	TXA Level III	(124 and 129) not (132 or 133 or 137 or 138)	1595	2647	2235
140	TEG/ROTEM Level I	(125 and 127) not (131 or 133)	81	121	127
141	TEG/ROTEM Level II	(125 and 128) not (132 or 133 or 140)	702	1011	946
142	TEG/ROTEM Level III	(125 and 129) not (132 or 133 or 140 or 141)	490	789	735
143	Cell Salvage Level I	(126 and 127) not (131 or 133)	197	261	245
144	Cell Salvage Level II	(126 and 128) not (132 or 133 or 143)	1603	1936	1779
145	Cell salvage Level III	(126 and 129) not (132 or 133 or 143 or 144)	1726	2163	1964
146	rFVIIa Level I [2019 update]	limit 134 to yr="2018 -Current"	NA	15	NA
147	rFVIIa Level II [2019 update]	limit 135 to yr="2018 -Current"	NA	27	NA
148	rFVIIa Level III [2019 update]	limit 136 to yr="2018 -Current"	NA	46	NA
149	TXA Level I [2019 update]	limit 137 to yr="2018 -Current"	NA	145	NA
150	TXA Level II [2019 update]	limit 138 to yr="2018 -Current"	NA	453	NA
151	TXA Level III [2019 update]	limit 139 to yr="2018 -Current"	NA	403	NA
152	TEG/ROTEM Level I [2019 update]	limit 140 to yr="2018 -Current"	NA	31	NA
153	TEG/ROTEM Level II [2019 update]	limit 141 to yr="2018 -Current"	NA	135	NA
154	TEG/ROTEM Level III [2019 update]	limit 142 to yr="2018 -Current"	NA	141	NA
155	Cell Salvage Level I [2019 update]	limit 143 to yr="2018 -Current"	NA	33	NA
156	Cell Salvage Level II [2019 update]	limit 144 to yr="2018 -Current"	NA	104	NA
157	Cell Salvage Level III [2019 update]	limit 145 to yr="2018 -Current"	NA	162	NA
146	rFVIIa Level I [2021 update]	limit 134 to yr="2019 -Current"	NA	NA	31[b]
147	rFVIIa Level II [2021 update]	limit 135 to yr="2019 -Current"	NA	NA	46[b]
148	rFVIIa Level III [2021 update]	limit 136 to yr="2019 -Current"	NA	NA	68[b]
149	TXA Level I [2021 update]	limit 137 to yr="2019 -Current"	NA	NA	222
150	TXA Level II [2021 update]	limit 138 to yr="2019 -Current"	NA	NA	639
151	TXA Level III [2021 update]	limit 139 to yr="2019 -Current"	NA	NA	546
152	TEG/ROTEM Level I [2021 update]	limit 140 to yr="2019 -Current"	NA	NA	39
153	TEG/ROTEM Level II [2021 update]	limit 141 to yr="2019 -Current"	NA	NA	203

#	Concept	Search string	Results 06 Aug 2018	Results [a] 12 Aug 2019	Results 29 Sep 2021
154	TEG/ROTEM Level III [2021 update]	limit 142 to yr="2019 -Current"	NA	NA	199
155	Cell Salvage Level I [2021 update]	limit 143 to yr="2019 -Current"	NA	NA	37
156	Cell Salvage Level II [2021 update]	limit 144 to yr="2019 -Current"	NA	NA	132
157	Cell Salvage Level III [2021 update]	limit 145 to yr="2019 -Current"	NA	NA	203

a. Due to an error, the literature search conducted 09 August 2019 was not focused, resulting in more search hits for exp hemorrhage/ (not exp *hemorrhage/).
b. Citations relating to rFVIIa were not exported or included in the screening process because the question was retired in March 2021.

A3.2 Medline

Table A3.2 Literature search results: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to August 07, 2019

Search via Ovid for Level I, Level II, and Level III studies

#	Concept	Search string	Results 06 Aug 2018	Results 09 Aug 2019	Results 29 Sep 2021
1	Population (critical bleeding)	exp *hemorrhage/	197317	318033 [a]	222453
2		oral hemorrhage/ or postoperative hemorrhage/ or peptic ulcer hemorrhage/ or gastrointestinal hemorrhage/ or uterine hemorrhage/ or obstetric hemorrhage/ or antepartum hemorrhage/ or intrapartum hemorrhage/ or postpartum hemorrhage/	70627	72991	77959
3		*shock/ or hemorrhagic shock/ or hypovolemic shock/ or traumatic shock/ or exsanguination/ or hemorrhagic hypotension/	30463	31064	32457
4		((hemorrhag* or haemorrhag* or bleed* or bleeding or blood?loss* or 'blood-loss*' or bloodloss*) adj3 (critical or severe or massive or major or life threatening or 'life?threatening')).mp.	40339	42872	49602
5		((haemorrhagic or hemorrhagic or hypovolemic or hypovolaemic) adj shock).ti,ab.	11517	11993	13051
6		or/1-5	265908	359324	301760
7	Population (requiring transfusion)	exp *blood transfusion/ or Erythrocyte Transfusion/	49321	50882	54188
8		blood autotransfusion/ or blood component therapy/ or plasma transfusion/ or thrombocyte transfusion/ or Platelet Transfusion/ or Blood Component Transfusion/	9971	10357	11226
9		(blood component adj (transfus* or therapy)).ti,ab,kw.	542	563	634
10		or/7-9	52186	53877	57492
11	Population (critical bleeding requiring transfusion)	6 or 10	311199	404208	351196
12	Population (wounds)	Multiple Trauma/	12039	12410	13031
13		trauma*.ab,ti,kw.	323568	343408	395691
14		(polytrauma* or poly?trauma* or 'poly trauma').ab,ti,kw.	3881	4180	4960
15		(multitrauma* or multi?trauma* or 'multi trauma').ab,ti,kw.	478	511	562
16		'multiple trauma*'.ab,ti,kw.	3360	3514	3907
17		blunt trauma/	0	0	0
18		traumatic hematoma/	0	0	0
19		exp amputation, traumatic/	4528	4646	4898
20		or/12-19	331994	352056	404771
21		exp wounds, nonpenetrating/	34311	35801	39630

#	Concept	Search string	Results 06 Aug 2018	Results 09 Aug 2019	Results 29 Sep 2021
22		exp wounds, penetrating/	34530	35441	37426
23		surgical wound/	339	636	1192
24		wound hemorrhage/	0	0	0
25		or/21-24	66087	68709	74929
26	Population (injury)	*injury/	54111	56051	60286
27		exp blast injuries/	3948	4126	4495
28		exp abdominal injuries/	19662	20064	20856
29		exp thoracic injuries/	25200	26152	28707
30		exp war-related injuries/	222	332	504
31		childhood injury/ or contusion/ or crush trauma/ or limb injury/	4706	4823	5053
32		organ injury/ or reperfusion injury/	24384	25710	29087
33		surgical injury/	30031	31038	32941
34		gunshot injury/	0	0	0
35		accidental injury/	0	0	151
36		battle injury/	0	0	0
37		or/26-36	155779	161647	175135
38	Population (emergency)	*accidents/	12902	13022	13244
39		*emergency/	12118	12513	13441
40		((major* or life threatening or life?threatening or substantial* or multip* or severe* or serious* or catastrophic* or critical* or massive* or penetrating) adj3 (trauma* or injur* or emergenc* or accident*)).ti,ab.	93075	98519	113072
41		or/38-40	116755	122676	138278
42	combine trauma and emergency	20 or 25 or 37 or 41	530618	558723	631184
43	Population (operative)	transplantation/	8815	8875	8985
44		emergency surgery/ or general surgery/ or major surgery/	37302	37970	39915
45		*surgery/ or abdominal surgery/ or cardiovascular surgery/ or thorax surgery/ or orthopedic surgery/	47148	48425	57544
46		pediatric surgery/ or obstetrics/ or obstetric care/	21312	21922	23535
47		(peri?operative or pre?operative or intra?operative or post?operative).ti,ab,kw.	626988	669009	777512
48		(surg* or operat* or resect* or perioperat*).ab,ti,kw.	2485886	2631882	3013591
49		exp operative blood loss/	0	0	0
50		peroperative care/	15858	16379	0
51		peroperative complication/ or postoperative complication/ or preoperative complication/	355274	370922	404865
52		exp perioperative period/	76525	83271	98007
53		exp preoperative period/	5341	6315	8888
54		or/43-53	2801924	2959596	3362538
55	combine population sets (trauma, emergency, operative)	42 or 54	3162893	3339511	3792050
56	Combine trauma, emergency, and operative with bleeding	11 and 55	94505	130513	109244
57	Intervention (factor VII)	exp Factor VIIa/ or exp recombinant blood clotting factor 7a/	3832	3905	4048
58		(recombinant f*VIIa or activated factor seven).ti,ab,kw.	248	265	292
59		(recombinant activated factor VII or recombinant activated VIIa).mp.	1184	1214	1262
60		((recombinant adj4 VIIa) or (recombinant adj4 FVIIa) or (recombinant adj4 VII) or (recombinant adj4 FVII)).mp.	3387	3469	3646
61		((recombinant adj3 factor 7) or (recombinant adj3 factor 7a)).mp.	8	8	9
62		(fVIIa or 'f VIIa' or f7a or 'f 7a' or rfVIIa or 'r fVIIa' or 'r f VIIa' or rf7a or 'r f7a' or 'r f 7a').mp.	3298	3388	3564

#	Concept	Search string	Results 06 Aug 2018	Results 09 Aug 2019	Results 29 Sep 2021
63		or/57-62	5284	5412	5685
64		eptacog*.mp.	28	34	40
65		feiba.mp.	276	289	309
66		niastase.mp.	4	4	4
67		(novoseven* or 'novo seven*').mp.	456	460	465
68		(novo7 or 'novo 7').mp.	12	12	13
69		('nn 1731' or nn1731).mp.	22	22	22
70		'102786-61-8'.rn.	0	0	0
71		proconvertin.mp.	153	153	154
72		or/64-71	882	900	933
73		63 or 72	5618	5752	6045
74	Intervention (antifibrinolytics)	exp Antifibrinolytic Agents/	25598	26670	29357
75		exp Fibrinolytic Agents/	162038	167267	176658
76		exp Fibrinolysis/dt	0	0	0
77		(antifibrinoly* or 'anti fibrinoly*').ab,ti,kw.	3001	3159	3522
78		(antiplasmin* or 'anti plasmin*').ab,ti,kw.	2804	2839	2956
79		(fibrinolysis inhibitor* or 'plasmin inhibitor*').ab,ti,kw.	2238	2277	2379
80		or/74-79	186960	193272	205382
81	Intervention (TXA)	exp Tranexamic Acid/	2857	3184	4144
82		'tranexamic acid'.ab,ti,kw,rn.	4232	4720	6095
83		cyklokapron.ab,ti,kw.	32	32	34
84		TXA.ab,ti,kw.	1484	1714	2311
85		Lysteda.ab,ti,kw.	7	7	8
86		('1197-18-8' or '701-54-2').rn.	0	0	0
87		or/81-86	5001	5498	6884
88	Intervention (aprotinin)	exp APROTININ/	6336	6355	6402
89		Aprotinin.ab,ti,kw,rn.	8123	8157	8239
90		Transylol.ab,ti,kw.	2	2	2
91		'9087-70-1'.rn.	6336	6355	6402
92		exp Aminocaproic Acid/	1641	1667	1714
93		'Aminocaproic Acid'.ab,ti,kw,rn.	2966	3005	3098
94		Amicar.ab,ti,kw.	71	71	74
95		('1319-82-0' or '60-32-2').rn.	0	0	0
96		or/88-95	10776	10842	11015
97	Intervention (EACA)	('epsilon aminocapr$' or 'epsilon?aminocapr$' or 'aminomethylbenz$').ab,ti,kw.	1834	1853	1894
98		EACA.ab,ti,kw.	570	585	604
99		56-91-7.rn.	71	71	76
100		('4?aminomethylbenz$' or '4 aminomethylbenz$').ab,ti,kw.	30	30	31
101		('p?aminomethylbenz$' or 'p aminomethylbenz$').ab,ti,kw.	54	54	54
102		PAMBA.ab,ti,kw.	95	98	101
103		or/97-102	2141	2167	2220
104		80 or 87 or 96 or 103	196068	202530	215110
105	Intervention (TEG/ROTEM)	exp Thrombelastography/	4635	4933	5665
106		goal directed therapy/	0	0	0
107		(thromb?elastograph* or thromb?elastomet*).mp.	6106	6560	7637
108		viscoelast*.mp.	13959	15214	18505
109		(TEG or ROTEG or ROTEM).mp.	2489	2792	3529
110		(h?emoscope* or H?emonet*).mp.	533	545	577
111		'activat* clot* time*'.mp.	1478	1533	1693
112		or/105-111	22081	23834	28302

#	Concept	Search string	Results 06 Aug 2018	Results 09 Aug 2019	Results 29 Sep 2021
113	Intervention (Cell Salvage)	exp Blood Transfusion, Autologous/	7019	7109	7322
114		'cell salvage'.mp.	553	594	685
115		'blood salvage'.mp.	736	788	860
116		('autologous adj5 transfusion*').mp.	7791	7918	8183
117		'blood conserv*'.mp.	945	982	1084
118		'cell saver''.mp.	662	689	749
119		('autotransfusion' or 'auto transfusion').mp.	1801	1829	1874
120		'salvage therap*'.mp.	15889	16893	19324
121		'erythrocyte salvage'.mp.	5	5	6
122		or/113-121	25140	26348	29237
123	Population and rFVIIa	56 and 73	1158	1292	1232
124	Population AND antifibrinolytics	56 and 104	6618	8726	8108
125	Population & TEG/ROTEM	56 and 112	1141	1390	1482
126	Population and Cell salvage	56 and 122	4551	4871	4812
127	Level I	exp meta analysis/ or meta analysis.mp. or exp systematic review/ or systematic review.mp. or pooled analysis.mp. or ((exp review/ or review.mp.) and (systemat* or pool*).mp.)	280162	322123	432608
128	Level II	exp comparative study/ or comparative study.mp. or exp clinical trial/ or clinical trial.mp. or randomized controlled trial.mp. or randomi?ed controlled trial.mp. or exp randomized controlled trial/ or exp randomization/ or randomization.mp. or randomi?ation.mp. or exp single blind procedure/ or single blind procedure.mp. or exp double blind procedure/ or double blind procedure.mp. or exp triple blind procedure/ or triple blind procedure.mp. or exp crossover procedure/ or crossover procedure.mp. or exp placebo/ or placebo*.mp. or random*.mp. or rct.mp. or single blind.mp. or single blinded.mp. or double blind.mp. or double blinded.mp. or treble blind.mp. or triple blind.mp. or triple blinded.mp. or exp prospective study/ or prospective study.mp.	3483178	3631252	3995294
129	Level III	exp clinical study/ or exp case control study/ or exp family study/ or exp longitudinal study/ or exp retrospective study/ or exp cohort analysis/ or (cohort adj1 stud*).mp. or (case control adj1 stud*).mp. or (exp prospective study/ not randomi?ed controlled trials.mp.) or (follow up adj1 stud*).mp. or (observational adj1 stud*).mp. or (epidemiologic* adj1 stud*).mp. or (cross sectional adj1 stud*).mp.	2992198	3196726	3751241
130	Study filters	case report/	1889194	2036570	2213316
131		(editorial or letter or comment or historical article).pt.	1975176	2083054	234340
132		130 or 131	3664177	3909974	43332658
133		(animals/ not humans/) or nonhuman/	4448309	4573930	4857428
134	rFVIIa Level I	(123 and 127) not (131 or 133)	50	54	54
135	rFVIIa Level II	(123 and 128) not (132 or 133 or 134)	183	209	189
136	rFVIIa Level III	(123 and 129) not (132 or 133 or 134 or 135)	131	143	144
137	TXA Level I	(124 and 127) not (131 or 133)	400	564	628
138	TXA Level II	(124 and 128) not (132 or 133 or 137)	2260	2992	2761
139	TXA Level III	(124 and 129) not (132 or 133 or 137 or 138)	753	996	1081
140	TEG/ROTEM Level I	(125 and 127) not (131 or 133)	28	36	46
141	TEG/ROTEM Level II	(125 and 128) not (132 or 133 or 140)	395	488	505
142	TEG/ROTEM Level III	(125 and 129) not (132 or 133 or 140 or 141)	98	127	165
143	Cell Salvage Level I	(126 and 127) not (131 or 133)	103	122	129
144	Cell Salvage Level II	(126 and 128) not (132 or 133 or 143)	1366	1456	1445

#	Concept	Search string	Results 06 Aug 2018	Results 09 Aug 2019	Results 29 Sep 2021
145	Cell salvage Level III	(126 and 129) not (132 or 133 or 143 or 144)	513	575	601
146	rFVIIa Level I [2019 update]	limit 134 to yr="2018 -Current"	NA	3	NA
147	rFVIIa Level II [2019 update]	limit 135 to yr="2018 -Current"	NA	3	NA
148	rFVIIa Level III [2019 update]	limit 136 to yr="2018 -Current"	NA	3	NA
149	TXA Level I [2019 update]	limit 137 to yr="2018 -Current"	NA	81	NA
150	TXA Level II [2019 update]	limit 138 to yr="2018 -Current"	NA	168	NA
151	TXA Level III [2019 update]	limit 139 to yr="2018 -Current"	NA	86	NA
152	TEG/ROTEM Level I [2019 update]	limit 140 to yr="2018 -Current"	NA	6	NA
153	TEG/ROTEM Level II [2019 update]	limit 141 to yr="2018 -Current"	NA	42	NA
154	TEG/ROTEM Level III [2019 update]	limit 142 to yr="2018 -Current"	NA	16	NA
155	Cell Salvage Level I [2019 update]	limit 143 to yr="2018 -Current"	NA	8	NA
156	Cell Salvage Level II [2019 update]	limit 144 to yr="2018 -Current"	NA	33	NA
157	Cell Salvage Level III [2019 update]	limit 145 to yr="2018 -Current"	NA	27	NA
	rFVIIa Level I [2021 update]	limit 134 to yr="2019 -Current"	NA	NA	3
	rFVIIa Level II [2021 update]	limit 135 to yr="2019 -Current"	NA	NA	3
	rFVIIa Level III [2021 update]	limit 136 to yr="2019 -Current"	NA	NA	12
	TXA Level I [2021 update]	limit 137 to yr="2019 -Current"	NA	NA	151
	TXA Level II [2021 update]	limit 138 to yr="2019 -Current"	NA	NA	342
	TXA Level III [2021 update]	limit 139 to yr="2019 -Current"	NA	NA	240
	TEG/ROTEM Level I [2021 update]	limit 140 to yr="2019 -Current"	NA	NA	13
	TEG/ROTEM Level II [2021 update]	limit 141 to yr="2019 -Current"	NA	NA	83
	TEG/ROTEM Level III [2021 update]	limit 142 to yr="2019 -Current"	NA	NA	47
	Cell Salvage Level I [2021 update]	limit 143 to yr="2019 -Current"	NA	NA	18
	Cell Salvage Level II [2021 update]	limit 144 to yr="2019 -Current"	NA	NA	51
	Cell Salvage Level III [2021 update]	limit 145 to yr="2019 -Current"	NA	NA	59

a. Due to an error, the literature search conducted 09 August 2019 was for exp hemorrhage/ (not exp *hemorrhage/). This has resulted in more hits than in 2018 as the search is not focused.

A3.3 EBM Reviews

EBM Reviews combines several resources into a single database and includes the following: Cochrane Database of Systematic Reviews (from 2005), ACP Journal Club (from 1991), Database of Abstracts of Reviews of Effects (from 1st Quarter 2016), Cochrane Clinical Answers (from July 2018), Cochrane Central Register of Controlled Trials (from June 2018), Cochrane Methodology Register (from 3rd Quarter 2012), Health Technology Assessment (from 4th Quarter 2016), and NHS Economic Evaluation Database (from 1st Quarter 2016)

Table A3.3 Literature search results: EBM Reviews

Search via Ovid for Level I, Level II, and Level III studies

#	Concept	Search string	Results 07 Aug 2018	Results 09 Aug 2018	Results 29 Sep 2021
1	Population (requiring transfusion)	exp *hemorrhage/	5624	13227 [a]	6393
2		oral hemorrhage/ or postoperative hemorrhage/ or peptic ulcer hemorrhage/ or gastrointestinal hemorrhage/ or uterine hemorrhage/ or obstetric hemorrhage/ or antepartum hemorrhage/ or intrapartum hemorrhage/ or postpartum hemorrhage/	4108	4308	4772
3		*shock/ or hemorrhagic shock/ or hypovolemic shock/ or traumatic shock/ or exsanguination/ or hemorrhagic hypotension/	469	523	738
4		((hemorrhag* or haemorrhag* or bleed* or bleeding or blood?loss* or 'blood-loss*' or bloodloss*) adj3 (critical or severe or massive or major or life threatening or 'life?threatening')).mp.	7312	9170	11095
5		((haemorrhagic or hemorrhagic or hypovolemic or hypovolaemic) adj shock).ti,ab.	259	334	427
6		or/1-5	14293	21273	19403
7		exp *blood transfusion/ or Erythrocyte Transfusion/	1091	1134	1257
8		blood autotransfusion/ or blood component therapy/ or plasma transfusion/ or thrombocyte transfusion/ or Platelet Transfusion/ or Blood Component Transfusion/	430	447	504
9		(blood component adj (transfus* or therapy)).ti,ab,kw.	84	108	142
10		or/7-9	1418	1498	1679
11	Population (critical bleeding requiring transfusion)	6 or 10	15409	22306	20711
12		Multiple Trauma/	216	220	238
13		trauma*.ab,ti,kw.	17202	22408	28485
14		(polytrauma* or poly?trauma* or 'poly trauma').ab,ti,kw.	157	187	244
15		(multitrauma* or multi?trauma* or 'multi trauma').ab,ti,kw.	17	29	38
16		'multiple trauma*'.ab,ti,kw.	293	409	480
17		blunt trauma/	0	0	0
18		traumatic hematoma/	0	0	0
19		exp amputation, traumatic/	45	47	59
20		or/12-19	17357	22575	28671
21		exp wounds, nonpenetrating/	600	639	806
22		exp wounds, penetrating/	347	356	374
23		surgical wound/	91	158	288
24		wound hemorrhage/	0	0	0
25	Population (wounds)	or/21-24	1000	1113	1426
26		*injury/	0	0	0
27		exp blast injuries/	20	20	21
28		exp abdominal injuries/	131	138	148
29		exp thoracic injuries/	350	389	542
30		exp war-related injuries/	0	0	0
31		childhood injury/ or contusion/ or crush trauma/ or limb injury/	109	112	128
32		organ injury/ or reperfusion injury/	474	503	597
33		surgical injury/	1594	1650	1785

#	Concept	Search string	Results 07 Aug 2018	Results 09 Aug 2018	Results 29 Sep 2021
34		gunshot injury/	0	0	0
35		accidental injury/	0	0	0
36		battle injury/	0	0	0
37	Population (injury)	or/26-36	2652	2784	3192
38		*accidents/	1	0	0
39		*emergency/	0	0	0
40		((major* or life threatening or life?threatening or substantial* or multip* or severe* or serious* or catastrophic* or critical* or massive* or penetrating) adj3 (trauma* or injur* or emergenc* or accident*)).ti,ab.	5516	6848	8470
41	Population (emergency)	or/38-40	5517	6848	8470
42	combine trauma and emergency	20 or 25 or 37 or 41	22798	28817	36237
43	Population (operative)	transplantation/	45	44	44
44		emergency surgery/ or general surgery/ or major surgery/	367	377	407
45		*surgery/ or abdominal surgery/ or cardiovascular surgery/ or thorax surgery/ or orthopedic surgery/	362	376	401
46		pediatric surgery/ or obstetrics/ or obstetric care/	175	185	214
47		(peri?operative or pre?operative or intra?operative or post?operative).ti,ab,kw.	86942	110381	135015
48		(surg* or operat* or resect* or perioperat*).ab,ti,kw.	190371	253065	310941
49		exp operative blood loss/	0	0	0
50		peroperative care/	1505	1566	1698
51		peroperative complication/ or postoperative complication/ or preoperative complication/	774	17118	18715
52		exp perioperative period/	7547	8024	9031
53		exp preoperative period/	223	251	345
54		or/43-53	208206	276125	336969
55	combine population sets (trauma, emergency, operative)	42 or 54	222785	294282	359909
56	Combine trauma, emergency, and operative with bleeding	11 and 55	5836	9205	8039
57		exp Factor VIIa/ or exp recombinant blood clotting factor 7a/	182	183	189
58		(recombinant f*VIIa or activated factor seven).ti,ab,kw.	17	23	25
59		(recombinant activated factor VII or recombinant activated VIIa).mp.	142	172	188
60		((recombinant adj4 VIIa) or (recombinant adj4 FVIIa) or (recombinant adj4 VII) or (recombinant adj4 FVII)).mp.	391	465	507
61		((recombinant adj3 factor 7) or (recombinant adj3 factor 7a)).mp.	94	73	73
62		(fVIIa or 'f VIIa' or f7a or 'f 7a' or rfVIIa or 'r fVIIa' or 'r f VIIa' or rf7a or 'r f7a' or 'r f 7a').mp.	330	401	435
63		or/57-62	527	623	677
64		eptacog*.mp.	14	31	43
65		feiba.mp.	54	60	68
66		niastase.mp.	5	9	10
67		(novoseven* or 'novo seven*').mp.	119	143	156
68		(novo7 or 'novo 7').mp.	2	2	2
69		('nn 1731' or nn1731).mp.	6	7	8
70		'102786-61-8'.rn.	0	0	0
71		proconvertin.mp.	7	9	12
72		or/64-71	176	210	232

#	Concept	Search string	Results 07 Aug 2018	Results 09 Aug 2018	Results 29 Sep 2021
73		63 or 72	578	682	742
74	Intervention (antifibrinolytics)	exp Antifibrinolytic Agents/	1483	1628	2078
75		exp Fibrinolytic Agents/	13245	13610	14919
76		exp Fibrinolysis/dt	0	0	0
77		(antifibrinoly* or 'anti fibrinoly*').ab,ti,kw.	589	693	842
78		(antiplasmin* or 'anti plasmin*').ab,ti,kw.	287	316	335
79		(fibrinolysis inhibitor* or 'plasmin inhibitor*').ab,ti,kw.	133	148	163
80		or/74-79	15095	15726	17552
81	Intervention (TXA)	exp Tranexamic Acid/	724	847	1190
82		'tranexamic acid'.ab,ti,kw,rn.	1698	2367	0
83		cyklokapron.ab,ti,kw.	13	30	33
84		TXA.ab,ti,kw.	410	636	1023
85		Lysteda.ab,ti,kw.	8	8	8
86		('1197-18-8' or '701-54-2').rn.	0	0	0
87		or/81-86	1768	2449	1776
88	Intervention (aprotinin)	exp APROTININ/	526	526	529
89		Aprotinin.ab,ti,kw,rn.	803	880	0
90		Transylol.ab,ti,kw.	0	0	0
91		'9087-70-1'.rn.	0	0	0
92		exp Aminocaproic Acid/	114	115	128
93		'Aminocaproic Acid'.ab,ti,kw,rn.	216	240	0
94		Amicar.ab,ti,kw.	19	21	21
95		('1319-82-0' or '60-32-2').rn.	0	0	0
96		or/88-95	1077	1166	642
97	Intervention (EACA)	('epsilon aminocapr$' or 'epsilon?aminocapr$' or 'aminomethylbenz$').ab,ti,kw.	171	188	203
98		EACA.ab,ti,kw.	81	89	101
99		56-91-7.rn.	0	0	0
100		('4?aminomethylbenz$' or '4 aminomethylbenz$').ab,ti,kw.	1	0	0
101		('p?aminomethylbenz$' or 'p aminomethylbenz$').ab,ti,kw.	3	3	3
102		PAMBA.ab,ti,kw.	6	6	6
103		or/97-102	188	206	223
104		80 or 87 or 96 or 103	16613	17798	18437
105	Intervention (TEG/ROTEM)	exp Thrombelastography/	222	233	266
106		goal directed therapy/	0	0	0
107		(thromb?elastograph* or thromb?elastomet*).mp.	643	803	968
108		viscoelast*.mp.	516	639	794
109		(TEG or ROTEG or ROTEM).mp.	398	541	688
110		(h?emoscope* or H?emonet*).mp.	82	92	99
111		'activat* clot* time*'.mp.	340	391	452
112		or/105-111	1573	1946	2348
113	Intervention (Cell Salvage)	exp Blood Transfusion, Autologous/	653	659	392
114		'cell salvage'.mp.	116	152	176
115		'blood salvage'.mp.	142	161	183
116		('autologous adj5 transfusion*').mp.	960	1042	1116
117		'blood conserv*'.mp.	213	243	266
118		'cell saver''.mp.	158	180	198
119		('autotransfusion' or 'auto transfusion').mp.	408	510	542
120		'salvage therap*'.mp.	1360	1650	1931
121		'erythrocyte salvage'.mp.	0	0	0
122		or/113-121	2755	3253	3682

#	Concept	Search string	Results 07 Aug 2018	Results 09 Aug 2018	Results 29 Sep 2021
123	Population and rFVIIa	56 and 73	82	114	112
124	Population AND antifibrinolytics	56 and 104	1276	1825	1573
125	Population & TEG/ROTEM	56 and 112	197	282	281
126	Population and cell salvage	56 and 122	375	496	425
127	Level I	exp meta analysis/ or meta analysis.mp. or exp systematic review/ or systematic review.mp. or pooled analysis.mp. or ((exp review/ or review.mp.) and (systemat* or pool*).mp.)	68951	85895	NA
128	Level II	exp comparative study/ or comparative study.mp. or exp clinical trial/ or clinical trial.mp. or randomized controlled trial.mp. or randomi?ed controlled trial.mp. or exp randomized controlled trial/ or exp randomization/ or randomization.mp. or randomi?ation.mp. or exp single blind procedure/ or single blind procedure.mp. or exp double blind procedure/ or double blind procedure.mp. or exp triple blind procedure/ or triple blind procedure.mp. or exp crossover procedure/ or crossover procedure.mp. or exp placebo/ or placebo*.mp. or random*.mp. or rct.mp. or single blind.mp. or single blinded.mp. or double blind.mp. or double blinded.mp. or treble blind.mp. or triple blind.mp. or triple blinded.mp. or exp prospective study/ or prospective study.mp.	973159	1200427	NA
129	Level III	exp clinical study/ or exp case control study/ or exp family study/ or exp longitudinal study/ or exp retrospective study/ or exp cohort analysis/ or (cohort adj1 stud*).mp. or (case control adj1 stud*).mp. or (exp prospective study/ not randomi?ed controlled trials.mp.) or (follow up adj1 stud*).mp. or (observational adj1 stud*).mp. or (epidemiologic* adj1 stud*).mp. or (cross sectional adj1 stud*).mp.	194352	208994	NA
130	Study filters	case report/	3	4	NA
131		(editorial or letter or comment or historical article).pt.	7523	8014	NA
132		130 or 131	7526	8018	NA
133	nonhuman study	(animals/ not humans/) or nonhuman/	25	27	NA
134	rFVIIa Level I	(123 and 127) not (131 or 133)	25	31	NA
135	rFVIIa Level II	(123 and 128) not (132 or 133 or 134)	48	70	NA
136	rFVIIa Level III	(123 and 129) not (132 or 133 or 134 or 135)	3	3	NA
137	TXA Level I	(124 and 127) not (131 or 133)	61	66	NA
138	TXA Level II	(124 and 128) not (132 or 133 or 137)	1090	1570	NA
139	TXA Level III	(124 and 129) not (132 or 133 or 137 or 138)	21	28	NA
140	TEG/ROTEMLevel I	(125 and 127) not (131 or 133)	14	15	NA
141	TEG/ROTEM level II	(125 and 128) not (132 or 133 or 140)	173	247	NA
142	TEG/ROTEM Level III	(125 and 129) not (132 or 133 or 140 or 141)	0	0	NA
143	Cell Salvage Level I	(126 and 127) not (131 or 133)	16	19	NA
144	Cell Salvage Level II	(126 and 128) not (132 or 133 or 143)	316	419	NA
145	Cell salvage Level III	(126 and 129) not (132 or 133 or 143 or 144)	9	12	NA
146	rFVIIa Level I [2019 update]	limit 134 to yr="2018 -Current" [Limit not valid in DARE; records were retained]	NA	13	NA
147	rFVIIa Level II [2019 update]	limit 135 to yr="2018 -Current" [Limit not valid in DARE; records were retained]	NA	0	NA
148	rFVIIa Level III [2019 update]	limit 136 to yr="2018 -Current" [Limit not valid in DARE; records were retained]	NA	0	NA
149	TXA Level I [2019 update]	limit 137 to yr="2018 -Current" [Limit not valid in DARE; records were retained]	NA	10	NA
150	TXA Level II [2019 update]	limit 138 to yr="2018 -Current" [Limit not valid in DARE; records were retained]	NA	108	NA

#	Concept	Search string	Results 07 Aug 2018	Results 09 Aug 2018	Results 29 Sep 2021
151	TXA Level III [2019 update]	limit 139 to yr="2018 -Current" [Limit not valid in DARE; records were retained]	NA	0	NA
152	TEG/ROTEM Level I [2019 update]	limit 140 to yr="2018 -Current" [Limit not valid in DARE; records were retained]	NA	6	NA
153	TEG/ROTEM Level II [2019 update]	limit 141 to yr="2018 -Current" [Limit not valid in DARE; records were retained]	NA	16	NA
154	TEG/ROTEM Level III [2019 update]	limit 142 to yr="2018 -Current" [Limit not valid in DARE; records were retained]	NA	0	NA
155	Cell Salvage Level I [2019 update]	limit 143 to yr="2018 -Current" [Limit not valid in DARE; records were retained]	NA	0	NA
156	Cell Salvage Level II [2019 update]	limit 144 to yr="2018 -Current" [Limit not valid in DARE; records were retained]	NA	12	NA
157	Cell Salvage Level III [2019 update]	limit 145 to yr="2018 -Current" [Limit not valid in DARE; records were retained]	NA	0	NA

a. Due to an error, the literature search conducted 09 August 2019 was for exp hemorrhage/ (not exp *hemorrhage/). This has resulted in more hits than in 2018 as the search is not focused.

A3.4 PubMed search

The PubMed search was restricted to records that are not indexed for MEDLINE (i.e. in-process citations and citations from journals (or parts of journals) that are not currently MEDLINE-indexed) and to records added to PubMed since January 2006. The search comprises free-text terms only and replicates the free-text sets in the Embase search (converted from the Ovid syntax).

Questions 5, 7, 8, and 9 were searched were searched separately as detailed below.

Table A3.4 Literature search results: PubMed (in-process and citations not indexed in MEDLINE): Question 5 (rFVIIa)

	Concept	Search string	Results 06 Aug 2018	Results 12 Aug 2019	Results 29 Sep 2021
1	Population (critical bleeding)	Search (hemorrhag* [tiab] or haemorrhag*[tiab])	241733	253627	282605
2		Search ((hemorrhag*[tiab] or haemorrhag*[tiab] or bleed*[tiab] or blood loss*[tiab] or blood-loss*[tiab] or bloodloss*[tiab]) AND (critical[tiab] or severe[tiab] or massive[tiab] or major[tiab] or life threatening[tiab] or serious[tiab] or significant[tiab] or substantial[tiab] or extreme[tiab] or catastrophic[tiab] or uncontrol*[tiab] or excess[tiab] or acute[tiab]))	210784	224862	260332
3		Search (#1 or #2)	336735	355789	402828
4	Population (transfusion)	Search (blood transfusion[tiab] or erythrocyte transfusion[tiab])	37037	38947	43511
5		Search (blood autotransfusion[tiab] or blood component therapy[tiab] or plasma transfusion[tiab] or thrombocyte transfusion[tiab] or platelet transfusion[tiab] or blood component transfusion[tiab] or blood component therapy[tiab])	3944	4219	5021
6		Search (#4 or #5)	40619	42770	48034
7	Combine population (bleeding and transfusion)	Search (#3 or #6)	369223	389764	440444
8	Population (trauma)	Search (trauma[tiab] or poly trauma[tiab] or polytrauma[tiab] or multitrauma[tiab] or multi trauma[tiab] or multiple trauma[tiab] or multiple wounds[tiab] or multiple wound[tiab] or multiple injuries[tiab] or multiple injury[tiab])	208965	222683	258022

	Concept	Search string	Results 06 Aug 2018	Results 12 Aug 2019	Results 29 Sep 2021
9		Search blunt trauma[tiab]	8512	8900	9870
10		Search (traumatic[tiab] AND (hematoma[tiab] or haematoma[tiab] or shock[tiab] or amputation[tiab]))	10132	10705	12215
11		Search (#8 or #9 or #10)	215807	229860	266053
12		Search ((wounds[tiab] or wound[tiab]) AND (nonpenetrating[tiab] or penetrating[tiab] or surgical[tiab] or haemorrhage[tiab]))	40088	42783	49304
13		Search (injur*[tiab] AND (blast[tiab] or abdominal[tiab] or thorax[tiab] or thoracic[tiab] or war related[tiab] or childhood[tiab] or limb[tiab] or organ[tiab] or reperfusion[tiab] or surgical[tiab] or gunshot[tiab] or accidental[tiab] or battle[tiab]))	168112	179829	209878
14		Search ((major[tiab] or life threatening[tiab] or substantial[tiab] or multiple[tiab] or severe[tiab] or serious[tiab] or catastrophic[tiab] or critical[tiab] or catastrophic[tiab] or massive[tiab] or penetrating[tiab]) AND (trauma[tiab] or traumatic[tiab] or injury[tiab] or injuries[tiab] or injured[tiab] or emergency[tiab] or emergencies[tiab] or accident[tiab]))	310734	334950	403486
15		Search (#11 or #12 or #13 or #14)	575735	617157	728977
16	Population (surgery)	Search transplantation[tiab]	323695	340223	397116
17		Search (surgery[tiab] AND emergency[tiab] or general[tiab] or major[tiab])	2065729	2191100	2501722
18		Search (surgery[tiab] or abdominal surgery[tiab] or cardiovascular surgery[tiab] or thorax surgery[tiab] or (orthopaedic[tiab] or orthopedic[tiab] AND surgery[tiab]))	1094668	1162676	1334226
19		Search ((pediatric[tiab] or paediatric[tiab] AND surgery[tiab]) or obstetrics[tiab] or maternity[tiab])	80535	86705	102062
20		Search ((peroperative[tiab] or intraoperative[tiab] or intra operative[tiab] or postoperative[tiab] or post operative[tiab] or preoperative[tiab] or pre operative[tiab]) AND complication[tiab])	57483	62764	76407
21		Search perioperative[tiab]	78693	86245	111758
22		Search (#16 or #17 or #18 or #19 or #20 or #21)	3366977	3569200	4072467
23	population (trauma or surgery)	Search (#15 or #22)	3750009	3978737	4554098
24	Group populations (critical bleeding and trauma or surgery)	Search (#7 AND #23)	138469	148278	172976
25	Intervention (factor VII)	Search ((factor VII[tiab] or factorVII[tiab] or fVII[tiab] or factorVIIa[tiab] or fVIIa[tiab] or factor7[tiab] or factor 7[tiab] or factor 7a[tiab] or factor seven[tiab]) AND (coagulat*[tiab] or clotting[tiab]))	3894	4007	4223
26		Search ((recombinant[tiab] or activated[tiab]) AND (factor VII[tiab] or factorVII[tiab] or fVII[tiab] or factorVIIa[tiab] or fVIIa[tiab] or factor7[tiab] or factor 7[tiab] or factor 7a[tiab] or factor seven[tiab]))	3435	3546	3774
27		Search (fVIIa[tiab] or f VIIa[tiab] or f7a[tiab] or f 7a[tiab] or rfVIIa[tiab] or r fVIIa[tiab] or r f VIIa[tiab] or rf7a[tiab] or rf 7a[tiab] or r f 7a[tiab])	2669	2748	3561
28		Search (#25 OR #26 OR #27)	6360	6540	7583
29		Search eptacog*[tiab]	28	34	40
30		Search feiba[tiab]	276	289	309
31		Search niastase[tiab]	4	4	4
32		Search (novoseven[tiab] or novo seven[tiab] or novo7[tiab] or novo 7[tiab])	12538	13623	17472
33		Search (nn 1731[tiab] or nn1731[tiab])	23	23	28
34		Search 102786-61-8[rn]	1577	1617	1684
35		Search proconvertin[tiab]	153	153	154
36		Search (#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35)	19198	20475	25397
37		Search (#28 OR #36)	19198	20475	25397

	Concept	Search string	Results 06 Aug 2018	Results 12 Aug 2019	Results 29 Sep 2021
38	Combine population and intervention	Search (#24 AND #37)	1395	1448	1595
39	Limit to PubMed	Search (#38 AND pubmednotmedline[sb])	80	91	121
40	Date limit [2019 update]	Search ((("2018/01/01"[Date - Entrez] : "3000"[Date - Entrez]) AND #39))	NA	17	NA
	Date limit [2021 update]	Search ((("2019/01/01"[Date - Entrez] : "3000"[Date - Entrez]) AND #39))	NA	NA	29

Table A3.5 Literature search results: PubMed (in-process and citations not indexed in MEDLINE): Question 7 (antifibrinolytics)

#	Concept	Search string	Results 06 Aug 2018	Results 12 Aug 2019	Results 29 Sep 2021
1	Population (critical bleeding)	Search (hemorrhag* [tiab] or haemorrhag*[tiab])	241733	253627	282605
2		Search ((hemorrhag*[tiab] or haemorrhag*[tiab] or bleed*[tiab] or blood loss*[tiab] or blood-loss*[tiab] or bloodloss*[tiab]) AND (critical[tiab] or severe[tiab] or massive[tiab] or major[tiab] or life threatening[tiab] or serious[tiab] or significant[tiab] or substantial[tiab] or extreme[tiab] or catastrophic[tiab] or uncontrol*[tiab] or excess[tiab] or acute[tiab]))	210784	224862	260332
3		Search (#1 or #2)	336735	355789	402828
4	Population (transfusion)	Search (blood transfusion[tiab] or erythrocyte transfusion[tiab])	37037	38947	43511
5		Search (blood autotransfusion[tiab] or blood component therapy[tiab] or plasma transfusion[tiab] or thrombocyte transfusion[tiab] or platelet transfusion[tiab] or blood component transfusion[tiab] or blood component therapy[tiab])	3944	4219	5021
6		Search (#4 or #5)	40619	42770	48034
7	Combine population (critical bleeding and transfusion)	Search (#3 or #6)	369223	389764	440444
8	Population (trauma)	Search (trauma[tiab] or poly trauma[tiab] or polytrauma[tiab] or multitrauma[tiab] or multi trauma[tiab] or multiple trauma[tiab] or multiple wounds[tiab] or multiple wound[tiab] or multiple injuries[tiab] or multiple injury[tiab])	208965	222683	258022
9		Search blunt trauma[tiab]	8512	8900	9870
10		Search (traumatic[tiab] AND (hematoma[tiab] or haematoma[tiab] or shock[tiab] or amputation[tiab]))	10132	10705	12215
11		Search (#8 or #9 or #10)	215807	229860	266053
12		Search ((wounds[tiab] or wound[tiab]) AND (nonpenetrating[tiab] or penetrating[tiab] or surgical[tiab] or haemorrhage[tiab]))	40088	42783	49304
13		Search (injur*[tiab] AND (blast[tiab] or abdominal[tiab] or thorax[tiab] or thoracic[tiab] or war related[tiab] or childhood[tiab] or limb[tiab] or organ[tiab] or reperfusion[tiab] or surgical[tiab] or gunshot[tiab] or accidental[tiab] or battle[tiab]))	168112	179829	209878
14		Search ((major[tiab] or life threatening[tiab] or substantial[tiab] or multiple[tiab] or severe[tiab] or serious[tiab] or catastrophic[tiab] or critical[tiab] or catastrophic[tiab] or massive[tiab] or penetrating[tiab]) AND (trauma[tiab] or traumatic[tiab] or injury[tiab] or injuries[tiab] or injured[tiab] or emergency[tiab] or emergencies[tiab] or accident[tiab]))	310734	334950	403486
15		Search (#11 or #12 or #13 or #14)	575735	617157	728977
16	Population (surgery)	Search transplantation[tiab]	323695	340223	397116
17		Search (surgery[tiab] AND emergency[tiab] or general[tiab] or major[tiab])	2065729	2191100	2501722
18		Search (surgery[tiab] or abdominal surgery[tiab] or cardiovascular surgery[tiab] or thorax surgery[tiab] or (orthopaedic[tiab] or orthopedic[tiab] AND surgery[tiab]))	1094668	1162676	1334226

#	Concept	Search string	Results 06 Aug 2018	Results 12 Aug 2019	Results 29 Sep 2021
19		Search ((pediatric[tiab] or paediatric[tiab] AND surgery[tiab]) or obstetrics[tiab] or maternity[tiab])	80535	86705	102062
20		Search ((peroperative[tiab] or intraoperative[tiab] or intra operative[tiab] or postoperative[tiab] or post operative[tiab] or preoperative[tiab] or pre operative[tiab]) AND complication[tiab])	57483	62764	76407
21		Search perioperative[tiab]	78693	86245	111758
22		Search (#16 or #17 or #18 or #19 or #20 or #21)	3366977	3569200	4072467
23	population (trauma or surgery)	Search (#15 or #22)	3750009	3978737	4554098
24	Group populations (critical bleeding and trauma or surgery)	Search (#7 AND #23)	138469	148278	172976
41	Intervention	Search (antifibrinolytic agents[tiab] or anti fibrinoly*[tiab] or fibrinolytic agents[tiab] or fibrinolysis[tiab] or antifibrinolytics[tiab] or antifibrinolysins[tiab] or plasmin Inhibitor*[tiab] or antiplasmin*[tiab] or anti plasmin*[tiab])	22413	22969	24422
42		Search (tranexamic acid[tiab] or cyklokapron [tiab] or TXA[tiab] or lysteda[tiab] or TXA[tiab] or 1197-18-8[rn] or 701-54-2[rn])	5043	5557	7116
43		Search (Aprotinin[tiab] or Trypsin inhibitor[tiab] or Transylol[tiab] or Aminocaproic acid[tiab] or amicar[tiab] or 1319-82-0[rn] or 60-32-2[rn])	13750	13920	14360
44		Search (epsilon aminocapr*[tiab] or aminomethylbenz*[tiab] or EACA[tiab] or 56-91-7[rn] or 4aminomethylbenz*[tiab] or â€˜4 aminomethylbenz*â€™[tiab] or â€˜p aminomethylbenz*â€™[tiab] or PAMBA[tiab])	2115	18741	2257
45		Search (#41 OR #42 OR #43 #44)	1707	1736	1777
46	Combine population and intervention	Search (#45 AND #24)	204	218	231
47	Limit to PubMed	Search (#46 AND pubmednotmedline[sb])	3	4	5
48	Date limit [2019 update]	Search ((("2018/01/01"[Date - Entrez] : "3000"[Date - Entrez]) AND #47))	NA	1	NA
	Date limit [2021 update]	Search ((("2019/01/01"[Date - Entrez] : "3000"[Date - Entrez]) AND #47))	NA	NA	1

Table A3.6 Literature search results: PubMed (in-process and citations not indexed in MEDLINE): Question 8 (TEG/ROTEM)

#	Concept	Search string	Results 06 Aug 2018	Results 12 Aug 2019	Results 29 Sep 2021
1	Population (critical bleeding)	Search (hemorrhag* [tiab] or haemorrhag*[tiab])	241733	253627	282605
2		Search ((hemorrhag*[tiab] or haemorrhag*[tiab] or bleed*[tiab] or blood loss*[tiab] or blood-loss*[tiab] or bloodloss*[tiab]) AND (critical[tiab] or severe[tiab] or massive[tiab] or major[tiab] or life threatening[tiab] or serious[tiab] or significant[tiab] or substantial[tiab] or extreme[tiab] or catastrophic[tiab] or uncontrol*[tiab] or excess[tiab] or acute[tiab]))	210784	224862	260332
3		Search (#1 or #2)	336735	355789	402828
4	Population (transfusion)	Search (blood transfusion[tiab] or erythrocyte transfusion[tiab])	37037	38947	43511
5		Search (blood autotransfusion[tiab] or blood component therapy[tiab] or plasma transfusion[tiab] or thrombocyte transfusion[tiab] or platelet transfusion[tiab] or blood component transfusion[tiab] or blood component therapy[tiab])	3944	4219	5021
6		Search (#4 or #5)	40619	42770	48034

#	Concept	Search string	Results 06 Aug 2018	Results 12 Aug 2019	Results 29 Sep 2021
7	Combine population (critical bleeding and transfusion)	Search (#3 or #6)	369223	389764	440444
8	Population (trauma)	Search (trauma[tiab] or poly trauma[tiab] or polytrauma[tiab] or multitrauma[tiab] or multi trauma[tiab] or multiple trauma[tiab] or multiple wounds[tiab] or multiple wound[tiab] or multiple injuries[tiab] or multiple injury[tiab])	208965	222683	258022
9		Search blunt trauma[tiab]	8512	8900	9870
10		Search (traumatic[tiab] AND (hematoma[tiab] or haematoma[tiab] or shock[tiab] or amputation[tiab]))	10132	10705	12215
11		Search (#8 or #9 or #10)	215807	229860	266053
12		Search ((wounds[tiab] or wound[tiab]) AND (nonpenetrating[tiab] or penetrating[tiab] or surgical[tiab] or haemorrhage[tiab]))	40088	42783	49304
13		Search (injur*[tiab] AND (blast[tiab] or abdominal[tiab] or thorax[tiab] or thoracic[tiab] or war related[tiab] or childhood[tiab] or limb[tiab] or organ[tiab] or reperfusion[tiab] or surgical[tiab] or gunshot[tiab] or accidental[tiab] or battle[tiab]))	168112	179829	209878
14		Search ((major[tiab] or life threatening[tiab] or substantial[tiab] or multiple[tiab] or severe[tiab] or serious[tiab] or catastrophic[tiab] or critical[tiab] or catastrophic[tiab] or massive[tiab] or penetrating[tiab]) AND (trauma[tiab] or traumatic[tiab] or injury[tiab] or injuries[tiab] or injured[tiab] or emergency[tiab] or emergencies[tiab] or accident[tiab]))	310734	334950	403486
15		Search (#11 or #12 or #13 or #14)	575735	617157	728977
16	Population (surgery)	Search transplantation[tiab]	323695	340223	397116
17		Search (surgery[tiab] AND emergency[tiab] or general[tiab] or major[tiab])	2065729	2191100	2501722
18		Search (surgery[tiab] or abdominal surgery[tiab] or cardiovascular surgery[tiab] or thorax surgery[tiab] or (orthopaedic[tiab] or orthopedic[tiab] AND surgery[tiab]))	1094668	1162676	1334226
19		Search ((pediatric[tiab] or paediatric[tiab] AND surgery[tiab]) or obstetrics[tiab] or maternity[tiab])	80535	86705	102062
20		Search ((peroperative[tiab] or intraoperative[tiab] or intra operative[tiab] or postoperative[tiab] or post operative[tiab] or preoperative[tiab] or pre operative[tiab]) AND complication[tiab])	57483	62764	76407
21		Search perioperative[tiab]	78693	86245	111758
22		Search (#16 or #17 or #18 or #19 or #20 or #21)	3366977	3569200	4072467
23	population (trauma or surgery)	Search (#15 or #22)	3750009	3978737	4554098
24	Group populations (critical bleeding and trauma or surgery)	Search (#7 AND #23)	138469	148278	172976
41	Intervention	Search ((goal directed therap*[tiab] OR early goal directed therap*[tiab]))	956	1030	1182
42		Search ((Thromboelasto*[tiab] OR thrombelasto*[tiab] OR thrombo elasto*[tiab]))	4903	5333	6321
43		Search viscoelast*[tiab]	13777	15017	19169
44		Search (((TEG[tiab] or ROTEG[tiab] or ROTEM[tiab])))	2469	2778	3882
45		Search ((haemoscope*[tiab] OR hemoscope*[tiab] OR haemonet*[tiab] OR hemonet*[tiab]))	532	544	576
46		Search (((activated[tiab] or activating[tiab]) AND (coagulation[tiab] or clot[tiab] or clotting[tiab]) AND (time[tiab] or times [tiab])))	8668	9131	10237
47		Search (#41 OR #42 OR #43 OR #44 OR #45 OR #46)	28166	30314	36894
48	Combine population and intervention	Search (#47 AND #24)	1973	2160	2604
49	Limit to PubMed	Search (#48 AND pubmednotmedline[sb])	120	158	265

#	Concept	Search string	Results 06 Aug 2018	Results 12 Aug 2019	Results 29 Sep 2021
50	Date limit [2019 update]	Search ((("2018/01/01"[Date - Entrez] : "3000"[Date - Entrez]) AND #49))	NA	42	NA
	Date limit [2021 update]	Search ((("2019/01/01"[Date - Entrez] : "3000"[Date - Entrez]) AND #49))	NA	NA	110

Table A3.7 Literature search results: PubMed (in-process and citations not indexed in MEDLINE) Question 9 (cell salvage)

#	Concept	Search string	Results 06 Aug 2018	Results 12 Aug 2019	Results 29 Sep 2021
1	Population (critical bleeding)	Search (hemorrhag* [tiab] or haemorrhag*[tiab])	241733	253627	282605
2		Search ((hemorrhag*[tiab] or haemorrhag*[tiab] or bleed*[tiab] or blood loss*[tiab] or blood-loss*[tiab] or bloodloss*[tiab]) AND (critical[tiab] or severe[tiab] or massive[tiab] or major[tiab] or life threatening[tiab] or serious[tiab] or significant[tiab] or substantial[tiab] or extreme[tiab] or catastrophic[tiab] or uncontrol*[tiab] or excess[tiab] or acute[tiab]))	210784	224862	260332
3		Search (#1 or #2)	336735	355789	402828
4	Population (transfusion)	Search (blood transfusion[tiab] or erythrocyte transfusion[tiab])	37037	38947	43511
5		Search (blood autotransfusion[tiab] or blood component therapy[tiab] or plasma transfusion[tiab] or thrombocyte transfusion[tiab] or platelet transfusion[tiab] or blood component transfusion[tiab] or blood component therapy[tiab])	3944	4219	5021
6		Search (#4 or #5)	40619	42770	48034
7	Combine population (critical bleeding and transfusion)	Search (#3 or #6)	369223	389764	440444
8	Population (trauma)	Search (trauma[tiab] or poly trauma[tiab] or polytrauma[tiab] or multitrauma[tiab] or multi trauma[tiab] or multiple trauma[tiab] or multiple wounds[tiab] or multiple wound[tiab] or multiple injuries[tiab] or multiple injury[tiab])	208965	222683	258022
9		Search blunt trauma[tiab]	8512	8900	9870
10		Search (traumatic[tiab] AND (hematoma[tiab] or haematoma[tiab] or shock[tiab] or amputation[tiab]))	10132	10705	12215
11		Search (#8 or #9 or #10)	215807	229860	266053
12		Search ((wounds[tiab] or wound[tiab]) AND (nonpenetrating[tiab] or penetrating[tiab] or surgical[tiab] or haemorrhage[tiab]))	40088	42783	49304
13		Search (injur*[tiab] AND (blast[tiab] or abdominal[tiab] or thorax[tiab] or thoracic[tiab] or war related[tiab] or childhood[tiab] or limb[tiab] or organ[tiab] or reperfusion[tiab] or surgical[tiab] or gunshot[tiab] or accidental[tiab] or battle[tiab]))	168112	179829	209878
14		Search ((major[tiab] or life threatening[tiab] or substantial[tiab] or multiple[tiab] or severe[tiab] or serious[tiab] or catastrophic[tiab] or critical[tiab] or catastrophic[tiab] or massive[tiab] or penetrating[tiab]) AND (trauma[tiab] or traumatic[tiab] or injury[tiab] or injuries[tiab] or injured[tiab] or emergency[tiab] or emergencies[tiab] or accident[tiab]))	310734	334950	403486
15		Search (#11 or #12 or #13 or #14)	575735	617157	728977
16	Population (surgery)	Search transplantation[tiab]	323695	340223	397116
17		Search (surgery[tiab] AND emergency[tiab] or general[tiab] or major[tiab])	2065729	2191100	2501722
18		Search (surgery[tiab] or abdominal surgery[tiab] or cardiovascular surgery[tiab] or thorax surgery[tiab] or (orthopaedic[tiab] or orthopedic[tiab] AND surgery[tiab]))	1094668	1162676	1334226
19		Search ((pediatric[tiab] or paediatric[tiab] AND surgery[tiab]) or obstetrics[tiab] or maternity[tiab])	80535	86705	102062
20		Search ((peroperative[tiab] or intraoperative[tiab] or intra operative[tiab] or postoperative[tiab] or post operative[tiab] or preoperative[tiab] or pre operative[tiab]) AND complication[tiab])	57483	62764	76407

#	Concept	Search string	Results 06 Aug 2018	Results 12 Aug 2019	Results 29 Sep 2021
21		Search perioperative[tiab]	78693	86245	111758
22		Search (#16 or #17 or #18 or #19 or #20 or #21)	3366977	3569200	4072467
23	Population (trauma or surgery)	Search (#15 or #22)	3750009	3978737	4554098
24	Group populations (critical bleeding and trauma or surgery)	Search (#7 AND #23)	138469	148278	172976
51	Intervention (cell salvage)	Search (((cell[tiab] OR cells[tiab] OR cellular[tiab]) AND salvag*[tiab]))	10752	11480	13126
52		Search blood salvage[tiab]	519	541	570
53		Search ((autologous[tiab] AND transfus*[tiab]))	4790	4939	5206
54		Search blood conserv*[tiab]	935	973	1074
55		Search (((cell[tiab] OR cells[tiab] OR cellular[tiab]) AND saver[tiab]))	682	714	780
56		Search ((autotransfusion[tiab] OR "auto transfusion"[tiab]))	1785	1811	1857
57		Search salvage therap*[tiab]	5226	5606	6592
58		Search erythrocyte salvage[tiab]	5	5	6
59		Search (#51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 or #58)	20761	21930	24577
60	Combine population and intervention	Search (#59 AND #24)	2429	2706	2974
61	Limit to PubMed	Search (#60 AND pubmednotmedline[sb])	93	156	201
62	Date limit [2019 update]	Search ((("2018/01/01"[Date - Entrez] : "3000"[Date - Entrez]) AND #61))	NA	23	NA
	Date limit [2021 update]	Search ((("2019/01/01"[Date - Entrez] : "3000"[Date - Entrez]) AND #61))	NA	NA	49

Ovid syntax

Exp explodes controlled vocabulary term (i.e. includes all narrower terms in the hierarchy)
* denotes a term that has been searched as a major subject heading
/ denotes controlled vocabulary terms (EMTREE)
$ truncation character (unlimited truncation)
$(n) truncation limited to specified number (n) of characters (e.g. time$1 identifies time, timed, timer, times but not timetable)
* truncation character (unlimited truncation)
? substitutes any letter (e.g. oxidi?ed identifies oxidised and oxidized)
adj(n) search terms within a specified number (n) of words from each other in any order
.ti. limit to title field
.ti,ab. limit to title and abstract fields
.kw,ti,ab. limit to keyword, title and abstract field
.pt limit to publication type

PubMed syntax

* truncation character (unlimited truncation)
[TI] limit to title field
[TIAB] limit to title and abstract fields
[EDAT] date citation added to PubMed
[SB] PubMed subset

Appendix B Literature screening results

B1 Question 1

Table B1.1 Literature screening results: Question 1 – 2018/2019

	Number of citations [a]			
Database	**Level I**	**PubMed (not Medline)**	**Level II (not Level I)**	**Level III**
Medline	187	0	2984	1833
Embase	718	0	6343	7307
Cochrane	28	0	1137	20
PubMed	0	2043	0	0
TOTAL	**933**	**2043**	**10 464**	**9160**
Protocol date limit (prior to 2009)	120	0	0	0
Additional date limit (prior to 2016)	0	1048	4088	2648
Duplicates (within Qs within Endnote)	118	150	3393	2789
Duplicates (across Qs within Covidence)	49	0	727	891
Available for Title/abstract screening	**646**	**845**	**2256**	**2832**
Number of citations excluded				
Additional duplicates identified	3	0	*Not screened*	*Not screened*
Nonhuman	3	24		
Population out of scope	358	533		
Prognostic factor (or intervention) out of scope	133	97		
Comparator out of scope	4	0		
Outcome out of scope	0	4		
Publication type out of scope (nonsystematic review)	33	3		
Publication type out of scope (opinion piece)	4	2		
Publication type out of scope (editorial)	3	0		
Publication type out of scope (protocol, other)	16	6		
Level II study included in Level I	0	0		
Study design out of scope (Level III)	0	0		
Study design out of scope (Level IV or below)	15	140		
Superseded	1	0		
TOTAL irrelevant	**573**	**809**		
Available for Full text screening	**73**	**36**		
Number of citations excluded				
Not available in English	2	0	*Not screened*	*Not screened*
Population out of scope	28	10		
Intervention out of scope	3	0		
Wrong prognostic factor	2	3		
Comparator out of scope	0	0		
Outcome out of scope	6	7		
Publication type out of scope (nonsystematic review)	6	0		
Publication type out of scope (opinion piece)	1	0		
Publication type out of scope (editorial)	0	0		
Publication type out of scope (protocol, other)	0	0		
Level II study included in Level I	0	0		
Study design out of scope (Level III)	0	0		
Study design out of scope (Level IV or below)	3	0		

	Number of citations [a]			
Database	**Level I**	**PubMed (not Medline)**	**Level II (not Level I)**	**Level III**
Insufficient adjustment of confounders	0	1		
No usable data	8	0		
Duplicate data	2	0		
TOTAL excluded	**61**	**21**		
TOTAL INCLUDED	12	15		

a. Inclusive of citations and articles identified through literature searches conducted in August 2018 and August 2019.

Table B1.2 Literature screening results: Question 1 – 2021

	Number of citations [a]			
Database	**Level I**	**PubMed (not Medline)**	**Level II (not Level I)**	**Level III**
Medline	50		323	*Not searched*
Embase	239		1428	
Cochrane	55		44	
PubMed		19	19	
TOTAL	**344**	**19**	**1814**	
Additional date limit (prior to 2019)			177	
Duplicates (within Qs within Endnote)	7		323	
Duplicates (across Qs within Covidence)	35		7	
Available for Title/abstract screening	**321**		**1307**	
Number of citations excluded				
Additional duplicates identified	22		10	*Not screened*
Nonhuman	0		10	
Population out of scope (screened in Endnote)	0		881	
Population out of scope	169		237	
Prognostic factor or intervention) out of scope	66		141	
Comparator out of scope	0		1	
Outcome out of scope	20		15	
Publication type out of scope (nonsystematic review)	14		0	
Publication type out of scope (opinion piece)	0		1	
Publication type out of scope (editorial)	0		0	
Publication type out of scope (protocol, other)	0		0	
Level II study included in Level I	0		0	
Study design out of scope (Level III)	8		0	
Study design out of scope (Level IV or below)	8		1	
Superseded	0		0	
TOTAL irrelevant	**307**		**1297**	
Available for Full text screening	**14**		**10**	
Number of citations excluded				
Not available in English	0		0	*Not screened*
Population out of scope	4		4	
Intervention out of scope	0		0	
Wrong prognostic factor	4		1	
Comparator out of scope	0		0	
Outcome out of scope	0		1	
Publication type out of scope (nonsystematic review)	3		0	
Publication type out of scope (opinion piece)	0		0	

	Number of citations [a]			
Database	**Level I**	**PubMed (not Medline)**	**Level II (not Level I)**	**Level III**
Publication type out of scope (editorial)	0		0	
Publication type out of scope (protocol, other)	1		1	
Level II study included in Level I	0		0	
Study design out of scope (Level III)	0		0	
Study design out of scope (Level IV or below)	0		0	
Insufficient adjustment of confounders	0		0	
No usable data	0		0	
Duplicate data	0		0	
TOTAL excluded	**12**		**7**	
TOTAL INCLUDED	2		3	

B2 Questions 2, 3, 4, & 6

Table B2.1 Literature screening results: Questions 2, 3, 4 & 6 – 2018/2019

	Number of citations [a]			
Database	**Level I**	**PubMed (not Medline)**	**Level II (not Level I)**	**Level III**
Medline	1101	0	8022	6582
Embase	2416	0	15277	20996
Cochrane	123	0	2799	250
PubMed	0	4175	0	0
TOTAL	**3640**	**4175**	**26 098**	**27 828**
Protocol date limit [b]	971	0	11789	5702
Additional date limit [c]	17	1376	5111	9714
Duplicates (within Qs)	706	1369	2269	2909
Duplicates (across Qs)	599	22	1600	2186
Available for Title/abstract screening	**1347**	**1408**	**5329**	**7317**
Number of citations excluded				
Additional duplicates identified	45	155	*Not screened*	*Not screened*
Nonhuman	0	12		
Population out of scope	377	805		
Intervention out of scope	628	285		
Comparator out of scope	5	10		
Outcome out of scope	11	25		
Publication type out of scope (nonsystematic review)	29	3		
Publication type out of scope (opinion piece)	2	1		
Publication type out of scope (editorial)	3	1		
Publication type out of scope (protocol, other)	1	0		
Level II study included in Level I	0	0		
Study design out of scope (Level III)	0	0		
Study design out of scope (Level IV or below)	1	35		
Publication not available in English				
Superseded	0	0		
Withdrawn	0	0		
TOTAL irrelevant	**1102**	**1332**		
Available for Full text screening	**245**	**76**		
Number of citations excluded				
Not available in English	11	0	*Not screened*	*Not screened*
Population out of scope	99	17		
Intervention out of scope	23	7		
Comparator out of scope	5	2		
Outcome out of scope	8	8		
Publication type out of scope (nonsystematic review)	44	7		
Publication type out of scope (opinion piece)	3	4		
Publication type out of scope (editorial)	0	1		
Publication type out of scope (protocol, other)	1	2		
Level II study included in Level I	0	0		
Study design out of scope (Level III)	0	0		
Study design out of scope (Level IV or below)	3	9		
Insufficient adjustment of confounders	1	1		
No usable data	17	5		

	Number of citations [a]			
Database	**Level I**	**PubMed (not Medline)**	**Level II (not Level I)**	**Level III**
Superseded	3	1		
Withdrawn	0	0		
Duplicate data	12	4		
Sample size	0	0		
TOTAL excluded	**230**	**68**		
TOTAL INCLUDED	**15**	**8**		

a. Inclusive of citations and articles identified through literature searches conducted in August 2018 and August 2019.
b. Protocol date limits as follows: Q2, studies published prior to 2013; Q3, studies published prior to 2009; Q4, studies published prior to 2009; Q6 (FFP, FC, PLT), studies published prior to 2009; Q6 (PCC), studies published prior to 1990.
c. Additional date limits for all questions: studies published prior to 2015.

Table B2.2 Literature screening results: 2, 3, 4 & 6 – 2021

	Number of citations			
Database	**Level I**	**PubMed (not Medline)**	**Level II (not Level I)**	**Level III**
Medline	382	0	1018	*Not searched*
Embase	954	0	3340	
Cochrane	3971	0	3971	
PubMed	0	2041	2064	
TOTAL	**5307**	**2041**	**10 393**	
Protocol date limit (prior to 2009)	0	0	0	
Wrong study design	2526		2791	
Duplicates (within Qs within Endnote)	2848		4393	
Duplicates (across Qs within Covidence)	273		1112	
Available for Title/abstract screening	**1701**		**2097**	
Number of citations excluded				*Not screened*
Additional duplicates identified	193			
Nonhuman	0			
Population out of scope	1462			
Intervention out of scope	1286			
Comparator out of scope	3			
Outcome out of scope	161			
Publication type out of scope (nonsystematic review)	24			
Publication type out of scope (opinion piece)	2			
Publication type out of scope (editorial)	9			
Publication type out of scope (protocol, other)	37			
Level II study included in Level I	0			
Study design out of scope (Level III)	369			
Study design out of scope (Level IV or below)	123			
No usable data	8			
Before date limit	4			
Identified in previous search	1			
Superseded				
TOTAL irrelevant	**3682**			
Available for Full text screening	**116**			
Number of citations excluded				
Not available in English	1			*Not screened*

	Number of citations			
Database	**Level I**	**PubMed (not Medline)**	**Level II (not Level I)**	**Level III**
Population out of scope		16		
Intervention out of scope		17		
Wrong prognostic factor		0		
Comparator out of scope		2		
Outcome out of scope		12		
Publication type out of scope (nonsystematic review)		9		
Publication type out of scope (opinion piece)		0		
Publication type out of scope (editorial)		1		
Publication type out of scope (protocol, other)		15		
Level II study included in Level I		0		
Study design out of scope (Level III)		4		
Study design out of scope (Level IV or below)		0		
Insufficient adjustment of confounders		0		
No usable data		7		
Duplicate data		14		
Full text not available		3		
Ongoing study		2		
TOTAL excluded		**103**		
TOTAL INCLUDED		13		

Note: Title/Abstract screening and full text screening for the Level I and Level II studies were conducted together

B3 Questions 5, 7, 8, & 9

Table B3.1 Literature screening results: Questions 5,7,8 & 9 – 2018/2019

	Number of citations screened [a]			
Database	**Level I**	**PubMed (not Medline)**	**Level II (not Level I)**	**Level III (not Level II)**
Medline	679		4450	1627
Embase	1202		4897	4977
Cochrane	145		1763	33
PubMed	0	379	0	0
TOTAL HITS	**2026**	**379**	**11 110**	**6637**
Protocol date limit [b]	96	0	2010	1027
Additional date limit [c]	0	144	5342	2964
Duplicates (within Qs removed in EndNote)	342	12	1273	856
Duplicates (across Qs removed in Covidence)	283	25	339	86
Available for title/abstract screening	**1305**	**198**	**2146**	**1704**
Number of citations excluded				
Additional duplicates identified	36	1	*Not screened*	*Not screened*
Nonhuman	0	8		
Population out of scope	403	88		
Intervention out of scope	413	41		
Comparator out of scope	32	0		
Outcome out of scope	9	10		
Publication type out of scope (nonsystematic review)	79	5		
Publication type out of scope (opinion piece)	20	1		
Publication type out of scope (editorial)	2	0		
Publication type out of scope (protocol, other)	41	3		
Study design out of scope (Level II)	0	0		
Study design out of scope (Level III)	4	3		
Study design out of scope (Level IV or below)	2	18		
Not available in English	4	3		
Superseded or withdrawn	2	0		
TOTAL irrelevant	**1047**	**181**		
Available for full text screening	**258**	**17**		
Number of citations excluded				
Not available in English	4		*Not screened*	*Not screened*
Population out of scope	129			
Intervention out of scope	8			
Comparator out of scope	1			
Outcome out of scope	2			
Publication type out of scope (nonsystematic review)	11			
Publication type out of scope (opinion piece)	8			
Publication type out of scope (editorial)	4			
Publication type out of scope (protocol, other)	3			
Level II study included in Level I	1			
Study design out of scope (Level III)	1			
Study design out of scope (Level IV or below)	5			
No usable or insufficient data	28			
Superseded	16			
Withdrawn	1			

	Number of citations screened [a]			
Database	**Level I**	**PubMed (not Medline)**	**Level II (not Level I)**	**Level III (not Level II)**
Duplicate data	12			
Sample size	0			
TOTAL excluded	**234**			
TOTAL INCLUDED	**41**			

a. Inclusive of citations and articles identified through literature searches conducted in August 2018 and August 2019.
b. Protocol date limits as follows: Q5, studies published prior to 2009; Q7, studies published prior to 2000; Q8, studies published prior to 2000; Q9, studies published prior to 1990.
c. Additional date limits for all questions: primary studies published prior to 2015.

Table B3.2 Literature screening results: Question 5, 7, 8 & 9 – 2021

	Number of citations [a]			
Database	**Level I**	**PubMed (not Medline)**	**Level II (not Level I)**	**Level III**
Medline	185	0	476	*Not searched*
Embase	329	0	974	
Cochrane	2391	0	2185	
PubMed	0	189	160	
TOTAL	**2905**	**189**	**3795**	
Additional date limit (prior to 2019)	0	0	290	
Duplicates (within Qs within Endnote)	144		692	
Duplicates (across Qs within Covidence)	5		140	
Available for Title/abstract screening	**2945**		**2673**	
Number of citations excluded				
Additional duplicates identified	51		41	*Not screened*
Population out of scope	295		163	
Intervention out of scope	189		128	
Comparator out of scope	9		3	
Outcome out of scope	9		3	
Publication type out of scope (nonsystematic review)	55		2	
Publication type out of scope (opinion piece)	4		5	
Publication type out of scope (editorial)	3		0	
Publication type out of scope (protocol, other)	2		1	
Level II study included in Level I	0		0	
Wrong study design (Level not assigned)	2313		2122	
Study design out of scope (Level II)	7		0	
Study design out of scope (Level III)	0		36	
Study design out of scope (Level IV or below)	0		20	
Not available in English	1		0	
Identified in previous search	0		21	
TOTAL irrelevant	**2938**		**2545**	
Available for Full text screening	**135**			
Number of citations excluded				
Not available in English	4			*Not screened*
Population out of scope	54			
Intervention out of scope	12			
Comparator out of scope	3			
Outcome out of scope	6			

	Number of citations [a]			
Database	**Level I**	**PubMed (not Medline)**	**Level II (not Level I)**	**Level III**
Publication type out of scope (nonsystematic review)	12			
Publication type out of scope (HTA/guidelines)	0			
Publication type out of scope (editorial)	2			
Publication type out of scope (protocol, other)	3			
Level II study included in Level I	0			
Study design out of scope (Level III)	15			
Study design out of scope (Level IV or below)	2			
Awaiting classification	6			
No usable data	0			
Duplicate data	5			
TOTAL excluded	**124**			
TOTAL INCLUDED	11			

Appendix C List of excluded studies

This appendix documents studies that potentially met the inclusion criteria as determined by the PICO criteria but were not included in the evidence evaluation. These studies, and their reasons for exclusion, are listed below.

C1 Studies excluded from Question 1

C1.1 Awaiting classification

Publication in a language other than English (2)

Irita, K., & Inada, E. (2011). Guidelines for management of critical bleeding in obstetrics. [Japanese]. *Japanese Journal of Anesthesiology, 60*(1), 14-22.

Llau, J. V., Acosta, F. J., Escolar, G., Fernandez-Mondejar, E., Guasch, E., Marco, P., . . . Torrabadella, P. (2016). [Multidisciplinary consensus document on the management of massive haemorrhage (HEMOMAS document)]. *Revista espanola de anestesiologia y reanimacion, 63*(1), e1-e22. doi:https://dx.doi.org/10.1016/j.redar.2015.11.002

C1.2 Not included

Duplicate data (2)

Gando, S., Sawamura, A., Hayakawa, M., Kubota, N., Sugano, M., Wada, T., & Katabami, K. (2009). Disseminated intravascular coagulation with a fibrinolytic phenotype modified through fibrinogenolysis at an early phase of trauma predicts mortality. *Journal of Thrombosis and Haemostasis, 7* (S2), 858-859. doi:http://dx.doi.org/10.1111/j.1538-7836.2009.03473-2.x

Reviews, C. f., & Dissemination. (2015). Review article: Shock Index for prediction of critical bleeding post-trauma: a systematic review (Provisional abstract). *Database of Abstracts of Reviews of Effects*(2).

No usable data (8)

Carson, L., & Carless, A. (2013). The evidence base for red blood cell transfusions. *Vox Sanguinis, 105 (SUPPL.1)*, 9. doi:http://dx.doi.org/10.1111/vox.12047

Lier, H., Bottiger, B. W., Hinkelbein, J., Krep, H., & Bernhard, M. (2011). Coagulation management in multiple trauma: a systematic review. *Intensive Care Medicine, 37*(4), 572-582. doi:https://dx.doi.org/10.1007/s00134-011-2139-y

Llau, J. V., Acosta, F. J., Escolar, G., Fernandez-Mondejar, E., Guasch, E., Marco, P., . . . Torrabadella, P. (2015). Multidisciplinary consensus document on the management of massive haemorrhage (HEMOMAS document). *Medicina Intensiva, 39*(8), 483-504. doi:https://dx.doi.org/10.1016/j.medin.2015.05.002

Mulier, J. P., & Dillemans, B. (2011). Importance of increasing blood pressure at end of operation to prevent postoperative blood loss. *Transfusion Alternatives in Transfusion Medicine, 12* (1), 39. doi:http://dx.doi.org/10.1111/j.1778-428X.2011.01149.x

Mulier, J. P., Dillemans, B., Akin, F., Sablon, T., & Reusens, H. (2012). Blood pressure increase during laparoscopy reduces post operative blood loss. *Surgical Endoscopy and Other Interventional Techniques, 1)*, S60. doi:http://dx.doi.org/10.1007/s00464-012-2199-2

Pavenski, K., Anderson, M., & Krok, E. (2018). Audit of cryoprecipitate use in academic centre. *Vox Sanguinis, 113 (Supplement 1)*, 311. doi:http://dx.doi.org/10.1111/vox.12658

Shah, A., Stanworth, S. J., & McKechnie, S. (2015). Evidence and triggers for the transfusion of blood and blood products. *Anaesthesia, 70*, 10-19, e13. doi:http://dx.doi.org/10.1111/anae.12893

Spahn, D. R., Bouillon, B., Cerny, V., Coats, T. J., Duranteau, J., Fernandez-Mondejar, E., . . . Rossaint, R. (2013). Management of bleeding and coagulopathy following major trauma: An updated European guideline. *Critical Care, 17* (2) *(no pagination)*(R76). doi:http://dx.doi.org/10.1186/cc12685

Insufficient adjustment for confounders (1)

Singla, A., Kaur, S., Kaur, N., & Gill, C. S. (2016). Arterial ammonia levels: Prognostic marker in traumatic hemorrhage. *Int J Appl Basic Med Res, 6*(4), 255-257. doi:10.4103/2229-516x.192601

C2 Studies excluded from Question 2, 3, 4 and 6

C2.1 Awaiting classification

Publication not available in English (12)

Akaraborworn, O. (2014). Damage control resuscitation for massive hemorrhage. *Chin J Traumatol, 17*(2), 108-111. doi:http://dx.doi.org/10.3760/cma.j.issn.1008-1275.2014.02.010

Andreu, G., Vasse, J., Tardivel, R., & Semana, G. (2009). Platelet transfusion: Products, indications, dose, threshold and efficacy. [French]. *Transfus Clin Biol, 16*(2), 118-133. doi:http://dx.doi.org/10.1016/j.tracli.2009.04.001

Carrillo-Esper, R., de los Monteros-Estrada, I. E., Rosales-Gutierrez, A. O., Zepeda-Mendoza, A. D., Alonso-Martinez, D., Sanchez-Moreno, M. A., & Cabrera-Joachin, C. M. (2015). Prothrombin complex concentrate in the perioperative. *38*(1), 35-43.

Gombotz, H., Hofman, A., Rehak, P., & Kurz, J. (2011). [Patient blood management (part 2). Practice: the 3 pillars]. *Anasthesiol Intensivmed Notfallmed Schmerzther, 46*(7-8), 466-474. doi:https://dx.doi.org/10.1055/s-0031-1284465

Gombotz, H., Hofmann, A., Rehak, P., & Kurz, J. (2011). [Patient blood management (part 1) - patient-specific concept to reduce and avoid anemia, blood loss and transfusion]. *Anasthesiol Intensivmed Notfallmed Schmerzther, 46*(6), 3 Kreuziger 96-401. doi:https://dx.doi.org/10.1055/s-0031-1280743

Irita, K. (2014). Present status of critical hemorrhage and its management in the operating room. [Japanese]. *The Japanese journal of clinical pathology, 62*(12), 1275-1279.

Irita, K., & Inada, E. (2011). Guidelines for management of critical bleeding in obstetrics. [Japanese]. *60*(1), 14-22.

Jin, X., Ma, H. P., Wang, J., & Zheng, H. (2014). Transfusion of red blood cells with different duration for patients' prognosis: A meta-analysis. [Chinese]. *14*(3), 299-305. doi:http://dx.doi.org/10.7507/1672-2531.20140052

Johanning, K. (2013). Intraoperative coagulation management. [German]. *Viszeralmedizin, 29*(5), 280-288. doi:http://dx.doi.org/10.1159/000355382

Maegele, M. (2017). Modern coagulation management in bleeding trauma patients: Point-of-care guided administration of coagulation factor concentrates and hemostatic agents. [German]. *Med Klin Intensivmed Notfmed, 114*(5), 1-10. doi:http://dx.doi.org/10.1007/s00063-017-0337-2

Pshenisnov K.V., & Aleksandrovich Yu.S. (2020). Massive blood loss in pediatric practice. [Russian]. *Russian journal of hematology and transfusiology*. *65*(1), 70-86. doi:https://doi.org/10.35754/0234-5730-2020-65-1-70-86

Wikkelso, A. J. (2015). The role of fibrinogen and haemostatic assessment in postpartum haemorrhage: preparations for a randomised controlled trial. *Dan Med J, 62*(4), B5055.

C2.2 Not included

Superseded (4)

Rossaint, R. (2012). Management of bleeding following major trauma: An updated European guideline. *1)*, 35-36.

Spahn, D. R., Cerny, V., Coats, T. J., Duranteau, J., Fernandez-Mondejar, E., Gordini, G., . . . Rossaint, R. (2007). Management of bleeding following major trauma: A European guideline. *Crit Care, 11 (no pagination)*(R17), R17. doi:http://dx.doi.org/10.1186/cc5686

Wikkelso, A., Lunde, J., Johansen, M., Stensballe, J., Wetterslev, J., Moller, A. M., & Afshari, A. (2013). Fibrinogen concentrate in bleeding patients. *Cochrane Database of Systematic Reviews, 2013 (8) (no pagination)*(CD008864). doi:http://dx.doi.org/10.1002/14651858.CD008864.pub2

Wikkelso, A., Lunde, J., Johansen, M., Stensballe, J., Wetterslev, J., Moller, M. A., & Afshari, A. (2018). Fibrinogen concentrate in bleeding patients. *Cochrane Database of Systematic Reviews*(12).

Duplicate data (30)

Anto, V. P., Guyette, F. X., Brown, J., Daley, B., Miller, R., Harbrecht, B., . . . Sperry, J. (2020). Severity of hemorrhage and the survival benefit associated with plasma: Results from a randomized prehospital plasma trial. *J Trauma Acute Care Surg, 88*(1), 141-147. doi:10.1097/ta.0000000000002530

Bhangu, A., Nepogodiev, D., Doughty, H., & Bowley, D. M. (2013). Meta-analysis of plasma to red blood cell ratios and mortality in massive blood transfusions for trauma. *Injury, 44*(12), 1693-1699. doi:10.1016/j.injury.2012.07.193

Centre for, R., & Dissemination. (2015). Impact of transfusion of fresh-frozen plasma and packed red blood cells in a 1: 1 ratio on survival of emergency department patients with severe trauma (Provisional abstract). (2).

Centre for, R., & Dissemination. (2015). The use of trauma transfusion pathways for blood component transfusion in the civilian population: a systematic review and meta-analysis (Provisional abstract). (2).

Curry, N., Stanworth, S., Hopewell, S., Doree, C., Brohi, K., & Hyde, C. (2011). Trauma-induced coagulopathy-A review of the systematic reviews: Is there sufficient evidence to guide clinical transfusion practice? *Transfus Med Rev, 25*(3), 217-231.e212. doi:http://dx.doi.org/10.1016/j.tmrv.2011.01.001

de Roulet, A., Kerby, J. D., Weinberg, J. A., Lewis, R. H., Jr., Hudgins, J. P., Shulman, I. A., . . . Inaba, K. (2020). Group A emergency-release plasma in trauma patients requiring massive transfusion. *J Trauma Acute Care Surg, 89*(6), 1061-1067. doi:10.1097/ta.0000000000002903

Gruen, D. S., Guyette, F. X., Brown, J. B., Okonkwo, D. O., Puccio, A. M., Campwala, I. K., . . . Sperry, J. L. (2020). Association of Prehospital Plasma With Survival in Patients With Traumatic Brain Injury: A Secondary Analysis of the PAMPer Cluster Randomized Clinical Trial. *JAMA Netw Open, 3*(10), e2016869. doi:10.1001/jamanetworkopen.2020.16869

Guyette, F. X., Sperry, J. L., Peitzman, A. B., Billiar, T. R., Daley, B. J., Miller, R. S., . . . Brown, J. B. (2021). Prehospital Blood Product and Crystalloid Resuscitation in the Severely Injured Patient: A Secondary Analysis of the Prehospital Air Medical Plasma Trial. *Ann Surg, 273*(2), 358-364. doi:10.1097/sla.0000000000003324

Hallet, J., Lauzier, F., Mailloux, O., Trottier, V., Archambault, P., Zarychanski, R., & Turgeon, A. F. (2012). Liberal use of platelet transfusions in the acute phase of trauma resuscitation: A systematic review. *Critical Care, 1)*(Suppl 1), S160. doi:http://dx.doi.org/10.1186/cc11056

Hallet, J., Lauzier, F., Mailloux, O., Trottier, V., Archambault, P., Zarychanski, R., & Turgeon, A. F. (2013). The use of higher platelet: Rbc transfusion ratio in the acute phase of trauma resuscitation: A systematic review*. *Crit Care Med, 41*(12), 2800-2811. doi:http://dx.doi.org/10.1097/CCM.0b013e31829a6ecb

Innerhofer, N., Treichl, B., Rugg, C., Fries, D., Mittermayr, M., Hell, T., . . . On Behalf Of The Retic Study, G. (2021). First-Line Administration of Fibrinogen Concentrate in the Bleeding Trauma Patient: Searching for Effective Dosages and Optimal Post-Treatment Levels Limiting Massive Transfusion-Further Results of the RETIC Study. *J Clin Med, 10*(17). doi:10.3390/jcm10173930

Johansson, P. I. (2012). Massive transfusion protocols are the answer. *1)*, 24.

Johansson, P. I., Oliveri, R. S., & Ostrowski, S. R. (2012). Hemostatic resuscitation with plasma and platelets in trauma. *J Emerg Trauma Shock, 5*(2), 120-125. doi:http://dx.doi.org/10.4103/0974-2700.96479

Kamyszek, R. W., Leraas, H. J., Reed, C., Ray, C. M., Nag, U. P., Poisson, J. L., & Tracy, E. T. (2019). Massive transfusion in the pediatric population: A systematic review and summary of best-evidence practice strategies. *J Trauma Acute Care Surg, 86*(4), 744-754. doi:10.1097/ta.0000000000002188

Kozek-Langenecker, S., Sørensen, B., Hess, J. R., & Spahn, D. R. (2011). Clinical effectiveness of fresh frozen plasma compared with fibrinogen concentrate: a systematic review. *Crit Care, 15*(5), R239. doi:10.1186/cc10488

Li, J. Y., Gong, J., Zhu, F., Moodie, J., Newitt, A., Uruthiramoorthy, L., . . . Martin, J. (2018). Fibrinogen concentrate in cardiovascular surgery: A meta-analysis of randomized controlled trials. *Anesthesia and Analgesia, 127*(3), 612-621. doi:http://dx.doi.org/10.1213/ANE.0000000000003508

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C3.2 Not included

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C4.1 Awaiting classification

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No usable Data (4)

Curry, N., Stanworth, S., Hopewell, S., Doree, C., Brohi, K., & Hyde, C. (2011). Trauma-induced coagulopathy-A review of the systematic reviews: Is there sufficient evidence to guide clinical transfusion practice? *Transfusion Medicine Reviews, 25*(3), 217-231.e212. doi:http://dx.doi.org/10.1016/j.tmrv.2011.01.001

McClure, E. M., Jones, B., Rouse, D. J., Griffin, J. B., Kamath-Rayne, B. D., Downs, A., & Goldenberg, R. L. (2015). Tranexamic acid to reduce postpartum hemorrhage: A MANDATE systematic review and analyses of impact on maternal mortality. *American Journal of Perinatology, 32*(5 Supplement 01), 469-474. doi:http://dx.doi.org/10.1055/s-0034-1390347

Mousa, H. A., Blum, J., Abou El Senoun, G., Shakur, H., & Alfirevic, Z. (2017). Treatment for primary postpartum haemorrhage. *Cochrane Database of Systematic Reviews*(9).

Slattery, C., Kark, J., Wagner, T., & Verma, K. (2019). The use of tranexamic acid to reduce surgical blood loss: A review basic science, subspecialty studies, and the evolution of use in spine deformity surgery. *Clinical Spine Surgery.* doi:http://dx.doi.org/10.1097/BSD.0000000000000808

C5 Studies excluded from Question 8

C5.1 Awaiting classification

Conference abstract with insufficient data (3)

Quinn, D. (2015). The clinical utility of thromboelastography in bleeding trauma: The CUT systematic review. *Anaesthesia, 2)*, 32. doi:http://dx.doi.org/10.1111/anae.12962

Subramanyam, R., Johnston, B. C., Faden, M., & Crawford, M. W. (2012). Does thromboelastography improve peri-operative outcomes? *Canadian Journal of Anesthesia. Conference, 59*(SUPPL. 1). doi:http://dx.doi.org/10.1007/s12630-012-9785-6

Weber, C., Deppe, A. C., Kuhn, E. W., Scherner, M., Slottosch, I., Liakopoulos, O. J., . . . Wahlers, T. (2015). Point-of-care TEG/ROTEM based coagulation management in cardiac surgery: A meta-analysis of 8,321 patients. *Thoracic and Cardiovascular Surgeon. Conference: 44th Annual Meeting of the German Society for Thoracic and Cardiovascular Surgery. Freiburg Germany. Conference Publication:, 63*(SUPPL. 1). doi:http://dx.doi.org/10.1055/s-0035-1544279

C5.2 Not included

Level II study already included in Level I (1)

De Pietri, L., Ragusa, F., Deleuterio, A., Begliomini, B., & Serra, V. (2016). Reduced Transfusion During OLT by POC Coagulation Management and TEG Functional Fibrinogen: A Retrospective Observational Study. *Transplant Direct, 2*(1), e49. doi:10.1097/txd.0000000000000559

Superseded (3)

Whiting, P., Al, M., Westwood, M., Ramos, I. C., Ryder, S., Armstrong, N., . . . Kleijnen, J. (2015). Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: A systematic review and cost-effectiveness analysis. *Health Technology Assessment, 19*(58), 1-228. doi:http://dx.doi.org/10.3310/hta19580

Wikkelso, A., Wetterslev, J., Moller, A. M., & Afshari, A. (2016). Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding. *Cochrane Database of Systematic Reviews, 2016 (8) (no pagination)*(CD007871). doi:http://dx.doi.org/10.1002/14651858.CD007871.pub3

Wikkelsoe, A. J., Afshari, A., Wetterslev, J., Brok, J., & Moeller, A. M. (2011). Monitoring patients at risk of massive transfusion with Thrombelastography or Thromboelastometry: A systematic review. *Acta Anaesthesiologica Scandinavica, 55*(10), 1174-1189. doi:http://dx.doi.org/10.1111/j.1399-6576.2011.02534.x

Duplicate data (3)

Drumheller BC, Stein DM, Moore LJ, Rizoli SB, Cohen MJ. Thromboelastography and rotational thromboelastometry for the surgical intensivist: A narrative review. *J Trauma Acute Care Surg.* 2019;86(4):710-21.

Franchini, M. M., C.; Cruciani, M.; Marietta, M.; Marano, G.; Vaglio, S.; Pupella, S.; Veropalumbo, E.; Masiello, F.; Liumbruno, G. M. (2018). The use of viscoelastic haemostatic assays in non-cardiac surgical settings: a systematic review and meta-analysis. *Blood Transfusion, 16*(3), 235-243.

Theusinger, O. M., Stein, P., & Levy, J. H. (2015). Point of care and factor concentrate-based coagulation algorithms. *Transfus Med Hemother, 42*(2), 115-121. doi:10.1159/000381320

Wikkelso, A. W., Jorn; Moller, Merete Ann; Afshari, Arash. (2018). Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding. *Cochrane Database of Systematic Reviews, 12*(12).

No usable data (3)

Bolliger, D., & Tanaka, K. A. (2013). Roles of thrombelastography and thromboelastometry for patient blood management in cardiac surgery. *Transfusion Medicine Reviews, 27*(4), 213-220. doi:http://dx.doi.org/10.1016/j.tmrv.2013.08.004

Brohi, K., & Eaglestone, S. (2017). *NIHR Journals Library Programme Grants for Applied Research, 11*, 11. doi:https://dx.doi.org/10.3310/pgfar05190

Wahlen, B. M., El-Menyar, A., Peralta, R., & Al-Thani, H. (2018). World Academic Council of Emergency Medicine Experience Document: Implementation of Point-of-Care Thromboelastography at an Academic Emergency and Trauma Center. *J Emerg Trauma Shock, 11*(4), 265-270. doi:10.4103/jets.jets_134_17

C6 Studies excluded from Question 9

C6.1 Awaiting classification

Publication not available in English (1)

Munoz, M., Campos, A., Ariza, D., Bisbe, E., Cuenca, J., & Garcia-Erce, J. A. (2005). Red cell salvage in major surgery. *Acta Medica Croatica, 59*(SUPPL. 1), 96-98.

Conference abstract with insufficient data (3)

Al-Khabori, M., Al-Riyami, A., Siddiqi, S., & Al-Sabti, H. (2015). Cell salvage during cardiac surgery may decrease red blood cell transfusion: A systematic review and meta-analysis. *Haematologica, 1)*, 138-139.

Cheriyan, T., Errico, T., Dua, A., & Kumar, V. (2018). Efficacy of intraoperative cell salvage in spine surgery: A meta-analysis. *Anesthesia and Analgesia, Conference*, International Anesthesia Research Society 2018 Annual Meeting and International Science Symposium, IARS 2018. United States. 2126 (2014 Supplement 2011) (pp 2087).

Crighton, G. (2016). Evidence-based patient bood management guidelines for neonatal and paediatric patients. Vox Sanguinis, 111 (Supplement 1), 18-19. doi:http://dx.doi.org/10.1111/vox.12429

Meier, J., Waters, J. H., Myers, G., Martinetti, M., & Bagnardi, V. (2017). Clinical efficacy of washed autotransfusion in non-cardiac settings such as vascular, orthopaedic and obstetric surgery: A systematic review and meta-analysis of randomised controlled trials. *Transfusion Medicine, 27 (Supplement 1)*, 40. doi:http://dx.doi.org/10.1111/tme.12417

C6.2 Not included

Duplicate data (1)

Li, J., Sun, L. S., Tian, H. J., Yang, K., Liu, R., & Li, J. (2015). Cell salvage in emergency trauma surgery. *Cochrane Database of Systematic Reviews*(1).

Superseded (2)

Carless, P., Moxey, A., O'Connell, D., & Henry, D. (2004). Autologous transfusion techniques: a systematic review of their efficacy. *Transfusion Medicine, 14*(2), 123-144.

Appendix D Critical appraisal

D1 Prognostic factors (Question 1)

Systematic review of observational /cohort studies

Citation Ref/Study ID	Razzaghi 2012	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PPO clearly defined
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No protocol provided and no statement regarding methods being established prior to conducting review
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Selection of study design was explained in the search strategy
4. Did the review authors use a comprehensive literature search strategy?	No	Insufficient details of search strategy were provided
5. Did the review authors perform study selection in duplicate?	No	Not reported
6. Did the review authors perform data extraction in duplicate?	No	Not reported
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	List of excluded studies not provided
8. Did the review authors describe the included studies in adequate detail?	No	Insufficient detail of included studies was provided
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	RoB not assessed
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Sources of funding was not disclosed
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis not performed
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis not performed
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	RoB not accounted for in interpretation of results
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Heterogeneity was briefly discussed, but not in sufficient detail

Citation Ref/Study ID	Razzaghi 2012	
Question	**Judgement**	**Comments**
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	No investigation of publication bias
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No	Conflicts of interest not stated
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Study ID	Abdul-Kadir 2014	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PPO clearly defined
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No protocol provided and no statement regarding methods being established prior to conducting review
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	Selection of study design was not explained
4. Did the review authors use a comprehensive literature search strategy?	No	Insufficient details of search strategy were provided
5. Did the review authors perform study selection in duplicate?	No	Not reported
6. Did the review authors perform data extraction in duplicate?	No	Not reported
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	List of excluded studies not provided
8. Did the review authors describe the included studies in adequate detail?	No	Insufficient detail of included studies was provided
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	RoB not assessed
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	Sources of funding was disclosed
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis not performed
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis not performed

Study ID	Abdul-Kadir 2014	
Question	**Judgement**	**Comments**
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	RoB not accounted for in interpretation of results
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Heterogeneity not discussed
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	No investigation of publication bias
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	No conflicts of interest were declared
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Citation Ref/Study ID	Haas 2015	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PPO defined
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No protocol provided and no statement regarding methods being established prior to conducting review
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	Selection of study design was not explained
4. Did the review authors use a comprehensive literature search strategy?	No	Search strategy was uncomprehensive and used search exclusion terms that may have removed relevant citations. Only one database was searched
5. Did the review authors perform study selection in duplicate?	Yes	Screening was performed in duplicate
6. Did the review authors perform data extraction in duplicate?	No	Data extraction not specified
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	List of excluded studies not provided
8. Did the review authors describe the included studies in adequate detail?	No	Included studies only briefly described
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	RoB not assessed

Citation Ref/Study ID	Haas 2015	
Question	**Judgement**	**Comments**
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Funding from CSL Behring to perform literature searches. There was no funding for the writing of the manuscript
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis not performed
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis not performed
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	RoB not accounted for in interpretation of results
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Heterogeneity not discussed
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Quantitative synthesis not performed
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Potential conflicts of interest and sources of funding reported in publication
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Citation Ref/Study ID	Baxter 2016	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PPO clearly defined
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial yes	Study inclusion and exclusion criteria predefined however other review methods were not specified
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	Selection of study design was not explained
4. Did the review authors use a comprehensive literature search strategy?	Yes	Search strategy and databases were comprehensive
5. Did the review authors perform study selection in duplicate?	Yes	Screening was performed in duplicate
6. Did the review authors perform data extraction in duplicate?	Yes	Data extraction was performed in duplicate

Citation Ref/Study ID	Baxter 2016	
Question	**Judgement**	**Comments**
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	List of excluded studies not provided
8. Did the review authors describe the included studies in adequate detail?	Yes	Details on each included studies provided
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	QUIPS RoB tool for prognostic studies was used
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Funding was not disclosed
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis not performed
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis not performed
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Individual study RoB was addressed briefly in discussion
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partial yes	Explanation of heterogeneity not given; however heterogeneity was discussed
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Publication bias not investigated in detail
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	No conflicts of interest were declared
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Citation Ref/Study ID	Poole 2016	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PICO defined in question 1
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial yes	Review states predefined plan was performed however protocol was not provided or pre-registered

Citation Ref/Study ID	Poole 2016	
Question	**Judgement**	**Comments**
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Rationale of study design stated. The review included RCTs and observational studies only if adjustment for confounders was performed. Letter, case reports and observational studies without controls and adjustment for important covariates were excluded.
4. Did the review authors use a comprehensive literature search strategy?	No	Search strategy provided as attachment file. Authors only searched Medline (using PubMed platform). A detailed search strategy was provided and they also included meta-analyses and reviews for manual evaluation of the bibliography of the articles as a source of literature that may have escaped the PubMed search.
5. Did the review authors perform study selection in duplicate?	No	Four groups of physicians, one for each PICO, were selected to screen the literature. Each group received the list of articles and performed the first selection on the basis of titles and abstracts excluding those that did not deal with the subject at hand.
6. Did the review authors perform data extraction in duplicate?	No	Data extraction was performed by the review group. Not explicitly stated if this was performed in duplicate
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	Reasons for exclusion presented in Figure 2. However, a list of the excluded studies was not provided.
8. Did the review authors describe the included studies in adequate detail?	Yes	Details on all included studies provided
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	GRADE methodology was employed to assess quality of evidence, which additionally assesses some bias
10. Did the review authors report on the sources of funding for the studies included in the review?	No	The review did not report on the sources of funding for the studies included in the review.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis not performed
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis not performed
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	RoB was addressed in the discussion
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Heterogeneity in results was explained in sufficient detail
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Partial yes	Publication bias was assessed for each included study. The authors were unable to formally assess the publication risk of bias due to insufficient number of studies retrieved to gain sufficient power for the test.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	No conflicts of interest were declared

Citation Ref/Study ID	Poole 2016	
Question	**Judgement**	**Comments**
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Citation Ref/Study ID	Levy 2017	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PPO clearly defined
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No protocol provided and no statement regarding methods being established prior to conducting review
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	Selection of study design was not explained
4. Did the review authors use a comprehensive literature search strategy?	No	Search strategy was not comprehensive and could have potentially missed relevant articles
5. Did the review authors perform study selection in duplicate?	Yes	Study selection was conducted collaboratively by 2 authors
6. Did the review authors perform data extraction in duplicate?	No	Not reported
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	List of excluded studies not provided
8. Did the review authors describe the included studies in adequate detail?	No	Insufficient detail of included studies was provided
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	RoB not assessed
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	Sources of funding was disclosed
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis not performed
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis not performed
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	RoB not accounted for in interpretation of results
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Heterogeneity was discussed in sufficient detail

Citation Ref/Study ID	Levy 2017	
Question	**Judgement**	**Comments**
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	No investigation of publication bias
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	No conflicts of interest were declared
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Citation Ref/Study ID	Lilitsis 2018	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	No	Population is poorly defined. Definition of massive transfusion is not defined
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	The review did not state if methods were established prior to review
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	Selection of study design not stated
4. Did the review authors use a comprehensive literature search strategy?	No	Search strategy was not comprehensive
5. Did the review authors perform study selection in duplicate?	No	Study selection methods not addressed
6. Did the review authors perform data extraction in duplicate?	No	Data extraction methods not addressed
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	List of excluded studies not provided
8. Did the review authors describe the included studies in adequate detail?	No	Details of included studies not provided in adequate detail (no table or list)
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	RoB assessment not addressed
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	No financial support or sponsorship was provided
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis not performed
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis not performed

Citation Ref/Study ID	Lilitsis 2018	
Question	**Judgement**	**Comments**
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	RoB not addressed in discussion
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Heterogeneity not discussed
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Quantitative synthesis not performed
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	No conflicts of interest were declared
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Citation Ref/Study ID	Tran 2018	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	All components of the PPO were addressed
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Complete protocol published prior to conducting the review
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Rationale of study design stated in protocol
4. Did the review authors use a comprehensive literature search strategy?	Yes	Search strategy provided as attachment
5. Did the review authors perform study selection in duplicate?	Yes	Screening was done independently and in duplicate
6. Did the review authors perform data extraction in duplicate?	Yes	Data extraction performed in duplicate as stated in the protocol
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	List of excluded studies not provided
8. Did the review authors describe the included studies in adequate detail?	Yes	Details on all included studies provided
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	CHARMS checklist was used to assess RoB and guide data extraction
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No sources of funding were declared

Citation Ref/Study ID	Tran 2018	
Question	**Judgement**	**Comments**
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Inverse variance random effects models were used to pool results, presented as odds ratios with 95% confidence intervals.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Partial yes	The author briefly discusses the impact of differences in thresholds used between studies
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	RoB was addressed in the discussion
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Heterogeneity in results was explained in sufficient detail
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Publication bias was not investigated in detail
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	No conflicts of interest were declared
Overall methodological quality of the review	***Low***	***One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.***

Citation Ref/Study ID	Shih 2019	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	No	Population outlined; massive blood transfusion is inconsistently defined across included studies
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	Protocol was not included in the SR
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Selection of study design was explained in the search strategy
4. Did the review authors use a comprehensive literature search strategy?	Yes	Search strategy and databases was sufficient
5. Did the review authors perform study selection in duplicate?	Yes	The studies were screened by 2 reviewers
6. Did the review authors perform data extraction in duplicate?	Yes	Data extraction was performed by 2 reviewers
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	List of excluded studies not provided

Citation Ref/Study ID	Shih 2019	
Question	**Judgement**	**Comments**
8. Did the review authors describe the included studies in adequate detail?	No	Insufficient detail of included studies was provided
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	RoB was assessed through the Cochrane RoB tool (RCTs) and Newcastle-Ottawa scale (Coh)
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Sources of funding was not disclosed
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis not performed
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis not performed
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	RoB not accounted for in interpretation of results
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partial Yes	Heterogeneity was briefly discussed, but not in sufficient detail
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	No investigation of publication bias
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No	One author reported a conflict of interest with the others declaring no conflicts. Details on funding was not provided
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Citation Ref/Study ID	Vasudeva 2021	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	Population clearly defined (p398)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Protocol was reported using PROSPERO CRD42020105135 (p397)

Citation Ref/Study ID	Vasudeva 2021	
Question	**Judgement**	**Comments**
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Selection of study design was explained in the search strategy. Due to the paucity of current literature on the topic, the authors chose not to apply further limits to the studies (p397)
4. Did the review authors use a comprehensive literature search strategy?	No	Search strategy was sufficient (p397), however the authors only searched only MEDLINE via Ovid (p398)
5. Did the review authors perform study selection in duplicate?	Yes	The studies were screened by 2 reviewers (p398)
6. Did the review authors perform data extraction in duplicate?	No	Not reported
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	List of excluded studies not provided (p398-399)
8. Did the review authors describe the included studies in adequate detail?	No	The authors provided a summary of results from the included studies, but did not report baseline characteristics or demographics (p399)
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	RoB was assessed using the Newcastle-Ottawa Scale (p399)
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Sources of funding was not disclosed
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis not performed
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis not performed
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	The authors noted that the systematic review was subject to publication bias (p400) and acknowledged the small sample size in Vasudeva 2020.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Heterogeneity was not discussed.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	The authors noted that the systematic review was subject to publication bias (p400)
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Partial yes	The authors declared no conflicts of interest (p401) however did not report on funding
Overall methodological quality of the review	***High***	***No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.***

Citation Ref/Study ID	Pacagnella 2013	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PPO clearly defined
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No protocol provided and no statement regarding methods being established prior to conducting review
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	Selection of study design was not explained
4. Did the review authors use a comprehensive literature search strategy?	No	Search strategy was not comprehensive and could have potentially missed relevant articles
5. Did the review authors perform study selection in duplicate?	Yes	Screening performed in duplicate
6. Did the review authors perform data extraction in duplicate?	Yes	Data extraction performed in duplicate
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	List of excluded studies not provided
8. Did the review authors describe the included studies in adequate detail?	No	Insufficient detail of included studies was provided
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	RoB assessed using Strengthening the Reporting of Observational studies in Epidemiology checklist with details provided
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	Sources of funding was disclosed
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis not performed
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis not performed
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	RoB not accounted for in interpretation of results
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Heterogeneity and the reasons for significant heterogeneity, were discussed in sufficient detail
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	No investigation of publication bias
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	No conflicts of interest were declared

Citation Ref/Study ID	Pacagnella 2013	
Question	**Judgement**	**Comments**
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Citation Ref/Study ID	Kamyszek 2019	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	No	Population outlined, massive blood transfusion is inconsistently defined across included studies
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	Protocol was not included in the SR
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	Selection of study design was not explained in the search strategy
4. Did the review authors use a comprehensive literature search strategy?	No	Insufficient details of search strategy were provided
5. Did the review authors perform study selection in duplicate?	Yes	The studies were screened by 2 reviewers
6. Did the review authors perform data extraction in duplicate?	No	Not reported
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	List of excluded studies not provided
8. Did the review authors describe the included studies in adequate detail?	Partial Yes	Insufficient detail of included studies was provided
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	RoB not assessed
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	The authors disclose no funding for the systematic review
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis not performed
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis not performed
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	RoB not accounted for in interpretation of results
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partial Yes	Heterogeneity was briefly discussed, but not in sufficient detail

Citation Ref/Study ID	Kamyszek 2019	
Question	**Judgement**	**Comments**
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	No investigation of publication bias
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflict of interest and stated that they received no extra funding
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Randomised controlled trials (single arm analysis)

Study ID	Moore 2020 (a) – COMBAT (Moore 2018)		
Question	**Judgement**	**Comments**	
Random sequence generation (selection bias)	Low	The 33 ambulances based at DHMC were loaded with pre-packaged coolers at the start of each shirt. Plasma and dummy (frozen water) loads were randomly assigned 1:1 in blocks of 20 according to a schedule generated by research coordinators	p. 4
Allocation concealment (selection bias)	Low	The prepacked coolers were sealed in aluminium cassettes by study staff not involved in enrolment of data analysis to mask allocation	p. 4
Blinding of participants and personnel (performance bias)	High	Further masking of the care team was not possible due to FDA restrictions. No mention of participants	p. 4
Blinding of outcome assessment (detection bias)	High	A team of on-site professional research assistants performed TEG on the blood samples, which were collected at the scene of injury and in hospital (immediately on arrival, at 2,4,6,12 and 24 hours after injury). The study did not report if the assessors were blinded to the blood samples.	p. 5
Incomplete outcome data addressed (attrition bias)	High	75 patients were assigned to plasma (ITT population), however 65 patients were included in the as-treated analysis. 69 patients were assigned to saline control (ITT population), however only 60 patients were included in the as-treated analysis (144 randomised, 125 assessed).	p. 14
Selective reporting (reporting bias)	Low	All 125 patients were assessed in the as-treated population, however out of 65 patients assigned to plasma, 2 patients received saline incorrectly because paramedics mistook the contents of the metal canister for the dummy load. As such, these patients were included in the control group in the as-treated analyses. However, the authors reported outcomes as planned.	p. 8
Other sources of bias	High	After 144 of 150 planned patients were enrolled, the DSMB, institutional review board and FDA approved termination of the study for futility because outcomes had not differed in any of the interim analyses indicating that no difference should be anticipated.	p. 8
Overall risk of bias	***High***	***The study has plausible bias that seriously weakens confidence in the results.***	

Study ID	Moore 2020 (b) – PAMPer (Sperry 2018)		
Question	**Judgement**	**Comments**	
Random sequence generation (selection bias)	Low	The authors used a single-stage cluster randomisation scheme, and used computer-generated block randomisation to assign air medical bases at each participating institution to the plasma or SOC group.	p. 317
Allocation concealment (selection bias)	Unclear	Due to the cluster design of the trial, the treatment group was based on the random assigned of the transporting base, irrespective of whether a patient received plasma or SOC resuscitation at an outside hospital. However, there was no mention of how the allocations were masked	p. 317
Blinding of participants and personnel (performance bias)	High	It was not possible for prehospital personnel and receiving physicians at the trial sites to be unaware of the treatment assignments because the trial intervention was a blood product which requires full traceability	p. 317
Blinding of outcome assessment (detection bias)	Low	Treatment assignments were concealed to personnel who assessed the trial outcomes (no mention of how)	p. 317
Incomplete outcome data addressed (attrition bias)	High	In the plasma group, 239 patients were enrolled at a base, however 19 were lost to follow-up (total of 220 patients). 230 patients were analysed for primary outcome. In the SOC group, 284 were rolled at a base, 23 were lost to follow-up. 271 were analysed for primary outcome.	p. 319
Selective reporting (reporting bias)	Low	The treatment effect on the primary outcome was analysed in pre-specified subgroups.	p. 317-318
Other sources of bias*	Low	This study was performed in a cluster randomised trial, therefore there may be recruitment bias. The study was funded by the US Army Medical Research and Material Command.	p. 315
Overall risk of bias	***High***	***The study has plausible bias that seriously weakens confidence in the results.***	

Observational /cohort studies

Study ID	Sawamura 2009		
Question	**Judgement**	**Comments**	
Bias due to failure to develop and apply appropriate eligibility criteria	Low	Eligibility criteria adequately matched PPO. Consecutive patients.	
Bias due to flawed measurement of both exposure and outcome	Low	Outcomes measured were ascertained from reliable methods (e.g. blood tests).	
Bias due to failure to adequately control confounding	Moderate	The study used a stepwise logistic regression analysis of the various variables for the prediction of death	
Bias due to incomplete or inadequately short follow-up	Moderate	Follow up was for ICU mortality including death in the ER as per study protocol. The study did not report on missing data	
Overall risk of bias	***Moderate***	***The study appears to provide sound evidence for a non-randomised study but cannot be considered comparable to a well-performed randomised trial.***	

Study ID	Magnotti 2011		
Question	**Judgement**	**Comments**	
Bias due to failure to develop and apply appropriate eligibility criteria	Moderate	Age and gender were given as population characteristics. Patients were recruited from a consecutive cohort from a single trauma centre.	
Bias due to flawed measurement of both exposure and outcome	Moderate	Blinding of prognostic factor or outcomes (mortality, multiple transfusions or massive transfusions) in the study were not reported. Outcomes measured were ascertained from reliable methods (e.g. blood tests).	
Bias due to failure to adequately control confounding	Moderate	Statistical modelling with multiple regression controlled for age, admission Glasgow Coma Score (GCS) and injury severity score (ISS) but not for other patient population characteristics such as gender and ethnicity	
Bias due to incomplete or inadequately short follow-up	Moderate	Follow up was for 24 hours after admission as per study protocol. The study did not report on dropouts or loss to follow up.	
Overall risk of bias	***Moderate***	***The study appears to provide sound evidence for a non-randomised study but cannot be considered comparable to a well-performed randomised trial.***	

Study ID	Kawatani 2016		
Question	**Judgement**	**Comments**	
Bias due to failure to develop and apply appropriate eligibility criteria	Serious	Subjects were all patients who underwent EVAR for rAAA at our hospital during the period from October 2013 to December 2015. Diagnosis of rAAA was made using simple computed tomography (CT) or contrast-enhanced CT. Decisions to perform EVAR over standard open repair may influence the results.	p.2
Bias due to flawed measurement of both exposure and outcome	Low	The study was a retrospective review of medical records. Outcomes measured were ascertained from reliable methods (e.g. blood tests).	p.2
Bias due to failure to adequately control confounding	Moderate	The study used Mann-Whitney and chi-squared tests for analysis. Confounders were not discussed.	p.2-3
Bias due to incomplete or inadequately short follow-up	Low	Focus was intra-operative death, or 24-hr and 30-day survival. No longer term followup reported or measured.	
Overall risk of bias	***Serious***	***The study has some important problems***	

Study ID	Noorbhai 2016		
Question	**Judgement**	**Comments**	
Bias due to failure to develop and apply appropriate eligibility criteria	Low	A retrospective analysis of the first 1000 patients admitted to the trauma unit during the years 2007 – 2011. Eligibility criteria addressed the PPO.	
Bias due to flawed measurement of both exposure and outcome	Moderate	Blinding was not reported, and measurements were not validated. Further analysis into factors that increased prevalence of coagulopathy in a subgroup of the study is required	
Bias due to failure to adequately control confounding	Serious	Confounders such as age and sex were adequately controlled for in the model However patient factors which could affect INR (prognostic factor) were not reported	

Study ID	Noorbhai 2016		
Question	**Judgement**	**Comments**	
Bias due to incomplete or inadequately short follow-up	Low	Focus was in-hospital mortality	
Overall risk of bias	***Serious***	***The study has some important problems***	

Study ID	Javali 2017		
Question	**Judgement**	**Comments**	
Bias due to failure to develop and apply appropriate eligibility criteria	Moderate	Patients were not from a consecutive cohort. Number of patients above and below the predictive threshold for outcomes not specified	
Bias due to flawed measurement of both exposure and outcome	Serious	Diagnostic cut-off value for mortality and transfusion requirements was not prespecified. Outcome assessment was not blinded, however measurement is objective and unblinding is unlikely to influence result. Details of outcome measurements were not adequately detailed in study.	
Bias due to failure to adequately control confounding	Critical	Study does not control for confounding. Reasons for individual patient exclusion not provided. Statistical methods to control for confounding were not detailed	
Bias due to incomplete or inadequately short follow-up	Moderate	Article states 100 patients were enrolled into the trial, however only 92 patients are included in analysis of base deficit on mortality. Article does not report any drop-outs or loss to follow-up, or why the 8 missing patients are not included in analysis	
Overall risk of bias	***Serious***	***The study has some important problems***	

Study ID	McQuilten 2017a		
Question	**Judgement**	**Comments**	
Bias due to failure to develop and apply appropriate eligibility criteria	Low	The study included patients aged 18 years or older who required massive transfusion between January 2008 and July 2011. Patients were identified from the Victorian trauma registry that uses a waived consent model.	p.132
Bias due to flawed measurement of both exposure and outcome	Moderate	Outcome assessment was not blinded; however most measurements were objective, and the study was retrospective review of medical records. Missing data for some measurables	
Bias due to failure to adequately control confounding	Low	Association between fibrinogen/predictors and in-hospital mortality was modelled by multiple logistic regression analysis. Variables considered for inclusion in the model were hospital, age, gender, clinical context, CCI, Hb, platelet count, aPTT, INR and base excess at massive transfusion commencement.	p.133
Bias due to incomplete or inadequately short follow-up	Low	Focus was in-hospital mortality	
Overall risk of bias	***Moderate***	***The study appears to provide sound evidence for a non-randomised study but cannot be considered comparable to a well-performed randomised trial.***	

Study ID	McQuilten 2017b		
Question	**Judgement**	**Comments**	
Bias due to failure to develop and apply appropriate eligibility criteria	Low	The study included patients aged 18 years or older who required massive transfusion between April 2011 and October 2015. Patients were identified from the ANZ trauma registry that uses a waived consent model.	p.132
Bias due to flawed measurement of both exposure and outcome	Moderate	Outcome assessment was not blinded; however most measurements were objective and the study was retrospective review of medical records. Missing data for some measurables	
Bias due to failure to adequately control confounding	Low	Association between plasma fibrinogen concentration and in-hospital mortality was modelled by multiple logistic regression analysis. Variables considered for inclusion in the model were hospital, age, gender, clinical context, CCI, Hb, platelet count, aPTT, INR and base excess at massive transfusion commencement.	p.133
Bias due to incomplete or inadequately short follow-up	Low	Focus was in-hospital mortality	
Overall risk of bias	***Moderate***	***The study appears to provide sound evidence for a non-randomised study but cannot be considered comparable to a well-performed randomised trial.***	

Study ID	Lester 2019		
Question	**Judgement**	**Comments**	
Bias due to failure to develop and apply appropriate eligibility criteria	Moderate	Eligibility criteria was all patients over the age of 15 that were admitted to the level one trauma centres and were expecting to have a massive blood transfusion	p. 459
Bias due to flawed measurement of both exposure and outcome	Moderate	Blinding was not reported however it would be unethical to potentially blind the medical practitioners in this context of this cohort study. The original paper by Baraniuk 2014 (Pragmatic Randomised Optimal Platelet and Plasma Ratios Trial: Design, rationale, and implementation) described the method of blinding and randomisation (p5)	
Bias due to failure to adequately control confounding	Low	The study used backwards stepwise negative binomial regression for transfusion and a backwards stepwise logistic regression for mortality	p. 460
Bias due to incomplete or inadequately short follow-up	Moderate	Follow up was not reported by focus was in-hospital mortality	
Overall risk of bias	***Moderate***	***The study appears to provide sound evidence for a non-randomised study but cannot be considered comparable to a well-performed randomised trial.***	

Study ID	Gaessler 2021		
Question	**Judgement**	**Comments**	
Bias due to failure to develop and apply appropriate eligibility criteria	Low	Eligibility criteria was clearly outlined in text. The study included all adult trauma patients regardless of the severity of injury. The study excluded pregnant women, patients with pre-existing coagulation disorders or receiving coagulation-influencing drugs long-term, patients who had already received TXA from ground-based EMSs and time interval between prehospital blood sampling and ROTEM assay >120 mins	p. 345

Study ID	Gaessler 2021		
Question	**Judgement**	**Comments**	
Bias due to flawed measurement of both exposure and outcome	Moderate	All relevant outcomes measured in a standard, valid, and reliable way. Outcome assessment was not blinded to exposure status, but unlikely to be influenced by lack of blinding as majority were objective (laboratory measures, mortality, transfusion volume).	p. 345
Bias due to failure to adequately control confounding	Low	All parameters of the 3 defined groups (demographic data, injury severity, prehospital infusions, blood transfusion needs, blood gas analysis and 28-day mortality) were analysed with one-way analysis of variance.	p. 346
Bias due to incomplete or inadequately short follow-up	Low	Follow-up was specified at either day 28 or discharge	p. 349
Overall risk of bias	***Moderate***	***The study appears to provide sound evidence for a non-randomised study but cannot be considered comparable to a well-performed randomised trial.***	

D2 Massive haemorrhage protocol (Question 2)

Systematic reviews of observational /cohort studies

Citation Ref/Study ID	Vogt 2012	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PICO is described in Table 1.
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	It is not clear whether the protocol was established prior to the conduct of the review.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	The authors included observational studies, and case series or observational studies without a control group were excluded.
4. Did the review authors use a comprehensive literature search strategy?	Yes	Multiple databases were searched. Search dates and search criteria are provided. Trial registry and hand searching of reference lists was searched.
5. Did the review authors perform study selection in duplicate?	Yes	Study selection was performed independently by 2 authors with discrepancies solved by consensus, or a third reviewer if required.
6. Did the review authors perform data extraction in duplicate?	Yes	Two reviewers independently abstracted data from each included study using standardised data abstraction forms.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	Reasons for exclusion presented in Figure 1. However, a list of the excluded studies was not provided.
8. Did the review authors describe the included studies in adequate detail?	Yes	Included studies are described in Table 2.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	RoB assessments are presented in Table 3 and p159. All included studies considered to have a high RoB using their outlined criteria.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Sources of funding for the included studies was not commented on.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Method described in p158. The review authors used adjusted estimates where available, pre-specified sensitivity analyses to assess effect of heterogeneity.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	*A priori* methodologic quality of studies (based on RoB) was assumed to affect effect sizes, which was identified as a potential source of heterogeneity.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	The authors attempted to perform sub-group analyses based on RoB as source of heterogeneity. However, there were insufficient number of studies with the required data available to conduct this analysis.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	The authors attempted to explore moderate heterogeneity seen for mortality outcome assessment but were hindered by low number of studies and with all included studies having high risk of bias.

Citation Ref/Study ID	Vogt 2012	
Question	**Judgement**	**Comments**
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	The authors concluded that there was some evidence that publication bias may have influenced the summary estimates calculated in the meta-analysis.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	There were no conflicts of interest.
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Citation Ref/Study ID	Mitra 2013	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PICO is described (p919).
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	It is not clear whether the protocol was established prior to the conduct of the review.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	The results were refined to clinical trials, clinical studies, guidelines and meta-analyses.
4. Did the review authors use a comprehensive literature search strategy?	Yes	Multiple databases were searched. Search dates and search criteria are provided. Trial registry was not searched.
5. Did the review authors perform study selection in duplicate?	Partial yes	The authors state that "Relevant studies were extracted by 2 blinded reviewers". However, it is not clear whether this refers to data extraction only.
6. Did the review authors perform data extraction in duplicate?	Yes	Relevant studies were extracted by 2 blinded reviewers (BM and GO).
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	Figure 1 shows the search and selection process. 15 studies fulfilled eligibility criteria and 7 were excluded. Reasons for exclusion are given for 5 studies.
8. Did the review authors describe the included studies in adequate detail?	Partial yes	Included studies are described in Tables 1 and 2, but not thoroughly.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Partial yes	Study quality assessed in Table 1 and p920. Blinding, study design and baseline characteristics are discussed. Study heterogeneity was measured (for mortality outcome) using Q test and I^2. Overall RoB was not assigned to each included study.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Sources of funding for the included studies was not commented on.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Confounding in the included studies was not explicitly discussed. Authors mention differences in baseline and explored differences in heterogeneity between studies by subgroups and sensitivity analysis.

Citation Ref/Study ID	Mitra 2013	
Question	**Judgement**	**Comments**
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Authors discuss issues with the study designs including effect size
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Authors discuss issues with the study designs
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Heterogeneity was measured and discussed
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Partial yes	A test for publication bias was not conducted. However, the authors acknowledge that one of the limitations of this review is the likely publication bias.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Partial yes	Details on funding or potential conflicts of interest not provided.
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Study ID	Cannon 2017	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	Authors defined the PICO for the research questions in the review. Only question 1 of the review is relevant to Question 2 of this review.
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial yes	A reference was made to planning and implementation in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education. (p605) Details were not provided regarding specific, pre-designed methods; but details of outcomes were prespecified and scored according to GRADE methodology prior to conduct of the review.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	The authors included RCTs, observational studies and retrospective studies. (p606) They did not provide an explicit explanation for their study inclusion criteria.
4. Did the review authors use a comprehensive literature search strategy?	Partial yes	Three databases were searched. Search dates and search criteria are provided. Trial registry or grey literature was not searched, and reference lists of included studies was not conducted.
5. Did the review authors perform study selection in duplicate?	No	Although more than one author conducted the literature search and review of studies, the review authors do not explicitly state that this was done in duplicate.
6. Did the review authors perform data extraction in duplicate?	No	One author extracted data.

Study ID	Cannon 2017	
Question	**Judgement**	**Comments**
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	Reasons for exclusion presented in Figure 1. However, a list of the excluded studies was not provided.
8. Did the review authors describe the included studies in adequate detail?	No	The included studies are outlined but there is insufficient details regarding baseline population characteristics, interventions and research designs for the included studies.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	The authors used GRADE to assess the quality of evidence for each PICO. GRADE table for PICO 1 can be found in Supplement Table 3.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Sources of funding for the included studies was not commented on.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Partial yes	Confounding in the included studies was not discussed. There was no adjustment for possible confounding prior to meta-analysis.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	RoB of individual studies factored during GRADE profile for each outcome.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	RoB of individual studies factored during GRADE profile for each outcome.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partial yes	Heterogeneity was assessed for each outcome and reported. The authors did not discuss the reasons for, or impacts of, heterogeneity in the pooled results.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Publication bias was assessed as part of the GRADE assessment and funnel plots were constructed for outcomes where appropriate. No evidence of publication bias was identified
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Authors declared no conflicts of interest. (p614) Financial disclosures are provided. (p605)
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Citation Ref/Study ID	Maw 2018	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	Authors defined the PICO for the research questions in the review in p595.

Citation Ref/Study ID	Maw 2018	
Question	**Judgement**	**Comments**
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	It is not specified whether the protocol was established prior to the conduct of the review.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Initial intention was to include only RCT. However, following literature search which found no RCTs, search criteria was expanded to non-RCTs
4. Did the review authors use a comprehensive literature search strategy?	Partial yes	Multiple databases were searched. Trial registry, grey literature and hand searching of reference lists was also included. However, search terms were not provided.
5. Did the review authors perform study selection in duplicate?	Yes	Two independent reviewers reviewed each citation. Any disagreement was resolved by a consensus view. If consensus could not be agreed, then independent review by a third author was performed.
6. Did the review authors perform data extraction in duplicate?	No	The authors did not specify whether data extraction was performed in duplicate.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	List of excluded studies and reasons for exclusion are not provided.
8. Did the review authors describe the included studies in adequate detail?	Yes	Included 4 studies are described in detail in the article and the supplementary material.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Risk of bias was assessed for the 4 studies included in the review and GRADE was used to assess quality of each included study.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Sources of funding for the included studies was not reported.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Partial yes	Reviewers considered data insufficient for meta-analysis, so a descriptive analysis was performed.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Partial yes	Meta-analysis was not conducted. RoB of each study was assessed. Reviewers assess validity of each included study's conclusion based on their RoB assessment.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Reviewers acknowledge their recommendation is based upon very low quality evidence.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partial yes	Meta-analysis was not conducted. Heterogeneity was not discussed.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Partial yes	Meta-analysis was not conducted. Publication bias was not discussed.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No	Details on funding were not provided. The authors declared no conflicts of interest.

Citation Ref/Study ID	Maw 2018	
Question	**Judgement**	**Comments**
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Citation Ref/Study ID	Kamyszek 2019	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	Authors defined the PICO for the research questions in the review in p744
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	The publication states that "A protocol for this systematic review is not included".
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	The authors did not specify a limit on study design for inclusion and included a heterogenous composite of studies including retrospective analyses, case series, case reports, review articles, prospective cohort studies, quality improvement assessments and surveys.
4. Did the review authors use a comprehensive literature search strategy?	Partial yes	Multiple databases were searched and search terms provided. Grey literature search was not reported.
5. Did the review authors perform study selection in duplicate?	Yes	Two independent reviewers reviewed each citation. Disagreements were resolved by consensus-based discussion.
6. Did the review authors perform data extraction in duplicate?	No	The authors did not specify whether data extraction was performed in duplicate.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	List of excluded studies and reasons for exclusion are not provided.
8. Did the review authors describe the included studies in adequate detail?	Partial yes	Included studies are described in Table 1.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	Review authors did not assess the risk of bias in individual studies that were included in the review.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Sources of funding for the included studies was not reported.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Due to the heterogeneity of the included studies, meta-analysis was not performed.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Due to the heterogeneity of the included studies, meta-analysis was not performed.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	Review authors did not assess the risk of bias in individual studies that were included in the review.

Citation Ref/Study ID	Kamyszek 2019	
Question	**Judgement**	**Comments**
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Meta-analysis was not conducted. Heterogeneity was not discussed.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Meta-analysis was not conducted. Heterogeneity was not discussed.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	There were no conflicts of interest.
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Citation Ref/Study ID	Sommer 2019	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	Included in the abstract.
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	It is not clear whether the protocol was established prior to the conduct of the review.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	The review states that non-original research articles such as literature reviews and letters to the editor were excluded.
4. Did the review authors use a comprehensive literature search strategy?	No	Only one database was searched (PubMed).
5. Did the review authors perform study selection in duplicate?	No	This is not reported.
6. Did the review authors perform data extraction in duplicate?	No	This is not reported.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	Reasons for exclusion are not provided.
8. Did the review authors describe the included studies in adequate detail?	Partial yes	Included studies are described in Table 1, but not thoroughly.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	RoB assessments are presented in Table 4, using the Newcastle-Ottawa Scale for cohort studies with mortality as outcome measure. The RoB tool includes selection bias and confounding.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Sources of funding for the included studies was not commented on.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Partial yes	Heterogeneity was assessed.

Citation Ref/Study ID	Sommer 2019	
Question	**Judgement**	**Comments**
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	RoB was not discussed as a factor. Studies comparing similarly defined outcomes in MTP and non-MTP groups were meta-analysed.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	This was not discussed.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	This was not discussed. The authors discussed that due to the small number of studies eligible for inclusion in meta-analysis, more statistical power is needed to confirm their hypothesis.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Partial yes	The authors state that funnel plots were not created due to the small number of studies included in the meta-analyses.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	There were no conflicts of interest.
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Citation Ref/Study ID	Consunji 2020	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	Authors defined the PICO for the research questions in the review (p435)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Protocol registered (PROSPERO CRD42020157042)
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	No limit on study design. Authors state only studies reporting on trauma populations included (studies reporting heterogenous populations included if trauma population reported separately).
4. Did the review authors use a comprehensive literature search strategy?	Yes	Multiple databases were searched and search terms provided. Additional manual searching of reference lists also conducted.
5. Did the review authors perform study selection in duplicate?	Yes	Three independent reviewers reviewed each citation. Disagreements were resolved by consensus-based discussion.
6. Did the review authors perform data extraction in duplicate?	Yes	Two reviewers independently extracted data from included studies. Disagreements resolved by third reviewer.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	List of excluded studies and exclusion reasons provided in PRISMA (p438). Full list of excluded studies not provided.

Citation Ref/Study ID	Consunji 2020	
Question	**Judgement**	**Comments**
8. Did the review authors describe the included studies in adequate detail?	Partial yes	Included studies are described in Table 1.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Partial yes	GRADE criteria used to assess the quality of the included studies.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Sources of funding for the included studies was not reported.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Data heterogeneity was assessed using the Cochrane Q homogeneity test; p<0.10 was considered statistically significant. If the studies were statistically homogeneous, fixed effect model was selected. A random effects model was used when studies were statistically heterogeneous.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Partial yes	RoB of individual studies factored during GRADE profile for each outcome.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Review authors discussed bias and heterogeneity of studies and potential limitations in interpretation.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Review authors discussed bias and heterogeneity of studies and potential limitations in interpretation.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Publication bias assessed
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	There were no conflicts of interest.
Overall methodological quality of the review	***High***	***No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.***

Citation Ref/Study ID	Kinslow 2020	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	Clear PICO outlined (p334)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	Prior preparation of the review methods was not reported.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	Inclusion and exclusion criteria were not clearly described by the authors

Citation Ref/Study ID	Kinslow 2020	
Question	**Judgement**	**Comments**
4. Did the review authors use a comprehensive literature search strategy?	Partial yes	The authors searched 6 databases and provided search term (p334)
5. Did the review authors perform study selection in duplicate?	No	Authors did not state if study selection performed in duplicate
6. Did the review authors perform data extraction in duplicate?	No	Authors did not state if data extraction was performed in duplicate.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No reasons for exclusion were reported.
8. Did the review authors describe the included studies in adequate detail?	Partial yes	The characteristics of the included studies were listed in Table 1 (p336), however lacked detail.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	No formal RoB assessment performed. Only qualitative assessment of potential biases likely in the included studies overall was presented.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	The review did not report on the sources of funding for the studies included in the review.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis was not performed and the review authors do not discuss the reasons for not performing a meta-analysis.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis was not performed and the review authors do not discuss the reasons for not performing a meta-analysis.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Partial yes	No formal RoB assessment performed. Authors provide a narrative on individual study limitations.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Heterogeneity within the included studies was not discussed.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Publication bias was not investigated.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflicts of interest.
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Randomised controlled trials

No additional studies identified.

Observational /cohort studies

No additional studies identified.

D3 RBC ratios, timing, dose (Question 3)

Systematic review of RCTs

Study ID	Rahouma 2017	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	Research question and PICO were defined.
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	Prior preparation of the review methods was not reported.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Inclusion and exclusion criteria clearly described (p2)
4. Did the review authors use a comprehensive literature search strategy?	Yes	The authors searched 6 databases and included the search strategy.
5. Did the review authors perform study selection in duplicate?	Yes	Study selection was performed in duplicate with disagreements resolved through a third reviewer.
6. Did the review authors perform data extraction in duplicate?	Yes	Data extraction was performed in duplicate with a third reviewer used to resolve disputes.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	Reasons for exclusion presented in Figure 1. However, a list of the excluded studies was not provided.
8. Did the review authors describe the included studies in adequate detail?	Yes	The characteristics of the included studies were listed in Table 1 (pg4)
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	No formal RoB assessment performed. Only qualitative assessment of potential biases likely in the included studies overall was presented.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	The review did not report on the sources of funding for the studies included in the review.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Meta analysis was conducted using appropriate methods. Random effects model was used to account for heterogeneity.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis was performed however, the impact of the RoB in individual studies on the results was not described.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Partial yes	Limitations of individual studies (including potential RoB) were considered in the discussion of the results
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Heterogeneity within the included studies was not discussed.

Study ID	Rahouma 2017	
Question	**Judgement**	**Comments**
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Publication bias was discussed and shown to not be likely to have had a significant impact on results.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflicts of interest.
Overall methodological quality of the review	***Low***	***One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.***

Study ID	McQuilten 2018	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	The review includes PICO components however no timeframe for follow up is stated
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	The systematic review was conducted in accordance with the protocol registered on PROSPERO. A search strategy was not provided in the publication.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	The review included only randomised or pseudo-randomised controlled studies with uncontrolled studies excluded. Previous review was not restricted by study design, therefore this review limited to RCTs only.
4. Did the review authors use a comprehensive literature search strategy?	Partial yes	The review searched multiple databases and there were no language or publication status restrictions. However, key words and/or the search strategy were not provided.
5. Did the review authors perform study selection in duplicate?	Yes	The reviewers performed the study selection in duplicate and assessed for eligibility against full eligibility criteria with disagreements resolved by consensus.
6. Did the review authors perform data extraction in duplicate?	Yes	Data was extracted by 2 reviewers independently using a standard data extraction form with disagreements resolved by consensus or by discussion with a third reviewer.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	A PRISMA flow chart was provided with stated reasons for exclusion. However a list of the excluded studies was not provided.
8. Did the review authors describe the included studies in adequate detail?	Yes	Authors provided adequate detail of the included studies including study setting, follow-up time, and detailed description of intervention and comparators
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Two independent reviewers assessed risk of bias described in Cochrane Handbook for Systematic Reviews of Interventions with quality of evidence for primary outcomes assessed according to GRADE methods. Authors assessed selection bias (random sequence generation and allocation concealment), performance bias, detection bias, attrition bias and reporting bias

Study ID	McQuilten 2018	
Question	**Judgement**	**Comments**
10. Did the review authors report on the sources of funding for the studies included in the review?	Partial yes	The review was funded by the Australian National Blood Authority with authors receiving funding support from the NHMRC
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Meta-analysis was performed using random effects models to account for clinical heterogeneity. Heterogeneity was assessed using chi-squared tests
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Authors noted the quality of the evidence for the outcomes investigated. RoB of individual studies factored during GRADE profile for each outcome.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Authors noted the quality of the evidence for the outcomes investigated. RoB of individual studies factored during GRADE profile for each outcome.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Statistical heterogeneity was I2=75%, which indicates moderate heterogeneity, however did not provide a satisfactory explanation for the heterogeneity (p14)
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Partial yes	The authors did not mention formal strategies to rate publication bias, however, it was assessed for individual papers (Table 3). A funnel plot was not provided.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The reviewers noted authors employment and financial support received.
Overall methodological quality of the review	***High***	***No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.***

Study ID	Ritchie 2020	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	All elements of PICO clearly described (p856)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	Prior preparation of the review methods was not reported.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Inclusion and exclusion criteria clearly described and used to guide study selection (p856)
4. Did the review authors use a comprehensive literature search strategy?	Yes	3 databases searched with full list of search terms provided in Appendix.
5. Did the review authors perform study selection in duplicate?	No	Authors did not state if study selection was performed in duplicate.

Study ID	Ritchie 2020	
Question	**Judgement**	**Comments**
6. Did the review authors perform data extraction in duplicate?	No	Authors did not state if data extraction was performed in duplicate.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	PRISMA diagram outlining exclusion reasons provided. List of excluded studies not provided (p857)
8. Did the review authors describe the included studies in adequate detail?	Yes	Characteristics and details of included studies are adequately described in tables and text.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Critical appraisal performed using the Scottish Intercollegiate Guidelines Ne2rk checklist for RCTs. Risk of bias assessed in accordance with Cochrane handbook (p856)
10. Did the review authors report on the sources of funding for the studies included in the review?	No	The review did not report on the sources of funding for the studies included in the review.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis was not performed.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis was not performed.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	RoB for all included studies assessed and discussed (p862-3)
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partial yes	Authors acknowledge differences between studies, however, lack adequate discussion on potential impact when interpreting results.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Publication bias was not investigated, most likely due to the small number of studies.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflicts of interest.
Overall methodological quality of the review	***Low***	***One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.***

Study ID	Kleinveld 2021	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Partial yes	Research question described; however, some elements of the PICO remain vague.

Study ID	Kleinveld 2021	
Question	**Judgement**	**Comments**
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	Prior preparation of the review methods was not reported.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Inclusion and exclusion criteria clearly described by the authors
4. Did the review authors use a comprehensive literature search strategy?	Yes	3 databases searched. Search strategy provided in Appendix S1.
5. Did the review authors perform study selection in duplicate?	Yes	Selection of articles was performed by 2 reviewers. Discrepancies in the inclusion of articles were discussed and, if needed, a third independent reviewer was consulted
6. Did the review authors perform data extraction in duplicate?	No	Authors did not state if data extraction was performed in duplicate.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	PRISMA diagram outlining number of excluded studies and reasons. List of excluded studies not provided (pS245)
8. Did the review authors describe the included studies in adequate detail?	Yes	The characteristics of the included studies were listed in Table 1 (pS246)
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	RCTs assessed using Cochrane tool (pS245)
10. Did the review authors report on the sources of funding for the studies included in the review?	No	The review did not report on the sources of funding for the studies included in the review.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Meta analysis was conducted using appropriate methods via RevMan 5 (pS245)
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	RoB of individual studies factored during the meta-analysis (pS247)
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Partial yes	Overall quality of studies was acknowledged but not further discussed in the discussion section.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partial yes	Heterogeneity within included studies assessed within the meta-analysis. No further discussion due to moderate-low heterogeneity found
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Publication bias was not investigated, most likely due to the small number of studies.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared necessary conflicts of interest (pS250).

Study ID	Kleinveld 2021	
Question	**Judgement**	**Comments**
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Systematic review of observational /cohort studies

Study ID	Tapia 2013	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	Research question with PICO was defined.
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	Prior preparation of the review methods was not reported.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	The authors state that they included RCT, prospective and retrospective observational studies or Level IV epidemiological studies. Case reports, letters, comments and reviews excluded.
4. Did the review authors use a comprehensive literature search strategy?	Yes	Multiple databases including a trial registry were searched. The search string used were provided.
5. Did the review authors perform study selection in duplicate?	No	Study selection was not performed in duplicate.
6. Did the review authors perform data extraction in duplicate?	No	Data extraction was not performed in duplicate.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	Reasons for exclusion presented in Figure 1. However, a list of the excluded studies was not provided.
8. Did the review authors describe the included studies in adequate detail?	Partial yes	PICO for included studies was provided and comparability of studies provided.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Partial yes	Newcastle-Ottawa Scale (NOS) was used to assess the quality of studies and only the studies scoring 6 or more were included in the review. However, no further detail about the NOS was provided.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	The review did not report on the sources of funding for the studies included in the review.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis was not performed and the review authors do not discuss the reasons for not performing a meta-analysis.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis was not performed, and the review authors do not discuss the reasons for not performing a meta-analysis.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	RoB was not discussed/considered when interpreting results

Study ID	Tapia 2013	
Question	**Judgement**	**Comments**
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partial yes	Heterogeneity was not formally discussed. However, the authors discuss the comparability of groups in the included studies.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Publication bias was not investigated.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflicts of interest including possible conflicts of interest due to funding.
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies***

Study ID	Jones 2016	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PICO components were described. However, due to variability in the definition of intervention and comparator between the studies, the study investigator's definition was used.
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	Prior preparation of the review methods was not reported.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	Study design, as a search criterion, was not mentioned.
4. Did the review authors use a comprehensive literature search strategy?	Partial yes	Multiple databases were searched, and the key words used were provided. Trial registries were not searched.
5. Did the review authors perform study selection in duplicate?	Yes	Each study was evaluated independently by 2 reviewers for inclusion in the analysis
6. Did the review authors perform data extraction in duplicate?	No	The review authors do not state that data extraction was performed in duplicate.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	Rationale for exclusion not provided in Figure 1. The review did not provide a list of excluded studies or the reason for their exclusion.
8. Did the review authors describe the included studies in adequate detail?	Yes	Included studies were described in detail (setting, MTP definition, population, methods, findings) in a supplementary table.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Two independent reviewers calculated the risk of bias for included studies using a nine-item instrument based on Viswanathan and Berkman 2012 study, who identified indicators of bias in observational studies.

Study ID	Jones 2016	
Question	**Judgement**	**Comments**
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Sources of funding for the included studies was not commented on.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis was not performed because of the inconsistent methods and variables included in the analyses.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis was not performed.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Risk of bias was assessed for the included studies and limitations are discussed.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Heterogeneity within the included studies was not discussed.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Publication bias was not investigated.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors reported no conflicts of interest.
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Study ID	Poole 2016	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PICO was defined in research question 2.
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial yes	The authors state that data extraction was performed according to a predefined, not pre-registered plan.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	The review included RCTs and observational studies only if adjustment for confounders was performed. Letter, case reports and observational studies without controls and adjustment for important covariates were excluded.

Study ID	Poole 2016	
Question	**Judgement**	**Comments**
4. Did the review authors use a comprehensive literature search strategy?	No	Authors only searched Medline (using PubMed platform). A detailed search strategy was provided and they also included meta-analyses and reviews for manual evaluation of the bibliography of the articles as a source of literature that may have escaped the PubMed search.
5. Did the review authors perform study selection in duplicate?	No	A group of physicians screened the studies. However, the authors do not explicitly state that this was done in duplicate.
6. Did the review authors perform data extraction in duplicate?	No	The authors do not state that data extraction was performed in duplicate.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	Reasons for exclusion presented in Figure 2. However, a list of the excluded studies was not provided.
8. Did the review authors describe the included studies in adequate detail?	Partial yes	Included studies described in Table 2 and further in S2. However, description of population is scarce.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	The authors ranked the included studies using GRADE criteria. Prior to applying GRADE, the authors verified that the included studies had high quality reporting (according to CONSORT or relevant criteria), had absence if methodological and statistical flaws and had absence of external validity issues.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	The review did not report on the sources of funding for the studies included in the review.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis was not performed due to study heterogeneity.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis was not performed due to study heterogeneity.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Each included study authors assessed according to GRADE criteria.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partial yes	Meta-analysis was not performed due to study heterogeneity. Two included studies considered high level of evidence were reported to be sufficiently homogenous to provide evidence of efficacy
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Publication bias was assessed for each included study. The authors were unable to formally assess the publication risk of bias due to insufficient number of studies retrieved to gain sufficient power for the test.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors reported no conflict of interest and stated they received no specific funding for this study.
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Study ID	Cannon 2017	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	Authors defined 3 PICO criteria for the research questions in the review. Only PICO in the study is relevant to Question 3 of this review.
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	It is not clear whether the protocol was established prior to the conduct of the review.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	All studies of adult patients including randomised controlled trials (RCTs), observational studies, and retrospective studies were considered.
4. Did the review authors use a comprehensive literature search strategy?	Partial yes	Multiple databases were searched. Search dates and search criteria are provided. Trial registry was not searched and reference lists of included studies was not conducted.
5. Did the review authors perform study selection in duplicate?	No	Although more than one author conducted the literature search and review of studies, the review authors do not explicitly state that this was done in duplicate.
6. Did the review authors perform data extraction in duplicate?	No	One author extracted data.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	Reasons for exclusion presented in Figure 1. However, a list of the excluded studies was not provided.
8. Did the review authors describe the included studies in adequate detail?	No	The included studies are not described (PICO).
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	The authors used GRADE to assess the quality of evidence for each PICO. GRADE table for PICO 2 can be found in Supplement Table 4.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Sources of funding for the included studies was not commented on.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Partial yes	Forest plots generated after calculating random effects RR and MD. Confounding in the included studies was not discussed. There was no adjustment for possible confounding prior to meta-analysis.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	RoB of individual studies factored during GRADE profile for each outcome.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	RoB of individual studies factored during GRADE profile for each outcome.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Heterogeneity included in GRADE assessment for each outcome.

Study ID	Cannon 2017	
Question	**Judgement**	**Comments**
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	No evidence of publication bias was identified.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	There were no conflicts of interest.
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Study ID	Maw 2018	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	Research question and PICO were clearly defined.
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	Prior preparation of the review methods was not reported.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	The authors initially only included RCT, but following the search there were no publications that fit the criteria. Subsequently, the search was expanded to include nonrandomised trials to enable a descriptive analysis.
4. Did the review authors use a comprehensive literature search strategy?	Yes	The authors searched 7 databases, including CENTRAL.
5. Did the review authors perform study selection in duplicate?	Yes	Two independent reviewers reviewed the title and abstract. Disagreement was resolved by a consensus view.
6. Did the review authors perform data extraction in duplicate?	Partial yes	Two authors extracted study data, meeting to decide upon inclusion and exclusion. Disagreements settled with third reviewer
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No reasons for exclusion were reported.
8. Did the review authors describe the included studies in adequate detail?	Partial yes	Characteristics of included studies are described, however lacked detail.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	RoB performed on each included study (provided in supplementary data). RoB methodology not clearly described.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	The review did not report on the sources of funding for the studies included in the review.

Study ID	Maw 2018	
Question	**Judgement**	**Comments**
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis was not performed due to insufficient data.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis was not performed due to insufficient data.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	GRADE quality of evidence assessed (supplementary data) and limitations of studies is considered in the discussion of results
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Heterogeneity within the included studies was not discussed.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Publication bias was not investigated.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflicts of interest.
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Study ID	da Luz 2019	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PICO clearly described (p3338)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial yes	Authors do not explicitly state review methods established prior to review. Clearly detailed methods and materials indicate approach established prior to review (p3338-3339)
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Inclusion and exclusion criteria clearly described for study design, population and intervention (p3338)
4. Did the review authors use a comprehensive literature search strategy?	Yes	5 databases searched. Search terms defined a priori. Sensitive search strategy combining keywords and MeSH headings. (p3338)
5. Did the review authors perform study selection in duplicate?	Yes	Two review authors independently examined eligible studies (p3338)
6. Did the review authors perform data extraction in duplicate?	Yes	Two review authors independently extracted data of included eligible studies (p3338-9)

Study ID	da Luz 2019	
Question	**Judgement**	**Comments**
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	PRISMA diagram outlining number of excluded studies and reasons. List of excluded studies not provided (p3340)
8. Did the review authors describe the included studies in adequate detail?	Yes	The characteristics of the included studies were provided in supplementary tables and described in detail in the paper
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	RCTs assessed using Cochrane tool. Cohort studies assessed using Newcastle-Ottawa Scale. Quality of evidence evaluated using GRADE (p3339)
10. Did the review authors report on the sources of funding for the studies included in the review?	No	The review did not report on the sources of funding for the studies included in the review.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Meta analysis was conducted using appropriate methods via RevMan 5.3 (p3339)
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	RoB of individual studies factored during GRADE profile for each outcome.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	GRADE profile for each outcome was provided
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Heterogeneity within included studies was acknowledged and discussed.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Publication bias not assessed with funnel plots due to small number of studies. Publication bias considered within GRADE evaluation
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflicts of interest.
Overall methodological quality of the review	***High***	***No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.***

Study ID	Kinslow 2020	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	Clear PICO outlined (p334)

Study ID	Kinslow 2020	
Question	**Judgement**	**Comments**
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	Prior preparation of the review methods was not reported.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	Inclusion and exclusion criteria were not clearly described by the authors
4. Did the review authors use a comprehensive literature search strategy?	Partial yes	The authors searched 6 databases and provided search term (p334)
5. Did the review authors perform study selection in duplicate?	No	Authors did not state if study selection performed in duplicate
6. Did the review authors perform data extraction in duplicate?	No	Authors did not state if data extraction was performed in duplicate.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No reasons for exclusion were reported.
8. Did the review authors describe the included studies in adequate detail?	Partial yes	The characteristics of the included studies were listed in Table 1 (p336), however lacked detail.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	No formal RoB assessment performed. Only qualitative assessment of potential biases likely in the included studies overall was presented.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	The review did not report on the sources of funding for the studies included in the review.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis was not performed and the review authors do not discuss the reasons for not performing a meta-analysis.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis was not performed and the review authors do not discuss the reasons for not performing a meta-analysis.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Partial yes	No formal RoB assessment performed. Authors provide a narrative on individual study limitations.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Heterogeneity within the included studies was not discussed.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Publication bias was not investigated.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflicts of interest.

Study ID	Kinslow 2020	
Question	**Judgement**	**Comments**
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Study ID	Meneses 2020	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	No	Authors do not clearly outline all components of the PICO. Interventions, comparators and outcomes are unclear
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	Prior preparation of the review methods was not reported.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	Inclusion and exclusion criteria were not clearly described by the authors
4. Did the review authors use a comprehensive literature search strategy?	No	Authors did not carry out a comprehensive search. Only one database searched with few keywords.
5. Did the review authors perform study selection in duplicate?	Yes	Authors state that articles were searched and initially reviewed by 2 authors and reviewed again by a senior author (p2663).
6. Did the review authors perform data extraction in duplicate?	No	Authors did not state if data extraction was performed in duplicate.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	PRISMA diagram outlining exclusion reasons provided, however, lacks detail. List of excluded studies not provided (p2662)
8. Did the review authors describe the included studies in adequate detail?	No	Characteristics and details of included studies are inadequately described.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	Authors did not conduct any RoB of included studies
10. Did the review authors report on the sources of funding for the studies included in the review?	No	The review did not report on the sources of funding for the studies included in the review.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis was not performed.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis was not performed.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	No formal RoB assessment performed.

Study ID	Meneses 2020	
Question	**Judgement**	**Comments**
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Heterogeneity within the included studies was not discussed.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Publication bias was not investigated, most likely due to the small number of studies.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflicts of interest.
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Study ID	Rodriguez 2020	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	All elements of PICO are clearly described (p127)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	The systematic review protocol was previously registered in PROSPERO (record ID 111387) prior to commencement (p128)
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Inclusion and exclusion criteria are clearly described (p128)
4. Did the review authors use a comprehensive literature search strategy?	Yes	Four different databases used. Details of search is provided (p128)
5. Did the review authors perform study selection in duplicate?	Yes	Two authors were involved in study selection with disputes settled through discussion (p128)
6. Did the review authors perform data extraction in duplicate?	No	Authors did not state if data extraction was performed in duplicate.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	PRISMA diagram outlining exclusion reasons provided. List of excluded studies not provided (p128)
8. Did the review authors describe the included studies in adequate detail?	No	Characteristics and details of included studies are inadequately described.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	The quality of the observational studies was assessed with the Newcastle- Ottawa scale (NOS) (128)
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	Review authors stated that there was no funding to be disclosed (p135)

Study ID	Rodriguez 2020	
Question	**Judgement**	**Comments**
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Meta regression was conducted using a random effects model (p129)
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Partial yes	The authors notes that observational studies published between 2007 and 2015 must be interpreted with caution due to their design (p133)
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Partial yes	RoB for individual studies is depicted by not accounted for or discussed to a strong enough extent
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Heterogeneity was assessed and stratified (p129)
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Publication bias was investigated through a funnel chart and Egger's test (p129)
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflicts of interest.
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Study ID	Wirtz 2020	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	All elements of PICO are clearly described (p1874)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	Prior preparation of the review methods was not reported.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	Inclusion and exclusion criteria are not clearly described
4. Did the review authors use a comprehensive literature search strategy?	Yes	Three different databases used. Details of search is provided (p1874)
5. Did the review authors perform study selection in duplicate?	Yes	Two authors were involved in study selection with disputes settled through discussion (p1874)
6. Did the review authors perform data extraction in duplicate?	No	Authors did not state if data extraction was performed in duplicate.

Study ID	Wirtz 2020	
Question	**Judgement**	**Comments**
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	PRISMA diagram outlining exclusion reasons provided. List of excluded studies not provided (p1876)
8. Did the review authors describe the included studies in adequate detail?	No	Characteristics and details of included studies are inadequately described.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	The quality of the studies was assessed through the Cochrane Collaboration Tool (1875)
10. Did the review authors report on the sources of funding for the studies included in the review?	No	The review did not report on the sources of funding for the studies included in the review.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Meta analysis of 2 studies was conducted through RevMan
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Studies at too great of risk of introducing bias were excluded from meta-analysis
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Studies with an I value of greater than 50 were excluded to reduce bias
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Heterogeneity was discussed and accounted for in the results (p1875)
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	No investigation of publication bias
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflicts of interest.
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Study ID	Phillips 2021	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	Elements of PICO described (p1439)

Study ID	Phillips 2021	
Question	**Judgement**	**Comments**
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial yes	Authors do not explicitly state review methods established prior to review. Clearly detailed methods and materials indicate approach established prior to review (p1439)
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Inclusion and exclusion criteria clearly described by the authors (p1439)
4. Did the review authors use a comprehensive literature search strategy?	Yes	4 databases searched. Details of search terms described (p1439)
5. Did the review authors perform study selection in duplicate?	Yes	Two authors independently reviewed studies (p1439)
6. Did the review authors perform data extraction in duplicate?	Yes	Two authors independently extracted study data (p1439)
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	PRISMA diagram outlining number of excluded studies and reasons. List of excluded studies not provided (p1441)
8. Did the review authors describe the included studies in adequate detail?	Yes	The characteristics of the included studies were listed in Table 1 (p1440)
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	RoB assessed using ROBINS-I (p1439)
10. Did the review authors report on the sources of funding for the studies included in the review?	No	The review did not report on the sources of funding for the studies included in the review.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis was not performed and the review authors do not discuss the reasons for not performing a meta-analysis.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis was not performed and the review authors do not discuss the reasons for not performing a meta-analysis.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Quality of studies and potential influence of RoB on interpretation of studies was discussed.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Heterogeneity within included studies included within discussion of individual studies.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Publication bias was not investigated, most likely due to the small number of studies.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflicts of interest.

Study ID	Phillips 2021	
Question	**Judgement**	**Comments**
Overall methodological quality of the review	***Low***	***One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.***

Study ID	Rijnhout 2021	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	All elements of PICO clearly described (p760)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Methods, including inclusion and exclusion criteria and outcome measures, were predefined and registered in PROSPERO under number CRD42020165648 (p760)
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	No restriction for publication year were included. Case reports, conference reports, and abstracts were excluded from data extraction (p760)
4. Did the review authors use a comprehensive literature search strategy?	Yes	4 databases searched. Details of search terms described and provided in Appendix (p760)
5. Did the review authors perform study selection in duplicate?	Yes	Three authors screened title/abstract (p760)
6. Did the review authors perform data extraction in duplicate?	Yes	Data were collected by 2 authors (p760)
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	PRISMA diagram outlining exclusion reasons provide. List of excluded studies not provided (p761)
8. Did the review authors describe the included studies in adequate detail?	Yes	Characteristics and details of included studies are adequately described in table 1 (p762-5)
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	To assess bias in RCTs, Cochrane RoB2 was used and ROBINS used for non-RCTs (p760)
10. Did the review authors report on the sources of funding for the studies included in the review?	No	The review did not report on the sources of funding for the studies included in the review.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Studies suitable for meta-analysis were analysed using RevMan 5.4. Heterogeneity assessed with I2 statistic and Mantel-Haenszel model with random effects (OR and CIs) used to calculate effect size (p760)
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	RoB assessed for individual studies included in the meta-analysis
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Individual study limitations and biases are considered by the authors in the discussion of the paper

Study ID	Rijnhout 2021	
Question	**Judgement**	**Comments**
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partial yes	Heterogeneity within included studies assessed within the meta-analysis. No further discussion or explanation
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Publication bias was not investigated
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflicts of interest (p769)
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Randomised controlled trials

No additional studies identified.

Observational /cohort studies

No additional studies identified.

D4 RBC volume (Question 4)

Systematic review of RCTs

Study ID	Balvers 2015	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	The authors clearly specified the PICO, inclusion and exclusion criteria for the review.
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	The authors note the review methodology was reported according to PRISMA guidelines. No explicit statement about establishing review methods prior.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	The review included randomised controlled trials and observational studies investigating TIC or transfusion strategies with MOF as primary/secondary outcome. Prospective and retrospective studies were included.
4. Did the review authors use a comprehensive literature search strategy?	Yes	The authors searched PubMed and EMBASE from 1986 to 20, performed a manual search of the reference list of included studies and searched for ongoing trials in trial registries. The authors provided the search terms (Table S2 in supplementary material). Language was restricted to English, Dutch or German.
5. Did the review authors perform study selection in duplicate?	Yes	Two independent reviewers conducted the search with discrepancies resolved by discussion between the reviewers with a third independent reviewer consulted if necessary.
6. Did the review authors perform data extraction in duplicate?	No	Not stated.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	A list of excluded studies and their reasons for exclusion were not provided.
8. Did the review authors describe the included studies in adequate detail?	No	The authors provided minimal details on the patient population, intervention (administration of fluids and RBC units), and outcomes (Morbidity due to multiple organ failure). However, detailed information on the patient population, intervention, the study setting or the timeframe for follow-up are not provided.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Partial yes	The quality of included cohort studies was assessed using the Newcastle-Ottawa Scale and each study was given a Delphi score. The quality assessment was provided as supplemental material. The items assessed included selection of study participants, comparability and outcome. However, reporting bias was not assessed. RCTs were assessed using the Cochrane Collaboration's tool evaluating sequence generation, allocation, concealment, blinding, attrition bias and selective reporting.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Sources of funding for included studies were not reported.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	The inverse variance method (random or fixed effects model) was used to assess heterogeneity studies pooled if homogeneity was obtained. Substantial heterogeneity was considered in I2>75%. Meta-analysis was performed to assess risk factors associated with MOF. However, the methodology for the meta-analysis was not provided.

Study ID	Balvers 2015	
Question	**Judgement**	**Comments**
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	The authors acknowledge the review was limited by the risk of bias and heterogeneity of included studies and the method used for assessing risk of bias. The authors noted no firm conclusions could be drawn due to these limitations; however, the authors did not undertake any analyses to investigate the impact of risk of bias on the summary estimates
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	The authors did not assess the impact of risk of bias on the results of pooled analysis.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	The authors only included studies with low heterogeneity (ie, I2<75%) in the pooled analyses. For those studies that were identified as having high heterogeneity, the sources of heterogeneity were not explored.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	The authors did not investigate publication bias.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors did not have any conflicts of interest.
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Systematic review of observational /cohort studies

Study ID	Patel 2014	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	The authors clearly specified the PICO criteria for the review with broad definitions of trauma, no limits to type and amount of RBC transfusion, a priori definitions of outcomes and no limit on follow-up time frames.
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	The authors note the review methodology conformed to PRISMA guidelines; however, it is not explicitly stated whether the review methods were established prior.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	The review included both observational and interventional studies, with studies needing to be to comparative.
4. Did the review authors use a comprehensive literature search strategy?	Partial yes	The authors searched EMBASE and MEDLINE and performed a manual search of the reference list of included studies. There were no language restrictions. The authors provided the search terms and operators used for the search. The search was conducted within 2 years of manuscript submission. Trial registry was not searched.

Study ID	Patel 2014	
Question	**Judgement**	**Comments**
5. Did the review authors perform study selection in duplicate?	Yes	Two independent reviewers performed the study selection using a predetermined selection criteria with disagreements resolved by a third independent reviewer.
6. Did the review authors perform data extraction in duplicate?	Partial yes	Data extraction was completed in duplicate using a standard extraction form.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	Reason for exclusion was provided in Figure 1 but list of excluded studies was not provided.
8. Did the review authors describe the included studies in adequate detail?	Partial yes	The authors described the population, intervention and outcomes from the included studies, however, the comparator, research designs, study setting, and follow-up were not described.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Partial yes	Study quality of included observational studies was evaluated using the Newcastle-Ottawa Scale. This evaluated participant selection (including representativeness, selection of non-exposed, and ascertainment of exposure) and outcome characteristics (including assessment of outcome, duration of follow-up and completeness of follow-up). However, the simplicity of the method did not provide adequate assessment. GRADE analysis was undertaken for each of the outcomes.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Sources of funding for included studies were not reported.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	The authors conducted 3 separate pooled analyses (using random effects model) for each outcome (RBC as dichotomous, continuous and categorical variable) to obtain OR and 95% CI. Heterogeneity was quantified using the I2 statistic.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Studies were included in the analysis if adjustments for confounders were performed with confounders decided a priori or through univariate analysis.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	The authors attempted to mitigate confounding by including studies that adjusted for injury severity.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	There was high heterogeneity in the pooled analyses of mortality and multiorgan failure. The authors discussed the source of heterogeneity likely being the diversity of the study population, injury severity and mechanisms of injury.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	The authors did not perform any graphical or statistical tests for publication bias.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors did not have any conflicts of interest.
Overall methodological quality of the review	***Low***	***One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.***

Randomised controlled trials

No studies identified.

Observational /cohort studies

Study ID	Hassanein 2015	
Question	**Judgement**	**Comments**
1. Bias due to failure to develop and apply appropriate eligibility criteria	Low	Retrospective study which enrolled eligible patients from a single hospital from a 14-month period
2. Bias due to flawed measurement of both exposure and outcome	Moderate	Does not mention if assessors were blinded to the status of the patients
3. Bias due to failure to adequately control confounding	Low	Multivariate models were adjusted for a possible list of confounders - age, gender, diagnosis, blood units, MELD score and serum sodium at registration
4. Bias due to incomplete or inadequately short follow-up	Moderate	Retrospective study which extracted hospital-based data for eligible patients
Overall risk of bias	***Moderate***	***The study appears to provide sound evidence for a non-randomised study but cannot be considered comparable to a well-performed randomised trial***

Study ID	Liu 2018	
Question	**Judgement**	**Comments**
1. Bias due to failure to develop and apply appropriate eligibility criteria	Low	Prospective study obtaining de-identified patient data from a single trauma centre over a 3-year period
2. Bias due to flawed measurement of both exposure and outcome	Moderate	Does not mention if assessors were blinded to the status of the patients
3. Bias due to failure to adequately control confounding	Serious	No adjustments made for possible confounders
4. Bias due to incomplete or inadequately short follow-up	Moderate	Prospective study which extracted hospital-based data for eligible patients. Endpoints were followed for the duration that the patient was being evaluated in the trauma facility
Overall risk of bias	***Serious***	***The study has some Important problems***

D5 Recombinant activated factor VII (Question 5)

Systematic review of RCTs

Study ID	Curry 2011	
Question	**Judgement**	**Comments**
1. Was an 'a priori' design provided?	Partial yes	Reference is made to a protocol (p2) but no reference is provided.
2. Was there duplicate study selection and data extraction?	Partial yes	Study selection was done by one reviewer, full publication of accepted studies was assessed by 2 reviewers. Data was abstracted by one reviewer and verified by a second reviewer.
3. Was a comprehensive literature search performed?	Yes	The authors searched 3 electronic bibliographic databases (p2), as well as 3 online registers. Reference lists of the identified RCTs and relevant narrative reviews were checked for additional trials. Search strings were provided (additional file 1)
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	Two online clinical trial registries were searched. (p2)
5. Was a list of studies (included and excluded) provided?	No	No list of excluded studies was provided, nor referenced.
6. Were the characteristics of the included studies provided?	Yes	Included studies with characteristics were listed in Additional file 2.
7. Was the scientific quality of the included studies assessed and documented?	Yes	The methodological quality of the included studies was assessed using Cochrane Handbook for Systematic Reviews of Interventions. (p2)
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	No meta-analyses were performed but the scientific quality of the included studies was discussed and considered in the conclusions of the review.
9. Were the methods used to combine the findings of studies appropriate?	Yes	No meta-analyses were performed due to the heterogenous nature of the identified studies (p3)
10. Was the likelihood of publication bias assessed?	No	The authors did not mention formal strategies to rate publication bias.
11. Was the conflict of interest stated?	No	Authors stated conflict of interest and declared funding source for the systematic review; however, there was no mention of conflict of interests of included studies.
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Study ID	Simpson 2012	
Question	**Judgement**	**Comments**
1. Was an 'a priori' design provided?	Yes	Protocol first published Issue 4, 2004 (noted under History, p119)
2. Was there duplicate study selection and data extraction?	Yes	Two independent reviewers selected studies from the results of the literature search and 2 reviewers independently extracted information from each included study using standardized data extraction forms. (p13)
3. Was a comprehensive literature search performed?	Yes	The authors searched thirteen electronic bibliographic databases, and supplemented by reviewing reference lists, contacting experts. (p12)

Study ID	Simpson 2012	
Question	**Judgement**	**Comments**
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	The searches were not restricted by publication status. (p12)
5. Was a list of studies (included and excluded) provided?	Yes	Included studies listed in Table 'Characteristics of included studies' (p35), information regarding excluded studies provided in Table (p71)
6. Were the characteristics of the included studies provided?	Yes	All included studies were described in Table 'Characteristics of included studies' (p35)
7. Was the scientific quality of the included studies assessed and documented?	Yes	The risk of bias was assessed according to the Cochrane Collaboration criteria (6 domains). (p13)
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	The results of the methodological rigor and scientific quality was considered in the analysis and the conclusions of the review.
9. Were the methods used to combine the findings of studies appropriate?	Yes	Data were pooled in meta-analyses and described as weighted mean differences with 95% CIs. Between-trial heterogeneity was identified using I2 statistics (p14).
10. Was the likelihood of publication bias assessed?	Yes	We examined publication bias using funnel plots produced using RevMan 5 software for each of the outcome measures. (p14)
11. Was the conflict of interest stated?	Yes	Authors stated conflict of interest and declared funding source for the systematic review. Authors also stated funding sources of included studies (p16).
Overall methodological quality of the review	***High***	***No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.***

Study ID	McQuilten 2015	
Question	**Judgement**	**Comments**
1. Was an 'a priori' design provided?	Yes	Reference is made to a protocol (p2) that aimed to address evidence gaps identified in Module 1 of the PBM guidelines. Available online.
2. Was there duplicate study selection and data extraction?	Yes	Study selection was performed by 2 of 3 review authors. Data extraction was conducted by 2 review authors, and any disagreements were resolved by consensus or with discussion with a third review author (p2)
3. Was a comprehensive literature search performed?	Yes	The authors searched 6 electronic bibliographic databases (p2)
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	No	No referral to attempt to source grey literature
5. Was a list of studies (included and excluded) provided?	No	No list of excluded studies was provided, nor referenced.
6. Were the characteristics of the included studies provided?	Yes	The included studies were listed in Table 3 and Table 4.
7. Was the scientific quality of the included studies assessed and documented?	Yes	The methodological quality of the included studies was assessed using AMSTAR (for systematic reviews) and the risk of bias tool provided in the Cochrane Handbook for Systematic Review of Interventions (for RCTs)
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	No meta-analyses were performed but the scientific quality of the included studies was discussed and considered in the conclusions of the review.

Study ID	McQuilten 2015	
Question	**Judgement**	**Comments**
9. Were the methods used to combine the findings of studies appropriate?	Yes	No meta-analyses were performed due to the heterogenous nature of the identified studies (p3)
10. Was the likelihood of publication bias assessed?	No	The authors did not mention formal strategies to rate publication bias.
11. Was the conflict of interest stated?	Yes	Authors stated conflicts of interest (p10) and funding sources. Funding sources of included studies listed in Table 1.
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Systematic review of observational /cohort studies

Study ID	Franchini 2010	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	No	The inclusion criteria and PICO were not clearly defined
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No reference is made to a protocol, a priori design or pre-specified methods.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	The authors stated that they were unable to find any RCTs, case controls or interventional cohort studies. Therefore case series with at least 10 cases were included (p221)
4. Did the review authors use a comprehensive literature search strategy?	Yes	The authors searched 2 electronic databases, and reference lists were manually searched for potential eligible studies. Grey literature was searched using "abstract books of the most important conferences" (p221)
5. Did the review authors perform study selection in duplicate?	No	No mention of methods for study selection.
6. Did the review authors perform data extraction in duplicate?	No	No mention of methods for data extraction.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No list of excluded studies was provided, nor referenced.
8. Did the review authors describe the included studies in adequate detail?	Yes	Included studies are outlined in Table 1 (p224)
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	The authors intended to use the Newcastle-Ottawa scale or the Cochrane RoB tool but no studies found.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	There was no mention of conflict of interests of included studies.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis was not conducted.

Study ID	Franchini 2010	
Question	**Judgement**	**Comments**
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Partial yes	The authors intended to use the Newcastle-Ottawa scale or the Cochrane RoB tool but no studies found.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	No mention of the quality of the included study in the discussion.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Heterogeneity was not discussed.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Quantitative synthesis was conducted on the cases identified. Authors acknowledge the limitations of the evidence.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No	There was no mention of conflict of interests or funding declared.
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Study ID	Yank 2011	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	Reference is made to protocol published online (access via AHRQ, reference 6 of the study)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Reference is made to protocol published online (access via AHRQ, reference 6 of the study)
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes, studies included RCTs, observational studies, retrospective studies were considered.
4. Did the review authors use a comprehensive literature search strategy?	Yes	The authors searched 10 bibliographic databases, contacted experts and reviewed references of identified systematic reviews. "a librarian expert on grey literature searched regulatory sites, clinical trial registries, conference proceedings etc." (p2)
5. Did the review authors perform study selection in duplicate?	Yes	Two reviewers independently screened, rated study quality, and abstracted study characteristics. Disagreements were resolved by discussion and, when necessary, reviewed by a third author (p2)

Study ID	Yank 2011	
Question	**Judgement**	**Comments**
6. Did the review authors perform data extraction in duplicate?	Yes	Two reviewers independently screened, rated study quality, and abstracted study characteristics. Disagreements were resolved by discussion and, when necessary, reviewed by a third author (p2)
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	List of excluded studies provided in supplementary material available online
8. Did the review authors describe the included studies in adequate detail?	Yes	All included studies were described in Table 1.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	The Jadad scale (Jadad et al., 1996) was used to assess the methodological quality of each selected study (described in reference 6 of the study)
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	The results of the methodological rigor and scientific quality was considered in the analysis and the conclusions of the review.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Yes. Studies of poor quality were not included or discussed in sensitivity analysis.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Yes. Studies of poor quality were not included or discussed in sensitivity analysis.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Between-trial heterogeneity was discussed, noting differences such as blunt and penetrating trauma, from civilian and military settings, but the authors provided reasons for appropriate combining of studies. (see p. 77 of full report)
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Publication bias was discussed in the full report p162. Number of studies was too small to perform funnel plot analysis.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Authors stated conflict of interest, but no declaration of funding source of included studies.
Overall methodological quality of the review	***High***	***No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.***

Study ID	Magon 2012	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	No	The inclusion criteria and PICO were not clearly defined

Study ID	Magon 2012	
Question	Judgement	Comments
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No reference is made to a protocol, a priori design or pre-specified methods.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	The inclusion of study designs was not explained.
4. Did the review authors use a comprehensive literature search strategy?	No	Only one electronic database was searched. The search strategy was not provided.
5. Did the review authors perform study selection in duplicate?	No	The study selection process was not outlined
6. Did the review authors perform data extraction in duplicate?	No	The data extract process was not outlined
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	No studies were identified.
8. Did the review authors describe the included studies in adequate detail?	Yes	No studies were identified.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	No studies were identified.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No studies were identified.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	No meta-analysis was performed.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	No meta-analysis was performed.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	No studies were identified.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	No studies were identified.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	No quantitative synthesis was conducted.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Conflict of interest and no funding was declared.

Study ID	Magon 2012	
Question	Judgement	Comments
Overall methodological quality of the review	***Low***	***One critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Study ID	Okanta 2012	
Question	Judgement	Comments
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	The inclusion criteria and PICO were clearly defined
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Reference is made to protocol published in ICTVS. (p1)
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	Protocol in ICTVS (refs 1) described 'best available' evidence is reviewed. It is not clear what is judged as "best"
4. Did the review authors use a comprehensive literature search strategy?	Yes	The authors searched 2 electronic bibliographic databases and supplemented by reviewing reference lists. Protocol in ICTVS (refs 1) described "no attempts are made to search the grey literature".
5. Did the review authors perform study selection in duplicate?	No	Protocol in ICTVS (refs 1) described a second author would re-run the search, review critical appraisals of the relevant papers, and check the reference lists of all papers. No duplicate study selection.
6. Did the review authors perform data extraction in duplicate?	No	Protocol in ICTVS (refs 1) described a second author would re-run the search, review critical appraisals of the relevant papers, and check the reference lists of all papers. No independent data extraction.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	No list of excluded studies was provided, nor referenced.
8. Did the review authors describe the included studies in adequate detail?	Yes	All included studies were described in Table 1.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	The authors did not mention formal strategies to rate the quality of the assembled evidence.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Authors stated conflict of interest, but no declaration of funding.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	No meta-analysis was performed by Okanta, 2012.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	No meta-analysis was performed by Okanta, 2012.

Study ID	Okanta 2012	
Question	**Judgement**	**Comments**
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	The authors did not mention scientific quality of included studies when formulating conclusions.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	The authors did not mention heterogeneity of included studies when formulating conclusions.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	No quantitative synthesis was conducted.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No	Authors stated conflict of interest, but no declaration of funding.
Overall methodological quality of the review	***Low***	***One critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Study ID	Cannon 2017	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	The inclusion criteria and PICO was clearly defined (p606)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial yes	A reference was made to planning and implementation in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education. (p605) Details were not provided regarding specific, pre-designed methods; but details of outcomes were prespecified and scored according to GRADE methodology prior to conduct of the review.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	The authors included RCTs, observational studies and retrospective studies. (p606) They did not provide an explicit explanation for their study inclusion criteria.
4. Did the review authors use a comprehensive literature search strategy?	Yes	The authors searched 3 electronic databases and provided their search strategy via supplemental digital content. (p606) No mention of attempts to source grey literature and they did not justify publication restrictions.
5. Did the review authors perform study selection in duplicate?	Yes	The study selection was performed in duplicate (p607)
6. Did the review authors perform data extraction in duplicate?	No	It is not known if data extraction was performed in duplicate. One author entered data into RevMan for quantitative analysis.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	The authors provided the number of excluded studies, in addition to reasons for exclusion, in Figure 1. (p607) However, no list of excluded studies was included.
8. Did the review authors describe the included studies in adequate detail?	No	The included studies are outlined but there is insufficient details regarding baseline population characteristics, interventions and research designs for the included studies.

Study ID	Cannon 2017	
Question	**Judgement**	**Comments**
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Partial yes	RoB was assessed as part of the GRADE assessment. (p608, Suppl tables) However, specific results of RoB assessment for each study was not provided.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No information was provided on funding sources for the included studies.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	The authors performed an appropriate meta-analysis. The compatibility of the included studies was considered in the combination of results. (p 608, 609, 611, 612)
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	The authors commented briefly on the overall impact of study limitations on synthesised evidence. (p613) Quality of evidence scores were also provided for pooled results in supplementary digital content. Risk of bias was discussed with relation to the outcomes assessed. (p 608, 609, 611, 612)
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	The quality of the evidence was accounted for when interpreting and discussing the results of the review. (p 608, 609, 611, 612)
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partial yes	Heterogeneity was assessed for each outcome and reported. The authors did not discuss the reasons for, or impacts of, heterogeneity in the pooled results.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Publication bias was assessed as part of the GRADE assessment and funnel plots were constructed for outcomes where appropriate. No evidence of publication bias was identified
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Authors declared no conflicts of interest. (p614) Financial disclosures are provided. (p605)
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Randomised controlled trials

Study ID	Lavigne-Lissalde 2015	
Domain	**Judgement**	**Description**
Random sequence generation (selection bias)	Low	Block randomization stratified by centre was used with balanced blocks of 6 patients with a 1:1 allocation ratio that was implemented at each centre.
Allocation concealment (selection bias)	Low	The randomization list was computer generated centrally by PFP, who was not involved in the patients' management. The personnel were not blinded to the allocation once it occurred.
Blinding of participants and personnel (performance bias)	High	The trial was not blinded; therefore personnel and the patients (or patient surrogate) was aware of the treatment. Knowledge of treatment may have affected the administration of blood products or other haemostatic procedures. The authors acknowledged that inclusion in the standard care arm during PPH could have led investigators to perform earlier second-line interventional therapies. However, no difference in the time to second-line treatment was detected between arms.
Blinding of outcome assessment (detection bias)	Unclear	The efficacy outcomes in this study are quantitative and therefore unlikely to be affected by lack of blinding when performing outcome assessment. The safety outcome of mortality is also quantitative and therefore unlikely to be affected by knowledge of the therapy. With regards to other safety outcomes, knowledge of the intervention may have led investigators to more thoroughly investigate adverse events in a particular arm.
Incomplete outcome data addressed (attrition bias)	Low	All patients that were enrolled in the study had outcomes reported. There were no patients lost to follow-up. The follow up was sufficient for the outcomes to occur.
Selective reporting (reporting bias)	Low	Primary outcome measures are different to those that are reported in the NCT00370877. Authors explained that blood loss failed to be collected in all cases, thus measurement of this outcome was not possible
Other sources of bias*	Unclear	Two of the authors received "non-financial support" from NovoNordisk. Eight of the 42 patients in the standard care arm received compassionate treatment in an attempt to avoid peripartum hysterectomy. Two were successfully avoided.
Overall risk of bias	***High***	***The study has plausible bias that seriously weakens confidence in the results.***

D6 Blood components (Question 6)

Systematic review of RCTs

Study ID	Fabes 2018	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PICO was outlined in text (p8-p9).
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	There was no protocol established prior to starting the review.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Clear inclusion and exclusion criteria described
4. Did the review authors use a comprehensive literature search strategy?	Yes	Multiple databases and trial registries were searched with years searched and search strategy provided (p9).
5. Did the review authors perform study selection in duplicate?	Partial yes	One author screened all search results for relevance and 3 review authors screened all the remaining results.
6. Did the review authors perform data extraction in duplicate?	Yes	Five review authors independently extracted data onto standardised forms. Two of the review authors piloted there forms and made changes that were agreed upon as needed, resolving disagreements by consensus with recourse to a third review author if needed (p10).
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	List of included and excluded studies were provided (p111-p114).
8. Did the review authors describe the included studies in adequate detail?	Yes	Characteristics of included studies was provided in individual tables
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Cochrane risk of bias tool was used to assess the quality of each included study (p10).
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	The authors reported on the sources of funding for each of the studies included in the review.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Meta analysis was performed on RevMan with heterogeneity measured (p11).
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	The review authors assessed the impact of RoB in individual studies
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Scientific quality of the included studies was used in formulating conclusions (p39-p42).
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	The review authors discussed sources of heterogeneity and performed a subgroup analysis to assess the impact of heterogeneity.

Study ID	Fabes 2018	
Question	**Judgement**	**Comments**
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Assessment of publication bias using a funnel plot was planned if they included 10 or more trials in any of the predefined comparison subgroups (p11).
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Review authors did not report conflicts of interest. Funding sources were included (p42).
Overall methodological quality of the review	***High***	***No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.***

Study ID	Coccolini 2019	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PICO was outlined in text (p2).
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	There was no protocol established prior to starting the review.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	The review authors described a clear inclusion criteria, however, did not define the exclusion criteria (p2)
4. Did the review authors use a comprehensive literature search strategy?	Yes	Multiple databases and trial registries were searched with years searched and search strategy provided (p1).
5. Did the review authors perform study selection in duplicate?	Yes	Two authors independently assessed eligibility with disagreements resolved by consensus in discussion with a third author.
6. Did the review authors perform data extraction in duplicate?	Yes	Two authors performed data extraction independently with disagreements resolved by consensus (p2).
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	List of excluded studies were not provided (p3).
8. Did the review authors describe the included studies in adequate detail?	Partial yes	The characteristics of included studies was provided in text (p3)
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Cochrane risk of bias tool was used to assess the quality of each included study (p2).
10. Did the review authors report on the sources of funding for the studies included in the review?	No	The review authors did not report on the sources of funding for each of the studies included in the review.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Meta-analysis conducted for both of the included trials (p4).

Study ID	Coccolini 2019	
Question	**Judgement**	**Comments**
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	The review authors considered the bias of the included studies and their impact on the results of the meta-analysis (p6)
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Scientific quality of the included studies was used in formulating conclusions (p6).
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partial yes	The review authors reported any heterogeneity across studies however did not provide any explanation.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	There is no explicit mention of the likelihood of publication bias being assessed.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Review authors reported no conflicts of interest and stated that there was no funding received for the review (p7).
Overall methodological quality of the review	***Low***	***One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.***

Study ID	McQuilten 2018	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	The review includes PICO components however no timeframe for follow up is stated
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	The systematic review was conducted in accordance with the protocol registered on PROSPERO. A search strategy was not provided in the publication.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	The review included only randomised or pseudo-randomised controlled studies with uncontrolled studies excluded. Previous review was not restricted by study design, therefore this review limited to RCTs only.
4. Did the review authors use a comprehensive literature search strategy?	Partial yes	The review searched multiple databases and there were no language or publication status restrictions. However, key words and/or the search strategy were not provided.
5. Did the review authors perform study selection in duplicate?	Yes	The reviewers performed the study selection in duplicate and assessed for eligibility against full eligibility criteria with disagreements resolved by consensus.
6. Did the review authors perform data extraction in duplicate?	Yes	Data was extracted by 2 reviewers independently using a standard data extraction form with disagreements resolved by consensus or by discussion with a third reviewer.

Study ID	McQuilten 2018	
Question	**Judgement**	**Comments**
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	A PRISMA flow chart was provided with stated reasons for exclusion. However a list of the excluded studies was not provided.
8. Did the review authors describe the included studies in adequate detail?	Yes	Authors provided adequate detail of the included studies including study setting, follow-up time, and detailed description of intervention and comparators
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Two independent reviewers assessed risk of bias described in Cochrane Handbook for Systematic Reviews of Interventions with quality of evidence for primary outcomes assessed according to GRADE methods. Authors assessed selection bias (random sequence generation and allocation concealment), performance bias, detection bias, attrition bias and reporting bias
10. Did the review authors report on the sources of funding for the studies included in the review?	Partial yes	The review was funded by the Australian National Blood Authority with authors receiving funding support from the NHMRC
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Meta-analysis was performed using random effects models to account for clinical heterogeneity. Heterogeneity was assessed using chi-squared tests
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Authors noted the quality of the evidence for the outcomes investigated. RoB of individual studies factored during GRADE profile for each outcome.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Authors noted the quality of the evidence for the outcomes investigated. RoB of individual studies factored during GRADE profile for each outcome.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Statistical heterogeneity was I2=75%, which indicates moderate heterogeneity, however did not provide a satisfactory explanation for the heterogeneity (p14)
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Partial yes	The authors did not mention formal strategies to rate publication bias, however, it was assessed for individual papers (Table 3). A funnel plot was not provided.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The reviewers noted authors employment and financial support received.
Overall methodological quality of the review	***High***	***No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.***

Systematic review of observational /cohort studies

Study ID	Warmuth 2012	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PICO defined in Table 1.
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Methods and inclusion criteria were defined in advance in a protocol.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	State that study design selected for efficacy outcomes was all prospective, controlled studies and for safety, all prospective studies. No explanations were provided.
4. Did the review authors use a comprehensive literature search strategy?	Yes	Comprehensive literature search strategy including multiple databases, HTA websites and hand searching.
5. Did the review authors perform study selection in duplicate?	Yes	Two researchers independently screened and assessed the abstract and full texts. Achieved consensus through discussion or by involving a third person, if disagreed.
6. Did the review authors perform data extraction in duplicate?	Partial yes	One researcher extracted the data, and second review author controlled the data concerning completeness and accuracy.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	Authors provide reasons for exclusion for full text screening (Figure 1). However, list of excluded studies was not provided.
8. Did the review authors describe the included studies in adequate detail?	Yes	Included studies described in Table 2 and 3.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Authors assessed the quality of eligible studies according to the Cochrane Handbook and the CRD's guidance for undertaking reviews.
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	Funding sources for all 4 included studies are provided.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Authors did not pool studies and do not comment on why this was not performed.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Authors note that the findings of the review have to be interpreted cautiously due to the poor quality of the studies identified.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Authors note that the findings of the review have to be interpreted cautiously due to the poor quality of the studies identified.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Heterogeneity not measured.

Study ID	Warmuth 2012	
Question	**Judgement**	**Comments**
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Publication bias was not investigated.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflict of interest and received only departmental funding for this review.
Overall methodological quality of the review	***Low***	***One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.***

Study ID	Aubron 2014	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	Research question is not comparative, the aim was to evaluate use of fibrinogen concentrate in management of severe trauma
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	There was no explicit statement concerning a prior protocol.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	The search was open to literature that reported FC in management of severe trauma, the only exclusions were for preclinical and paediatric studies.
4. Did the review authors use a comprehensive literature search strategy?	Partial yes	Authors search 2 databases but did not include a trial registry. Key words are provided and publication restrictions were also provided.
5. Did the review authors perform study selection in duplicate?	No	Authors did not mention if study selection was performed in duplicate.
6. Did the review authors perform data extraction in duplicate?	No	Data was extracted by one reviewer.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	Authors provide reasons for exclusion for full text screening. However, list of excluded studies was not provided.
8. Did the review authors describe the included studies in adequate detail?	Partial yes	PICO (in brief) for included studies are provided
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	There was no formal method for assessing risk of bias of included studies. The authors describe the limitation of the available literature - most studies are retrospective with small sample sizes, have a high degree of heterogeneity of the comparator, and heterogeneity in the measures of effect, the included studies lack rigorous analyses.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Sources of funding for the included studies are not reported.

Study ID	Aubron 2014	
Question	**Judgement**	**Comments**
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis was not performed, the review authors do not state the reason for not conducting meta-analysis but do state that there was high degree of heterogeneity
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis was not performed
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	Meta-analysis was not performed
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Meta-analysis was not performed, the review authors do not state the reason for not conducting meta-analysis but do state that there was high degree of heterogeneity
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Publication bias was not investigated.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The study is part of a research program funded by the NHMRC. The authors declared no conflicts of interest.
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Study ID	Lunde 2014	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	The review also searched for non-comparative studies, for the evidence for use and efficacy of FC and its possible benefits and harms in treatment of bleeding patients.
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	There was no explicit statement concerning a prior protocol.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	The authors conducted a systematic evaluation of the evidence with the aim of reviewing RCTs but taking into account findings of large prospective observational and retrospective studies.
4. Did the review authors use a comprehensive literature search strategy?	Yes	Authors searched multiple databases including databases of ongoing trials. The authors also contacted trial authors, authors of previous reviews and manufacturers in the field.

Study ID	Lunde 2014	
Question	**Judgement**	**Comments**
5. Did the review authors perform study selection in duplicate?	No	Authors did not mention if study selection was performed in duplicate.
6. Did the review authors perform data extraction in duplicate?	No	Authors did not mention if data extraction was performed in duplicate.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	Authors did not provide a list of excluded studies nor the reasons for exclusion.
8. Did the review authors describe the included studies in adequate detail?	Partial yes	PICO (in brief) for included studies are provided in Table 1.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Partial yes	The risk of bias in included RCTs was accessed using Cochrane guideline although the review only provides the overall rating. Non-randomised studies were not assessed.
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	Only included for the RCTs (Table 1).
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Review authors do not explain the method used for meta-analysis.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Unclear as the review authors do not explain the method used for meta-analysis of selected outcomes.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	Unclear as the review authors do not explain the method used for meta-analysis of selected outcomes.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partial yes	Heterogeneity was measured (I^2), substantial heterogeneity was noted when discussing an outcome. However, there was no direct explanation about it.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Publication bias was not investigated.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflicts of interest and received no funding for this review.
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Study ID	Mengoli 2017	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	Systematic analysis of available literature evaluating the role of fibrinogen concentrate in the management of severe trauma.

Study ID	Mengoli 2017	
Question	**Judgement**	**Comments**
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	There was no explicit statement concerning a prior protocol.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	The authors selected studies that enrolled at least 10 patients.
4. Did the review authors use a comprehensive literature search strategy?	Partial yes	Comprehensive literature search strategy including multiple databases and hand searching of reference lists of relevant studies and reviews. Trial registry was not searched.
5. Did the review authors perform study selection in duplicate?	Yes	Two reviewers independently performed study selection with disagreements resolved through discussion and on the basis of the opinion of a third reviewer.
6. Did the review authors perform data extraction in duplicate?	Yes	Data extracted by 2 reviewers independently.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	Authors provide reasons for exclusion for full text screening (Figure 1). However, list of excluded studies was not provided.
8. Did the review authors describe the included studies in adequate detail?	Partial yes	PICO (in brief) for included studies are provided in Table 1. Control groups not well defined.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Quality of the included studies was assessed according to GRADE to be poor. Did not provide full result of the assessment.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Sources of funding for the included studies are not reported.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	In order to proceed to meta-analytical pooling, all outcomes were reviewed and, if observed in at least 3 of the included studies, used as a measure of the effect of fibrinogen concentrate in a therapeutic efficacy evaluation.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Authors comment on the methodological flaws of the studies used in the meta-analysis when assessing the outcome.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Authors comment on the methodological flaws of the studies used in the meta-analysis.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Heterogeneity was measured (I^2), and no heterogeneity was detected for mortality outcome.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Publication bias was not investigated.

Study ID	Mengoli 2017	
Question	**Judgement**	**Comments**
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflict of interest while funding sources was not reported.
Overall methodological quality of the review	***Low***	***One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.***

Study ID	Rijnhout 2019	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	The review was performed for matched trauma patients receiving pre-hospital blood transfusion with the primary outcomes of 24 hour and long-term mortality. Secondary outcome of adverse events was also defined.
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial yes	No protocol was registered for this review. The review was based on a systematic search and pre-defined inclusion and exclusion criteria. The meta-analysis was performed according to a pre-defined analysis plan.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	Studies were selected for meta-analysis when they contained cohorts with matched patients. No explanations were provided.
4. Did the review authors use a comprehensive literature search strategy?	Partial yes	Authors searched 4 databases but did not include a trial registry. Key words are provided, and publication restrictions were also provided.
5. Did the review authors perform study selection in duplicate?	Yes	Unique references were imported into EROS and screened in duplicate by at least 2 of the 6 independent reviewers.
6. Did the review authors perform data extraction in duplicate?	No	Data was extracted by one reviewer.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	Authors did not provide a list of excluded studies nor the reasons for exclusion.
8. Did the review authors describe the included studies in adequate detail?	Partial yes	PICO for included studies described in table 1. Control groups are not well defined.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	The reviewers performed a risk of bias assessment using the Cochrane risk of bias tool. The risk of bias in the retrospective cohort was evaluated using the ROBINS-I tool.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Sources of funding for the included studies are not reported.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Review authors used RevMan 5.3.5 to perform the meta-analysis.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Authors note that the findings of the review have to be interpreted with care due to the poor quality of the studies identified.

Study ID	Rijnhout 2019	
Question	**Judgement**	**Comments**
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Authors comment on the risk of bias when discussing studies published over a 30-year time span, and that protocols may be outdated. They addressed the low patient numbers in each study.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partial yes	Heterogeneity was measured (I^2) and was explained as a result of variations in study design and quality, however, did not go into detail.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Partial yes	This review addressed 2 studies that appeared to be at risk of reporting bias, however, did not discuss its impact on the results.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflicts of interest and received no funding for this review.
Overall methodological quality of the review	***Low***	***One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.***

Study ID	Stabler 2020	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PICO outlined in text (p1213).
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	This systematic review was conducted in accordance with the protocol registered on PROSPERO (CRD42017075525) (p1213).
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	The authors selected studies that evaluated the use of FC in patients with trauma-related haemorrhage. Studies that evaluated patients younger than 16 years, individual case reports, and studies not specific to trauma patients were excluded.
4. Did the review authors use a comprehensive literature search strategy?	Partial yes	Eight electronic databases were searched. Search strings were provided in Supplemental Table 1 (p1213). Trial registries were searched. There was no restriction on publication language or date (p1213)
5. Did the review authors perform study selection in duplicate?	Yes	Two authors independently performed study selection. Disagreements regarding inclusion were resolved by consensus with the assistance of a third reviewer (p1213)
6. Did the review authors perform data extraction in duplicate?	Yes	Two authors independently performed data extraction. Disagreements regarding inclusion were resolved by consensus with the assistance of a third reviewer (p1213). Characteristics of included studies provided in Table 1 (p1215).

Study ID	Stabler 2020	
Question	**Judgement**	**Comments**
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	List of excluded studies was not provided (p1214)
8. Did the review authors describe the included studies in adequate detail?	Partial yes	Characteristics of included studies were described in Table 1 (p1215-1216). The results of the methodological rigor and scientific quality was considered in the analysis and the conclusions of the review (p1214, p1220).
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Cochrane risk of bias tool was used to assess the quality of each included study (p1213) by 2 reviewers. Any disagreements were resolved by consensus with the assistance of a third reviewer. GRADE assessment was reported in Table 3.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Sources of funding for the included studies are not reported.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	A meta-analysis was performed for 5 RCTs. Data for dichotomous outcomes were analysed as Mantel-Haenszel risk ratios with 95% Cis. The meta-analysis was performed using a random-effects model since there was significant heterogeneity. Statistical heterogeneity was assessed by the I^2 and x^2 statistics. All analyses were performed using RevMan 5.3 (p1214)
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	The authors assessed the quality of evidence using GRADE.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	The authors assessed the quality of evidence using GRADE.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Heterogeneity was measured (I2). Authors noted significant and substantial heterogeneity for mortality outcome. This was eliminated with the removal of high risk of bias study (p1214)
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	The authors noted that publication bias was not assessed due to the small number of trials identified for the meta-analysis (p1213)
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflicts of interest (p1222). However, the authors did not report on sources of funding.
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Study ID	van den Brink 2020	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PICO outlined in text (p2458-2459)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial yes	No review protocol is available (p2458). The systematic review and meta-analysis was conducted according to the PRISMA methodology.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Clear inclusion and exclusion criteria described (p2458)
4. Did the review authors use a comprehensive literature search strategy?	Partial yes	Three electronic databases were searched. The search strategies were provided in the appendix (p2458). Trial registries were not searched (p2458). The review included only studies published in English.
5. Did the review authors perform study selection in duplicate?	Yes	The title selection was done by one reviewer. Two authors independently performed the abstract and full-text selection. Differences in judgment were resolved by discussion.
6. Did the review authors perform data extraction in duplicate?	Yes	Data extraction was collected independently by 2 authors (p2458)
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	List of excluded studies was not provided (p2462)
8. Did the review authors describe the included studies in adequate detail?	Partial yes	Characteristics of included studies were described in Table 1 (p2460-2461), however it was lacking in detail.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	The risk of bias of cohort and case-controlled studies were assessed using the Newcastle-Ottawa quality assessment scale (p2459). Details were provided in Supplemental Table S2.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Sources of funding for the included studies are not reported.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Meta-analysis was performed using RevMan 5.3, statistical heterogeneity across the studies was assessed using the Cochran's Q test and I^2 values. Sensitivity analysis to exclude outliers was performed using RevMan 5.3. Odds ratios were pooled using the Mantel-Haenszel procedure which assumes a random-effects model. Mean differences were pooled using the Inverse variance procedure which also assumes a random effects model (p2459).
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	The results of the methodical rigor and scientific quality were considered in the analysis and the conclusions of the review in the discussion (p2464-2465)
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	The results of the methodical rigor and scientific quality were considered in the analysis and the conclusions of the review in the discussion (p2464-2465)
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	

Study ID	van den Brink 2020	
Question	**Judgement**	**Comments**
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	The authors did not assess publication bias.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Partial yes	The authors declared no conflicts of interest (p2466). However, the authors did not report on sources of funding.
Overall methodological quality of the review	***Low***	***One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.***

Study ID	Zaidi 2020	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PICO was outlined in the text (p102)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	The protocol was registered on PROSPERO CRD42018085167 in accordance with PRISMA guidelines (p102)
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Studies were fibrinogen replacement therapy was administered in the context of PPH were included. Studies comparing fibrinogen replacement therapy with another haemostatic intervention were excluded.
4. Did the review authors use a comprehensive literature search strategy?	Yes	Ten electronic databases were searched. The search strategies were provided as a supplemental document (p102). Trial registries were searched (p102). There were no restrictions on publication date, language or publication status or study design.
5. Did the review authors perform study selection in duplicate?	Yes	Two authors screened titles and abstracts. Full text articles were assessed for eligibility by 2 review authors. Any disagreements were resolved by consensus or after discussion with a third author (p102).
6. Did the review authors perform data extraction in duplicate?	Yes	Data extraction was performed by 2 reviewers (p103)
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	List of excluded studies was provided as a supplemental table (Table S1) (p104)
8. Did the review authors describe the included studies in adequate detail?	Partial yes	Characteristics of included studies were described in Table 1 (p104).
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	The risk of bias was assessed by 2 authors using the Cochrane Risk of Bias tool (p103).
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Sources of funding for the included studies are not reported.

Study ID	Zaidi 2020	
Question	**Judgement**	**Comments**
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis was not performed
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis was not performed
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	The results of the methodological rigor and scientific quality was considered in formulating conclusions (p107)
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Qualitative assessment of heterogeneity between studies was considered in the interpretation of the results (p105-106)
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	The authors did not assess publication bias.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared potential conflicts of interest and funding sources (p107)
Overall methodological quality of the review	***Low***	***One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.***

Randomised controlled trials

No additional studies identified.

Observational /cohort studies

Study ID	Inokuchi 2017	
Domain	Judgement	Description
Bias due to failure to develop and apply appropriate eligibility criteria	Low	Retrospective study of 224 consecutive eligible patients.
Bias due to flawed measurement of both exposure and outcome	Serious	Activation of MTP was left to clinical decision, meaning consistency not guaranteed. Consistency of implementation of surgical and radiological interventions was also not guaranteed.
Bias due to failure to adequately control confounding	Low	Intergroup differences in patient characteristics were assessed. Impact of intervention on mortality was assessed using a multivariate model with covariates.
Bias due to incomplete or inadequately short follow-up	Low	Proportion of patients with missing data was consistent across the groups.
Overall risk of bias	***Serious***	***The study has some important problems***

D7 Tranexamic acid (Question 7)

Systematic review of RCTs

Study ID	Bennett 2014	
Question	**Judgement**	**Comments**
1. Was an 'a priori' design provided?	Yes	Reference was made to a protocol based on the MECIR standards for the conduct and reporting of systematic reviews. The authors outline all methods used for updating the protocol, in compliance with current evidence and guidelines. (p20 and p61)
2. Was there duplicate study selection and data extraction?	Yes	Three independent reviewers selected studies from the results of the literature search. Two reviewers independently extracted information, while a third reviewer verified these data. (p7)
3. Was a comprehensive literature search performed?	Yes	The authors searched 4 electronic bibliographic databases, and supplemented by reviewing reference lists, conference proceedings, and the International Clinical Trials Registry Platform. The authors also supplemented by writing to authors of the included trials. (p7)
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	The authors did not restrict the search by language or publication status. Only RCTs were eligible for inclusion in the review. (p1)
5. Was a list of studies (included and excluded) provided?	Yes	Lists of both included and excluded studies were provided, along with reasons for exclusion. (p24 to p34)
6. Were the characteristics of the included studies provided?	Yes	Outlined in 'Characteristics of Studies' section. (p24 to p33)
7. Was the scientific quality of the included studies assessed and documented?	Yes	The quality of the evidence was assessed using the 'Risk of Bias' tool from the Cochrane Handbook for the Systematic Review of Interventions (for RCTs). (p7)
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	The results of the methodological rigor and scientific quality was considered in the analysis and the conclusions of the review. Quality of evidence for each primary outcome was evaluated using the GRADE system. (p3, p4, p17 and p18)
9. Were the methods used to combine the findings of studies appropriate?	Yes	Outcome data were pooled in meta-analyses and described as risk ratios with 95% CIs. Between-trial heterogeneity was identified using I2 statistics.
10. Was the likelihood of publication bias assessed?	No	The authors did not analyse the risk of publication bias, due to the limited number of identified trials. (p20)
11. Was the conflict of interest stated?	Yes	The authors stated that there were no reported conflicts of interest. One author disclosed the funding source for their contribution to the review. Funding sources for 2 individual studies were disclosed and vested interests were reported for 2 individual studies. The authors reported where information regarding funding for individual studies was not provided. (p24 to p33, and p60)
Overall methodological quality of the review	***High***	***No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.***

Study ID	Ker 2015	
Question	**Judgement**	**Comments**
1. Was an 'a priori' design provided?	Yes	Reference is made to previous Cochrane review 'Haemostatic drugs for traumatic brain injury' (Perel 2010). (p50)

Study ID	Ker 2015	
Question	**Judgement**	**Comments**
2. Was there duplicate study selection and data extraction?	Yes	Two independent reviewers selected studies from the results of the literature search and 2 reviewers independently extracted information. (p9 and p10)
3. Was a comprehensive literature search performed?	Yes	The authors searched 7 electronic bibliographic databases, and supplemented by reviewing reference lists, contacting experts. (p9)
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	In order to reduce publication and retrieval bias the authors did not restrict the search by language, date or publication status (p9).
5. Was a list of studies (included and excluded) provided?	Yes	Included are both a list of included studies (p24) and a list of references of excluded studies (p28).
6. Were the characteristics of the included studies provided?	Yes	Characteristics of included studies were described in the Table (p24)
7. Was the scientific quality of the included studies assessed and documented?	Yes	The authors assessed the risk of bias in the included trials using The Cochrane Collaboration's 'Risk of bias' tool, as described by Higgins 2011.
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	The results of the methodological rigor and scientific quality was considered in the analysis and the conclusions of the review.
9. Were the methods used to combine the findings of studies appropriate?	Yes	Data were pooled in meta-analyses and described as weighted mean differences with 95% CIs. Between-trial heterogeneity was identified using I2 statistics.
10. Was the likelihood of publication bias assessed?	No	The authors planned to investigate the presence of reporting (publication) bias using funnel plots, however there were too few included studies to enable meaningful analysis. (p10)
11. Was the conflict of interest stated?	No	Authors only stated conflict of interest and declared funding source for the systematic review (p50).
Overall methodological quality of the review	***High***	***No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.***

Study ID	Gayet-Ageron 2018	
Question	Judgement	Comments
1. Was an 'a priori' design provided?	Yes	The authors referenced registration of, in addition to providing a hyperlink to, a PROSPERO study protocol. (p126).
2. Was there duplicate study selection and data extraction?	Yes	One author screened for potentially eligible studies. Full texts were then selected, and discrepancies solved via consensus. (supplementary appendix) In addition, 2 reviewers independently extracted all data. (p126)
3. Was a comprehensive literature search performed?	Yes	The authors searched via an antifibrinolytic trial register that comprised multiple databases. (p126) Search terms/strategies were also provided in the supplementary appendix.
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	The authors did not restrict the search by language or publication status. Only RCTs were eligible for inclusion in the review. (supplementary appendix)
5. Was a list of studies (included and excluded) provided?	No	A list of included and ongoing studies was included in the supplementary appendix. However, no list of excluded studies was provided.

6. Were the characteristics of the included studies provided?	Yes	The characteristics of the included studies, including participant, intervention and outcome summaries, were provided in table format in the supplementary appendix. Participant characteristics are also outlined in more detail in Table 1. (p128)
7. Was the scientific quality of the included studies assessed and documented?	Yes	The authors assessed risk of bias for both articles, outlining levels of risk and justifications for assessments in the supplementary appendix. RoB was reportedly assessed in line with the Cochrane handbook for systematic reviews. (p126)
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	The authors assessed RoB for both included studies to be low. This was mentioned in the results section of the review and in the research in context summary (p128 and p126). The authors did not refer to level of bias in their conclusions, but this was likely due to the minimal impact they determined any such bias would have.
9. Were the methods used to combine the findings of studies appropriate?	Yes	Outcome data were pooled in meta-analyses and described as risk ratios with 95% CIs. Between-trial heterogeneity between trials was also identified, although the author's assessment/identification technique was not outlined. (p127 and p128)
10. Was the likelihood of publication bias assessed?	No	The authors did not report on publication bias assessment.
11. Was the conflict of interest stated?	Yes	Declarations of interest and funding sources were listed for the review in the study protocol. (p3) Funding sources of included studies listed in publication (p125)
Overall methodological quality of the review	***High***	***No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.***

Study ID	**Shakur 2018**	
Question	**Judgement**	**Comments**
1. Was an 'a priori' design provided?	Yes	Reference is made to protocol published in PROSPERO. (p74)
2. Was there duplicate study selection and data extraction?	Yes	Two independent reviewers selected studies from the results of the literature search and 2 reviewers independently extracted information. (p12 and p14)
3. Was a comprehensive literature search performed?	Yes	The authors searched 4 electronic bibliographic databases, and supplemented by reviewing reference lists (p11)
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	Authors also searched for unpublished, planned and ongoing trial reports (p11)
5. Was a list of studies (included and excluded) provided?	Yes	Included are both a list of included studies and a list of references of excluded studies (p27).
6. Were the characteristics of the included studies provided?	Yes	Characteristics of included studies were described in the Table (p31)
7. Was the scientific quality of the included studies assessed and documented?	Yes	The quality of the evidence was assessed using the GRADE approach as outlined in the GRADE handbook. (p15)
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	The results of the methodological rigor and scientific quality was considered in the analysis and the conclusions of the review.
9. Were the methods used to combine the findings of studies appropriate?	Yes	Data were pooled in meta-analyses and described as weighted mean differences with 95% CIs. Between-trial heterogeneity was identified using I2 statistics.

Study ID	Shakur 2018	
Question	**Judgement**	**Comments**
10. Was the likelihood of publication bias assessed?	No	The authors planned to investigate the presence of reporting (publication) bias using funnel plots, however there were too few included studies to enable meaningful analysis. (p10)
11. Was the conflict of interest stated?	Yes	Authors stated conflict of interest and declared funding source for the systematic review (p73). Authors also stated funding sources of included studies (in table included studies).
Overall methodological quality of the review	***High***	***No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.***

Study ID	Ageron 2020	
Question	**Judgement**	**Comments**
1. Was an 'a priori' design provided?	Yes	The authors referenced registration of a PROSPERO study protocol (p677).
2. Was there duplicate study selection and data extraction?	No	The number of authors who screened the studies was not reported. Three reviewers independently extracted the data (p677).
3. Was a comprehensive literature search performed?	Yes	The authors searched via a permanent register of antifibrinolytic trials maintained by the London School of Hygiene and Tropical Medicine Clinical Trials Unit that comprised of MEDLINE, EMBASE, CENTRAL, Web of Science, PubMed, Popline and the WHO International Clinical Trials Registry Platform. Search terms/strategies were provided in the supplementary appendix (p677).
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	The authors searched for ongoing trials. The authors searched Web of Science. Only RCTs were eligible for inclusion in this review (p677).
5. Was a list of studies (included and excluded) provided?	Yes	A list of included and ongoing studies was included in the supplementary appendix. A list of excluded studies was also provided.
6. Were the characteristics of the included studies provided?	Yes	Table 1 shows characteristics of each study including information on patient numbers, intervention and control
7. Was the scientific quality of the included studies assessed and documented?	Yes	Authors assessed study quality for both trials provided in the supplementary index (p679). The RoB tool used by the authors was not specified.
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	The authors assessed RoB for both included studies to be low (p679). The authors addressed the level of bias in their conclusions (p681).
9. Were the methods used to combine the findings of studies appropriate?	Yes	Analyses were done according to the ITT principle. Continuous variables were reported as mean (SD) and median (IQR). Categorical variables were reported as numbers and proportions. Frequency distributions or baseline for baseline risk were plotted. Estimations on the effect of antifibrinolytics on death were based within categories of baseline risk and provided crude risk ratios. The homogeneity of treatment effect across between categories of risk were conducted using the x(2 test. The authors used logistic regression to assess the effects of antifibrinolytics on death as a result of bleeding and reported treatment effects with odds ratios and 95% CI (p677).
10. Was the likelihood of publication bias assessed?	No	The authors did not report on publication bias.

Study ID	Ageron 2020	
Question	**Judgement**	**Comments**
11. Was the conflict of interest stated?	No	Declarations of interest and funding sources were listed (p682). Sources of funding from included studies was not assessed.
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Study ID	Chen 2020	
Question	**Judgement**	**Comments**
1. Was an 'a priori' design provided?	No	No reference was made to a protocol or a priori. The authors noted trials could be eligible for inclusion if they met the following criteria: RCT, study population are patients with traumatic brain injury and intervention treatments are tranexamic acid versus matched placebo (p365).
2. Was there duplicate study selection and data extraction?	Yes	Two authors independently searched the articles, extracted data and assessed the quality of included studies (p365)
3. Was a comprehensive literature search performed?	Yes	The keywords used included: tranexamic acid, and brain or cerebral, and injury. The authors searched several databases including PubMed, EMBASE, Web of Science, EBSCO and Cochrane library (p365).
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	The authors searched Web of Science. Only RCTs were eligible for inclusion in this review (p365).
5. Was a list of studies (included and excluded) provided?	No	No list of excluded studies specified.
6. Were the characteristics of the included studies provided?	Yes	Table 1 shows characteristics of each study including information on patient numbers, intervention and control
7. Was the scientific quality of the included studies assessed and documented?	Yes	Authors assessed study quality (see Figure 2). GRADE analysis was used to determine quality of the evidence for each outcome in accordance with the Cochrane Handbook for Systematic Reviews of Interventions.
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	The authors assessed one study with a high risk of bias as it was an open-label trial (p367).
9. Were the methods used to combine the findings of studies appropriate?	Yes	The meta-analysis was conducted with RevMan 5.3. The authors calculated the risk ratio with 95% CI for dichotomous outcomes. Heterogeneity was quantified with the I^2 statistic. The random-effect model with DerSimonion and Laird weights was applied for all the meta-analyses regardless of heterogeneity (p365)
10. Was the likelihood of publication bias assessed?	Yes	The authors did not assess publication bias due to the limited number (<10) (p365)
11. Was the conflict of interest stated?	No	The authors declared no conflicts of interest. The source of funding was not reported. Sources of funding from included studies was not assessed.
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Study ID	Della Corte 2020	
Question	**Judgement**	**Comments**
1. Was an 'a priori' design provided?	Yes	The authors stated that the review was performed according to a protocol recommended for systematic review (p870).
2. Was there duplicate study selection and data extraction?	No	The authors did not mention if study selection and data extraction were performed in duplicate (p870).
3. Was a comprehensive literature search performed?	Yes	The keywords used included: PPH, tranexamic, delivery, bleeding and randomized. The authors searched Medline, EMBASE, Web of Science, Scopus. ClinicalTrials.gov, Ovid and Cochrane Library (p870).
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	No restrictions for language or geographic location were applied. Ongoing trials were searched (p870).
5. Was a list of studies (included and excluded) provided?	No	All included studies were provided. The excluded studies were included in the references (p870).
6. Were the characteristics of the included studies provided?	Yes	Table 1 shows characteristics of each study including information on patient numbers, intervention and control
7. Was the scientific quality of the included studies assessed and documented?	Yes	Authors assessed study quality (see Figure 2). The risk of bias was assessed bin accordance with the Cochrane Handbook for Systematic Reviews of Interventions (p870).
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	The authors acknowledged that the 2 included trials had a low risk of allocation bias. Only one trial used placebo as control and was double-blind (p871).
9. Were the methods used to combine the findings of studies appropriate?	Yes	The meta-analysis was conducted independently by 2 authors with RevMan 5.3. The completed analyses were compared and any difference was resolved by discussion. The summary measures were reported as relative risk with 95% CI using the random effects model of DerSimonian and Laird. Higgins I^2 greater than 0% was used to identify heterogeneity. A 2-by-2 table was assessed for relative risk, for continuous outcomes means+/- SD were extracted and imported into RevMan 5.3 (p870).
10. Was the likelihood of publication bias assessed?	Yes	The authors did not assess publication bias due to the limited number of studies (2 studies).
11. Was the conflict of interest stated?	No	The authors declared no conflicts of interest. Sources of funding was not reported. Sources of funding from included studies was not evaluated.
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Systematic review of observational /cohort studies

Study ID	Ausset 2015	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	No	Inclusion criteria and research question were not specified.
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No reference was made to a protocol, a priori design or pre-specified methods.

Study ID	Ausset 2015	
Question	**Judgement**	**Comments**
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	No explanation was provided regarding study design selection.
4. Did the review authors use a comprehensive literature search strategy?	No	The authors did not provide any specific search methods.
5. Did the review authors perform study selection in duplicate?	No	No specifics were provided on whether study selection occurred in duplicate, in addition to whether consensus was attained.
6. Did the review authors perform data extraction in duplicate?	No	No specifics were provided on data extraction, in addition to whether consensus was attained.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No reference was made to excluded studies.
8. Did the review authors describe the included studies in adequate detail?	No	The authors described the included studies throughout the review. However, the level of detail was inconsistent and information regarding populations, interventions, comparators, outcomes and study designs was frequently insufficient. No tables outlining study characteristics were provided.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	The authors rated available meta-analyses using the GRADE method. (pS72) They also discussed limitations of a number of the included studies. However, they did not undertake a comprehensive assessment or discussion regarding RoB for individual studies.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No information was provided on funding sources for the included studies.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	No meta-analysis was undertaken by the reviewers.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	No meta-analysis was undertaken by the reviewers.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	The authors did not discuss the impact of RoB on individual studies when discussing the overall results of the review.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	The authors did not analyse or discuss the presence or impact of heterogeneity across the included studies.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	The authors did not conduct a quantitative synthesis, nor did they mention an investigation of publication bias.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflicts of interest. (pS74)

Study ID	Ausset 2015	
Question	**Judgement**	**Comments**
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Study ID	Cannon 2017	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	The inclusion criteria and PICO was clearly defined. (p606)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	A reference was made to planning and implementation in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education. (p605) Details were not provided regarding specific, pre-designed methods; but details of outcomes were prespecified and scored according to GRADE methodology prior to conduct of the review.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	The authors included RCTs, observational studies and retrospective studies. (p606) They did not provide an explicit explanation for their study inclusion criteria.
4. Did the review authors use a comprehensive literature search strategy?	Yes	The authors searched 3 electronic databases and provided their search strategy via supplemental digital content. (p606) No mention of attempts to source grey literature and they did not justify publication restrictions.
5. Did the review authors perform study selection in duplicate?	Yes	Two authors conducted the literature search and study selection. (p607)
6. Did the review authors perform data extraction in duplicate?	No	It is not known if data extraction was performed in duplicate. One author entered data into RevMan for quantitative analysis.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	The authors provided the number of excluded studies, in addition to reasons for exclusion, in Figure 1. (p607) However, no list of excluded studies was included.
8. Did the review authors describe the included studies in adequate detail?	No	The included studies are outlined but there are insufficient details regarding baseline population characteristics, interventions and research designs for the included studies.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Partial yes	RoB was assessed as part of the GRADE assessment. (p608, Suppl tables) However, specific results of RoB assessment for each study was not provided.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No information was provided on funding sources for the included studies.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	The authors performed an appropriate meta-analysis. The compatibility of the included studies was considered in the combination of results.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	The authors commented briefly on the overall impact of study limitations on synthesised evidence. (p613) Quality of evidence scores were also provided for pooled results in supplementary digital content. Risk of bias was discussed with relation to the outcomes assessed.

Study ID	Cannon 2017	
Question	**Judgement**	**Comments**
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	The quality of the evidence was accounted for when interpreting and discussing the results of the review. (p613 and p614)
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partial yes	Heterogeneity was assessed for each outcome and reported. The authors did not discuss the reasons for, or impacts of, heterogeneity in the pooled results.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Publication bias was assessed as part of the GRADE assessment and funnel plots were constructed for outcomes where appropriate.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Authors declared no conflicts of interest. (p614) Financial disclosures are provided. (p605)
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Study ID	Gausden 2017	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	All PICO components were suitably outlined in the review's inclusion criteria. (p514)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial yes	Reference is made to performing the review in accordance with the PRISMA checklist. (p513 and p514) However, the authors do not state whether the review has been registered.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	The authors outlined that they would only include studies with comparison groups (RCTs and Cohort). (p514) However, they did not explain why other study designs were excluded from the review. This is not expected to seriously alter the evidence base
4. Did the review authors use a comprehensive literature search strategy?	Yes	The authors searched 2 electronic databases, in addition to conference proceedings and a clinical trials registry. (p514) They did not justify exclusion based on language, but this is not expected to seriously affect the evidence base
5. Did the review authors perform study selection in duplicate?	Yes	Abstracts were reviewed by 2 authors in determining which studies to include in the review. A third author helped achieve consensus when disagreements arose. (p514)
6. Did the review authors perform data extraction in duplicate?	Yes	All data was extracted by one author and verified by a second. Disagreements were resolved via joint re-review. (p514)

Study ID	Gausden 2017	
Question	**Judgement**	**Comments**
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	The authors provided numbers of and explanations for excluded studies in Figure 1. (p514). However, they did not include a list of excluded studies. The authors also noted 4 abstracts that did not provide sufficient data to be included in the analysis. (p517)
8. Did the review authors describe the included studies in adequate detail?	Yes	The authors outlined individual study characteristics across Table 1 and Table 2. (p515 and p516) They also provided details regarding secondary outcome measures in the review text and supplemental digital content. (p515 and p516)
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	The authors explained that they graded evidence quality based on whether studies were double blinded or unblinded. (p514) However, no information was provided on whether allocation concealment was considered for RCTs, or whether selection bias and confounding was considered for the included cohort study.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No information was provided on funding sources for the included studies.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	The authors accommodated for heterogeneity by reporting the random effects results for their analysis. (p518) A meta-regression was used to assess effect modification of one variable, and several subgroup analyses were performed. (p516) A 'one removed' meta-analysis also demonstrated that the removal of the cohort study from the model had no significant impact on results. (p517)
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Partial yes	The authors tested the sensitivity of the meta-analysis by removal of each individual study from the analysis, stating there was no evidence of any study sufficiently influenced the results. No formal RoB of the studies was conducted
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	The authors explain that individual studies were underpowered to detect significant effects regarding one secondary outcome. (p517) However, further details and discussion regarding studies' blinding or other RoB was not included.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	The authors discussed the likely causes for heterogeneity for each individual outcome, in addition to the impact on overall results. (p515 and p518)
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	The authors discussed potential sources of publication bias, in addition to the findings from studies in abstract form that were excluded due to insufficient detail. (p517) Funnel plot analyses were conducted to assess for publication bias. (p515)
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflicts of interest, and disclosed the funding source for the review. (p513)
Overall methodological quality of the review	***Low***	***One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.***

Study ID	Huebner 2017	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	Intervention and population specified as part of inclusion criteria (p S53)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No reference was made to a protocol, a priori design or pre-specified methods.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	No explanation was provided regarding study design selection.
4. Did the review authors use a comprehensive literature search strategy?	No	The authors did not provide any specific search methods.
5. Did the review authors perform study selection in duplicate?	No	No specifics were provided on whether study selection occurred in duplicate, in addition to whether consensus was attained.
6. Did the review authors perform data extraction in duplicate?	No	No specifics were provided on data extraction, in addition to whether consensus was attained.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No reference was made to excluded studies.
8. Did the review authors describe the included studies in adequate detail?	Yes	The authors described the included studies in sufficient detail throughout the review. No tables outlining study characteristics were provided.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	The review discussed limitations of each included study but no details were provided regarding use of a satisfactory technique for assessing RoB.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No information was provided on funding sources for the included studies.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	No meta-analysis was undertaken by the reviewers.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	No meta-analysis was undertaken by the reviewers.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Partial yes	The authors did not discuss the impact of RoB on individual studies when discussing the overall results of the review. Limitations of each study were discussed.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	The authors did not analyse or discuss the presence or impact of heterogeneity across the included studies.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	The authors did not conduct a quantitative synthesis, nor did they mention an investigation of publication bias.

Study ID	Huebner 2017	
Question	**Judgement**	**Comments**
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Partial yes	No financial/material support reported. No explicit mention of conflicts of interest.
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Study ID	Nishida 2017	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	The inclusion criteria and PICO was clearly defined. (p4)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No reference was made to a protocol, a priori design or pre-specified methods.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	The authors included RCTs and observational studies. (p4) However, they did not provide an explanation for their study inclusion criteria.
4. Did the review authors use a comprehensive literature search strategy?	No	The authors searched one electronic database. (p4) No details of attempts to source grey literature were provided. Moreover, the authors gave no details regarding search strategies or publication restrictions.
5. Did the review authors perform study selection in duplicate?	No	The study selection was performed in duplicate. (p7) However, no information is provided on independent selection, agreement or consensus on which studies to include.
6. Did the review authors perform data extraction in duplicate?	No	No details were provided on whether data extraction occurred in duplicate.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No list of excluded studies was provided, nor referenced.
8. Did the review authors describe the included studies in adequate detail?	No	Population and outcome data were summarised in Table 2. (p5) However, insufficient information was provided regarding comparators and research designs, along with intervention dose, frequency or duration.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	No details were provided regarding use of a satisfactory technique for assessing RoB.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No information was provided on funding sources for the included studies.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	The authors considered the compatibility of the results and provided separate summary estimates for RCTs and observational studies. However, pooled data were not adjusted for heterogeneity. (p4 and p6)

Study ID	Nishida 2017	
Question	**Judgement**	**Comments**
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	RoB was discussed with relation to the outcomes assessed. However, the authors did not conduct specific analyses to investigate likely effects of RoB on the outcome in question.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	The quality of the evidence and RoB was accounted for when interpreting and discussing the overall results of the review. (p4 and p6)
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Heterogeneity was assessed for the outcome of interest, and for each sub-analysis. (p6) However, the authors do not investigate the reasons for, or impacts of, heterogeneity in the pooled results.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	No information was provided regarding an assessment of publication bias.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors stated that no funding has been supplied for the review and declared no conflicts of interest. (p6)
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Study ID	Baskaran 2018	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PICO elements are outlined in the inclusion criteria (p4)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial yes	The report was conducted using PRISMA guidelines (p4). There was no mention if the report was registered
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	No explanation was provided regarding study design selection.
4. Did the review authors use a comprehensive literature search strategy?	Yes	The authors searched multiple databases including Pubmed, Medline, Embase, CCTR, Ovid, Trip and Google. The search terms included 'hip', 'fracture', 'tranexamic acid', 'hemiarthroplasty', 'total hip replacement', 'open reduction and internal fixation', 'dynamic hip screw', 'intramedullary nail' and 'blood loss' (p4).
5. Did the review authors perform study selection in duplicate?	Yes	Two authors conducted the study selection with disputes settled by the senior author (p4).
6. Did the review authors perform data extraction in duplicate?	Yes	Data extraction was performed in duplication. With disagreements resolved by the senior author. (p4)

Study ID	Baskaran 2018	
Question	**Judgement**	**Comments**
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	The authors provided the number of excluded studies, in addition to reasons for exclusion, in Figure 1. (p5) However, no list of excluded studies was included.
8. Did the review authors describe the included studies in adequate detail?	No	The authors described the included studies throughout the report. There was not sufficient detail given on the baseline characteristics of the subjects within the studies.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Analysed the risk of bias in the individual studies (Table II). The authors used the Cochrane risk of bias tool for RCTs and ROBINS-I tool for non-randomised studies.
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	No financial support declared (p9)
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	The meta-analysis was conducted using RevMan v5. For continuous variables, the OR was calculated with the Mantle-Haenszel chi-square method using a random effects model. For studies that presented continuous data as median and/or range values, the standard deviation was calculated using statistical algorithms.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Meta-analysis was performed and the inclusion of potentially high bias studies was mentioned (p9). The authors acknowledge that the unclear or serious risk of bias in most studies would limit the conclusions drawn from the analysis. Only a few studies met the inclusion criteria suggesting there may be publication bias which may have overestimated TXA clinical efficacy.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	The authors admit that the bias that could arise from the included studies limits the conclusions that can be drawn from the reported results
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Heterogeneity was analysed for each study, with potential reasons for it being provided in the discussion (p7).
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Partial yes	The authors reference that publication bias could be present leading to the overestimation of the effect of TXA. No quantitative analysis was undertaken to investigate further or to provide evidence of this.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflict of interest (p9)
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Study ID	El-Menyar 2018	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	The inclusion criteria and PICO was clearly defined. (p1080)

Study ID	El-Menyar 2018	
Question	**Judgement**	**Comments**
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	The authors based their methods and reporting on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. They registered the review at the International prospective register of systematic reviews. (p1080)
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	The authors appropriately explained their study selection criteria. All original, English language studies with comparisons, outcome measures and that had been published from January 2000 were considered. (p1080)
4. Did the review authors use a comprehensive literature search strategy?	Yes	The authors searched 8 electronic databases, including clinical trials registries. Literature from reference lists and review articles was also considered. Their search strategy was also outlined. (p1080)
5. Did the review authors perform study selection in duplicate?	No	No details were provided on whether study selection occurred in duplicate.
6. Did the review authors perform data extraction in duplicate?	Yes	Articles were reviewed and data extracted independently by 2 researchers. Any disagreement by these researchers on the quality of the articles was resolved via consensus among the authors. (p1080)
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	The authors refer to 90 excluded articles, but no list or references were provided. However, they did justify the exclusions of the key studies. (p1081)
8. Did the review authors describe the included studies in adequate detail?	Partial yes	The included studies were summarised in Table 1. (p1082) However, data were not available regarding intervention timing and dosages. Population characteristics for the studies was also limited.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	RoB was assessed using Cochrane Grade pro software. (p1080) Details regarding assessment of included studies provided in Table 2. (p1082)
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No information was provided on funding sources for the included studies.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	The authors considered study compatibility when selecting their statistical combination methods. As the studies were statistically homogenous, a fixed effect model was used. Specific software for pooling data was also referenced. (p1080)
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	RoB was discussed with relation to the individual study results. (p1082)
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	RoB was considered when interpreting the overall review results. (p1085)
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	There was no significant heterogeneity in the results. (p1083 and p1084)

Study ID	El-Menyar 2018	
Question	**Judgement**	**Comments**
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	The authors acknowledged the risk of publication bias due to the absence of grey literature. (p1085) However, no statistical or graphical tests were carried out.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared that there were no conflicts of interest or funding for this review. (p1086)
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Study ID	Chornenki 2019	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PICO elements are outlined in the inclusion criteria (p82)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	The Cochrane Risk of Bias was used independently to assess the bias of included studies. Established prior to searching and adhered to during search (pp.82-83)
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	The authors outlined that they would only include RCTs. They did not provide an explanation as to why only RCTs were included (p82)
4. Did the review authors use a comprehensive literature search strategy?	Yes	The authors searched 3 databases (MEDLINE, EMBASE & CENTRAL) (p82). Search strategy and terms listed (p85).
5. Did the review authors perform study selection in duplicate?	Yes	Two authors conducted the study selection including the reviewing of the titles and abstracts, followed by the full texts. Disagreements were settled through discussion (p82)
6. Did the review authors perform data extraction in duplicate?	Yes	Data extraction was performed in duplication. With disagreements resolved through consensus.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	The authors provided the number of excluded studies, in addition to reasons for exclusion, in Figure 1. (p607) However, no list of excluded studies was included.
8. Did the review authors describe the included studies in adequate detail?	Partial yes	Adequately described the studies components through Table 1 (p83). Also depicted the settings of the included studies including dosage in Table 1.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	RoB is accounted for the individual studies using the Cochrane Risk of Bias Tool (Figure 4 p85). The impact of bias on the interpretation and summary of results is discussed (p83)
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	Sources for funding the review are listed (p85)
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	The authors performed an appropriate meta-analysis. The compatibility of the included studies was considered in the combination of results.

Study ID	Chornenki 2019	
Question	**Judgement**	**Comments**
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	The authors discussed the impact of RoB of individual studies on the overall results of the meta-analysis. They showed the impact of removing the low bias studies from the analysis on the results, but did not formally analyse the RoB of the studies.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Partial yes	Briefly discussed the effect of individual study bias in the discussion but not fully accounted for when interpreting the results (p83)
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Heterogeneity was analysed in the meta-analysis, and an explanation was provided (p83)
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	The authors did not conduct a quantitative synthesis, nor did they mention an investigation of publication bias.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflict of interest (p84/85)
Overall methodological quality of the review	***High***	***No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.***

Study ID	Al-Jeabory 2021	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PICO elements are outlined in the inclusion criteria (p2)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial yes	The report was conducted using PRISMA guidelines (p2). There was no mention if the report was registered
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	The authors included randomized controlled trials, quasi-randomised or observational studies. No explanation was provided regarding the study design selection (p2)
4. Did the review authors use a comprehensive literature search strategy?	Yes	The keywords included: "tranexamic acid" OR "tranexamic" OR "TXA" OR "hemorrhage control" AND "injuries*" OR "trauma" OR "wounds" AND "prehospital" OR "military" OR "combat" OR "civil*" OR "emergency medicine" OR "ER" OR "ED". The authors searched PubMed, Scopus, EMBASE Web of Science and CENTRAL (p2).
5. Did the review authors perform study selection in duplicate?	Yes	Two authors conducted the study selection with disputes settled through discussion with a third researcher (p3).
6. Did the review authors perform data extraction in duplicate?	Yes	Data extraction was performed in duplication. Disagreements were resolved through discussion with a third researcher (p3)

Study ID	Al-Jeabory 2021	
Question	**Judgement**	**Comments**
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	The authors provided the number of excluded studies, in addition to reasons for exclusion, in Figure 1. (p4) However, no list of excluded studies was included.
8. Did the review authors describe the included studies in adequate detail?	Yes	A list of included studies, including baseline characteristics are provided in Table 1.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Analysed the risk of bias of the RCTs in Supplemental Figure 4 and Supplemental Figure 5. The risk of bias assessment for the non-RCT studies presented in Supplemental Figure 6 and Supplemental Figure 7. The authors used the ROBINS-I tool to assess the non-randomised studies and the RoB 2 tool was used to assess the quality of randomised studies (p3)
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	No financial support declared (p10)
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	The meta-analysis was conducted using RevMan 5.4. The outcomes were summarised using the Mantel-Haenszel odds ratios or mean differences. All results were presented with their 95% CIs. When the continuous outcome was reported in a study as median, range and IQR, the authors estimated means and standard deviations using the formula described by Hozo et al. Homogeneity of the effect size across trials was tested using the Cochrane Q statistic and the I2 statistic, which indicates the percentage of variability due to heterogeneity rather than sampling error. The authors performed sensitivity analysis using the Hartung–Knapp–Sidik–Jonkman method, when the number of studies was small (<10). The random effects model was used for I2 > 50%; the fixed effects model was employed. A p-value <0.05 was taken to indicate statistical significance. Statistical testing was 2-tailed (p3).
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Partial yes	Meta-analysis was preformed and the risk of bias of the included studies were addressed (p9). However, the authors did not address the potential impact of RoB in individual studies on the results of the meta-analysis.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	The authors did not account for RoB in individual studies when discussing the results of the review.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Heterogeneity was analysed for each study, with potential reasons for it being provided in the discussion (p9).
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	The authors assessed potential publication bias using a funnel plot if more than 10 trials were included for an outcome (p3)
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflict of interest (p10)

Study ID	Al-Jeabory 2021	
Question	**Judgement**	**Comments**
Overall methodological quality of the review	***High***	***No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.***

Study ID	Almuwallad 2021	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PICO elements are outlined in the inclusion criteria (p902)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	The report was conducted using the Cochrane guidance for Systematic Review and Meta-analysis and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis. The reported was registered in the International Prospective Register of Systematic Reviews (p902)
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	No explanation was provided regarding study design selection (p902)
4. Did the review authors use a comprehensive literature search strategy?	Yes	The authors searched multiple databases including EMBASE, Medline (PubMed), BNI, EMCARE, and HMIC. Other databases included were SCOPUS and Cochrane Central Register for Clinical Trials Library. A grey literature search was performed and focused on the following databases: World Health Organization, International Clinical Trial Registry Platform, Clinicaltrials.gov, European Clinical Trial Registry, University of Toronto Library, Google search and Google scholar. Five keywords were used for the search strategy: tranexamic acid, trauma, haemorrhage, coagulation and prehospital (p902)
5. Did the review authors perform study selection in duplicate?	Yes	Two authors conducted the study selection with disputes resolved in discussion with a third reviewer (p902).
6. Did the review authors perform data extraction in duplicate?	Yes	Data extraction was performed in duplication. Discrepancies and conflicts were resolved in discussion with a third reviewer (p902).
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	The authors provided the number of excluded studies, in addition to reasons for exclusion, in Figure 1 (p903). However, a list of excluded studies was not included.
8. Did the review authors describe the included studies in adequate detail?	No	The authors described the included studies in Table 1. There was not sufficient detail given on the baseline characteristics of the subjects within the studies (p904).
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	The authors used the Cochrane collaborative Risk of Bias assessment tool for RCTs and the Newcastle-Ottawa Scale was used to assess the quality and risk of bias in the non-randomised studies (p902).
10. Did the review authors report on the sources of funding for the studies included in the review?	No	The authors did not report on sources of funding.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	The meta-analysis with a random effects model was conducted using RevMan 5.3. An odds ratio with 95% CI was calculated for each mortality time point presented and the incidence of VTE using binary logistic regression, IBM SPSS v24. Heterogeneity between studies reported as the I^2 statistic (p902)

Study ID	Almuwallad 2021	
Question	**Judgement**	**Comments**
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Meta-analysis was preformed and the risk of bias of the included studies were addressed (p903-904). The authors assessed the potential impact of RoB in individual studies on the results of the meta-analysis (p905-906).
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	The authors acknowledged that the systematic review was limited by the quality of evidence it has evaluated (p905-906).
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Heterogeneity was analysed for each study however it was not explained (p902).
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	The authors assessed for publication bias with the inverted or asymmetrical funnel plots which indicate potential risk of publication bias due to the small number of included studies in Supplemental Figure 1.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared no conflict of interest (p906)
Overall methodological quality of the review	***High***	***No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.***

Randomised controlled trials

Study ID	Roberts 2020	
Domain	**Judgement**	**Description**
Random sequence generation (selection bias)	Low	Study describes the method of randomisation in sufficient detail. The intervention and placebo groups are well balanced.
Allocation concealment (selection bias)	Low	The lowest numbered treatment pack was taken from a box of 8 packs.
Blinding of participants and personnel (performance bias)	Low	Patients, caregivers, and those assessing outcomes were masked to allocation.
Blinding of outcome assessment (detection bias)	Unclear	The study states that outcome assessors were blinded to allocation but does not provide any further details. Adequate blinding of outcome assessors is possible with the study method.
Incomplete outcome data addressed (attrition bias)	Low	Provides a detailed description of patient disposition. Exclusions from analyses are described. Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other sources of bias*	Low	Nil.
Overall risk of bias	***Unclear***	***The study has plausible bias that raises some doubt about the results.***

Observational /cohort studies

Study ID	Marsden 2017	
Question	**Judgement**	**Comments**
Bias due to failure to develop and apply appropriate eligibility criteria	Low	Retrospective study of 661 major trauma patients analysed from time from injury to TXA administration. Patients of all ages were included if they had a hospital admission duration of 3 days or longer, critical care admission, transfer to specialist centre or in-hospital death within 30 days. The exclusion criteria was defined (p396)
Bias due to flawed measurement of both exposure and outcome	Low	The authors used the current NICE guideline as the standard to assess the time to TXA administration, over 2017 (1 year period) (p396)
Bias due to failure to adequately control confounding	Moderate	Subgroup analysis was performed to assess the potential for confounding (only from one of the five sites) (p396)
Bias due to incomplete or inadequately short follow-up	Low	Proportion of missing data across the MTCs were manually entered from the patients' original medical records (p396)
Overall risk of bias	***Moderate***	***The study appears to provide sound evidence for a non-randomised study but cannot be considered comparable to a well-performed randomised trial.***

Study ID	Myers 2017	
Question	**Judgement**	**Comments**
Bias due to failure to develop and apply appropriate eligibility criteria	Serious	Appropriate eligibility criteria was developed (p21)
Bias due to flawed measurement of both exposure and outcome	Serious	Dose of TXA not specified and varied. Administration of TXA was at the discretion of the treating trauma surgeon, generally recommended by institutional guidelines when MTP is activated. The patients presented between Jan 2012 to December 2016 (5 year period) (p21)
Bias due to failure to adequately control confounding	Moderate	ISS and VTE may be confounders, the authors adjusted for these in the regression model. While the multivariate analysis was intended to adjust for confounding, biases may remain (p24,26)
Bias due to incomplete or inadequately short follow-up	Low	Missing data did not exceed 5%, imputations were deemed unnecessary (p21)
Overall risk of bias	***Serious***	***The study has some important problems***

D8 Viscoelastic testing (Question 8)

Systematic review of RCTs

Study ID	Fahrendorff 2017	
Question	**Judgement**	**Comments**
1. Was an 'a priori' design provided?	No	No reference is made to a protocol, a priori design or pre-specified methods.
2. Was there duplicate study selection and data extraction?	No	Study selection was performed by one author (p2)
3. Was a comprehensive literature search performed?	Yes	The authors searched 2 electronic bibliographic databases (EMBASE and PubMed). (p2) Search terms were provided. Literature search date was not provided.
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	No	No referral to attempt to source grey literature. Included studies in a language other than English.
5. Was a list of studies (included and excluded) provided?	Yes	Excluded studies with reason for exclusion (Table 2). Included studies listed (Table 4)
6. Were the characteristics of the included studies provided?	Yes	Characteristics of included studies are provided (Table 3, Table 4)
7. Was the scientific quality of the included studies assessed and documented?	No	The scientific quality of the included studies was not formally assessed.
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	No	The authors did not mention scientific quality of included studies when formulating conclusions.
9. Were the methods used to combine the findings of studies appropriate?	Yes	Data was pooled where appropriate for meta-analyses and described as Odds ratios and weighted mean differences with 95% CIs. Between trial heterogeneity was identified using I2 statistics (p7)
10. Was the likelihood of publication bias assessed?	No	The authors did not mention formal strategies to rate publication bias.
11. Was the conflict of interest stated?	No	Authors stated conflict of interest, and funding (p9) but no declaration of funding source of included studies.
Overall methodological quality of the review	***Low***	***One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.***

Study ID	Serraino 2017	
Question	**Judgement**	**Comments**
1. Was an 'a priori' design provided?	Yes	Protocol approved and available on PROSPERO register (p824; CRD:42016033831).
2. Was there duplicate study selection and data extraction?	Yes	Two authors independently undertook study selection and data extraction (p824)
3. Was a comprehensive literature search performed?	Yes	The authors searched 5 electronic bibliographic databases
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	The authors searched clinicaltrials.gov
5. Was a list of studies (included and excluded) provided?	Yes	Excluded studies with reasons for exclusion were provided (p825, Supp Table 1)
6. Were the characteristics of the included studies provided?	Yes	Characteristics of included studies is outlined in Table 1 (p826)

Study ID	Serraino 2017	
Question	**Judgement**	**Comments**
7. Was the scientific quality of the included studies assessed and documented?	Yes	Risk of bias was formally assessed using Cochrane Collaboration tool (p824) And was well reported with reasons for each assessment (Fig 1)
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Pooled effect estimates were expressed as risk ratios (RR) with the 95% confidence interval (CI). For continuous outcomes, we pooled mean differences (MD) or standardized mean differences (SMD) with 95% CI by using the inverse variance method. Subgroup analyses were performed (p825)
9. Were the methods used to combine the findings of studies appropriate?	Yes	Random effects model was used due to high heterogeneity when performing meta-analysis. Between trial heterogeneity was assessed (I2)
10. Was the likelihood of publication bias assessed?	Yes	There were 2 outcomes where publication bias was able to be assessed. Egger's test was used to determine publication bias (p828)
11. Was the conflict of interest stated?	Yes	Authors stated conflict of interest and declared funding source for the systematic review. Funding of individual studies was discussed but not reported (p827-828)
Overall methodological quality of the review	***High***	***No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.***

Study ID	Wikkelso 2016	
Question	**Judgement**	**Comments**
1. Was an 'a priori' design provided?	Yes	Cochrane review. Protocol first published: Issue 3, 2009
2. Was there duplicate study selection and data extraction?	Yes	Two review authors independently evaluated all relevant trials (p17). Two authors independently extracted and collected the data; they resolved any disagreements by discussion (p19).
3. Was a comprehensive literature search performed?	Yes	The authors searched eleven electronic bibliographic databases, and supplemented by reviewing reference lists, contacting experts. (p16-17)
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	We included parallel group randomized controlled trials (RCTs) irrespective of quasi-randomizations, publication status, blinding status, or language of the report.
5. Was a list of studies (included and excluded) provided?	Yes	Included are both a list of included studies (p50) and a list of excluded studies (p75).
6. Were the characteristics of the included studies provided?	Yes	Characteristics of included studies were described in Table 1 (p130)
7. Was the scientific quality of the included studies assessed and documented?	Yes	We used the principles of the GRADE system to assess the quality of the body of evidence associated with specific outcomes. (p21)
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	The results of the methodological rigor and scientific quality was considered in the analysis and the conclusions of the review.
9. Were the methods used to combine the findings of studies appropriate?	Yes	Data were pooled in meta-analyses and described as weighted mean differences with 95% CIs. Between-trial heterogeneity was identified using I2 statistics (p20).
10. Was the likelihood of publication bias assessed?	Yes	Authors examined this by providing a funnel plot in order to detect either publication bias or a difference between smaller and larger studies. (p20)

Study ID	Wikkelso 2016	
Question	**Judgement**	**Comments**
11. Was the conflict of interest stated?	Yes	Authors stated conflict of interest and declared funding source for the systematic review (p145). Authors also stated funding sources of included studies (p28).
Overall methodological quality of the review	***High***	***No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.***

Systematic review of observational /cohort studies

Study ID	Da Luz 2014	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PICO was defined (p2)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No reference is made to a protocol.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	The inclusion of study designs was outlined for each research question; however, rationale was not provided (p2)
4. Did the review authors use a comprehensive literature search strategy?	Yes	The authors searched 3 electronic bibliographic databases. The search date month (no date) and search strings are provided (p2)
5. Did the review authors perform study selection in duplicate?	Yes	Study selection was performed in duplicate (p2), consensus was assessed using Cohen K, and in the case of a disagreement, a third reviewer settled disputes.
6. Did the review authors perform data extraction in duplicate?	Partial yes	Unclear if data extraction was performed in duplicate, but seems likely. Quality assessment was carried out in duplicate (p2)
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	List of excluded studies, with reasons was provided (Supp 1)
8. Did the review authors describe the included studies in adequate detail?	Yes	Characteristics of included studies were provided in Table 1
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Quality of the included studies was assessed using the Newcastle-Ottawa Scale for cohort studies, and QUADAS-2 for diagnostic accuracy studies (p2). The assessments are provided in Table 2 and Table 3.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	There was no mention of funding sources of included studies.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Partial yes	No meta-analysis was performed.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Partial yes	The assessments are provided in Table 2 and Table 3. No meta-analysis was performed.

Study ID	Da Luz 2014	
Question	**Judgement**	**Comments**
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	The major limitations due to the study quality were discussed when discussing the review (p22)
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partial yes	Study heterogeneity was not assessed, but diversity in the patient populations was discussed.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Publication bias was not assessed and quantitative synthesis was not performed.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared conflict of interest. The study was funded by a National Blood Foundation Grant.
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Study ID	Haas 2014	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	No	The inclusion criteria and PICO were not clearly defined
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No reference is made to a protocol, a priori design or pre-specified methods.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	The inclusion of study designs was not explained.
4. Did the review authors use a comprehensive literature search strategy?	No	The search strategy was not provided
5. Did the review authors perform study selection in duplicate?	No	The study selection process was not outlined
6. Did the review authors perform data extraction in duplicate?	No	The data extract process was not outlined
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No list of excluded studies was provided, nor referenced.
8. Did the review authors describe the included studies in adequate detail?	Yes	The included studies are outlined in Table 1
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	No tools were used to assess the quality of included studies.

Study ID	Haas 2014	
Question	**Judgement**	**Comments**
10. Did the review authors report on the sources of funding for the studies included in the review?	No	There was no mention of conflict of interests of included studies.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Partial yes	No meta-analysis was performed. Narrative review.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Partial yes	No meta-analysis was performed. Narrative review.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	There was no mention of RoB when discussing the review.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Study heterogeneity was not assessed or discussed.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Quantitative synthesis was not performed.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Conflict of interest was reported and funding declared. (p1335)
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Study ID	Corredor 2015	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	The inclusion criteria and PICO was clearly defined (p716)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	Reference is made to following the PRISMA /PICOT guidelines, but no reference to protocol provided.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	The inclusion of study designs was outlined for each research question, however full rationale was not provided (p716)
4. Did the review authors use a comprehensive literature search strategy?	Yes	The authors searched 3 electronic bibliographic databases and date of search and search strings are provided (p716-717, Table 2). No mention of attempts to source grey literature was made.

Study ID	Corredor 2015	
Question	**Judgement**	**Comments**
5. Did the review authors perform study selection in duplicate?	Yes	Study selection was performed in duplicate (p718)
6. Did the review authors perform data extraction in duplicate?	Yes	The data extraction was performed in duplicate (p718)
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	Full list of excluded studies not provided. The included studies are referenced (p719) and PRISMA diagram provides some indication of reasons for exclusion (Fig 1)
8. Did the review authors describe the included studies in adequate detail?	Yes	Included studies are outlined in Table 3 and Table 4
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	RoB was assessed using the SIGN framework. (p 719)
10. Did the review authors report on the sources of funding for the studies included in the review?	No	There was no mention of funding sources of included studies.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	A M-H model was used for dichotomous outcomes, and the results are reported as RR with 95% CI and p values. Continuous outcomes were analysed using an inverse variance method and values reported as mean differences, 95% CI and p values. (p719)
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	The SIGN rating was presented in Table 3
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Methodological issues were discussed in the discussion of results (p728-729)
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Heterogeneity was assessed using the I2 statistic.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Publication bias was assessed both by visual analysis of a funnel plot and by using Egger's regression test (Fig 4, p727)
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Conflict of interest was reported and funding declared. (p729)
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Study ID	Deppe 2016	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PICO and inclusion criteria was clearly defined in the Abstract (p 424)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No reference is made to a protocol, a priori design or pre-specified methods.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	The inclusion of study designs was outlined for each research question, however, rationale was not provided (p425)
4. Did the review authors use a comprehensive literature search strategy?	Yes	The authors searched 3 electronic bibliographic databases. The search date and search strings are provided (p425, Supp 1)
5. Did the review authors perform study selection in duplicate?	Yes	Study selection was performed in duplicate (p425)
6. Did the review authors perform data extraction in duplicate?	No	Unclear if the data extraction was performed in duplicate, but seems likely (p425)
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	List of excluded studies, with reasons was provided (Supp 2)
8. Did the review authors describe the included studies in adequate detail?	Partial yes	Characteristics of included studies was provided (Table 1). Comparators in each of the studies are not outlined.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Quality of the included studies was assessed using the Downs and Black score for all studies, and the Jaded score for RCTs by 2 assessors (p425)
10. Did the review authors report on the sources of funding for the studies included in the review?	No	There was no mention of funding sources of included studies.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	A M-H fixed effects model was used for mortality and morbidity outcomes (with low heterogeneity) and the results were reported as OR with 95%CI and p value. A DerSimonian-Laird random effects was used for outcomes with high heterogeneity (I2 >50%).
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Partial yes	Quality score was presented in Table 1. The authors discussed bias however did not assess the impact of the bias on the meta-analysis.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	The authors conducted a subgroup analysis on RCTs to assess the impact of the implementation of transfusion algorithms (p431)
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	The authors discussed heterogeneity and stated that it had unclear influence on reported effect estimates (p431)
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Publication bias was assessed using visual examination of a funnel plot (Supp 3) and Eggers weighted regression statistics. Publication bias was reported where identified (p428)

Study ID	Deppe 2016	
Question	**Judgement**	**Comments**
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors reported no conflicts of interest and no funding received for the study (p431)
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Study ID	Saner 2016	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	No	The inclusion criteria and PICO were not clearly defined
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No reference is made to a protocol, a priori design or pre-specified methods.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	The inclusion of study designs was not explained.
4. Did the review authors use a comprehensive literature search strategy?	No	Only one electronic database (PubMed) was used
5. Did the review authors perform study selection in duplicate?	No	The study selection process was not outlined
6. Did the review authors perform data extraction in duplicate?	No	The data extract process was not outlined
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No list of excluded studies was provided, nor referenced.
8. Did the review authors describe the included studies in adequate detail?	No	The included studies were not clearly outlined
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	No tools were used to assess the quality of included studies.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	There was no mention of funding sources of included studies.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	No meta-analysis was performed. No discussion of study quality provided
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	No formal assessment of RoB in included studies

Study ID	Saner 2016	
Question	**Judgement**	**Comments**
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	There was no mention of RoB when discussing the review.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Study heterogeneity was not assessed or discussed.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Quantitative synthesis was not performed.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No	The authors declared conflict of interest but did not disclose funding.
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Study ID	Li 2018	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Partial yes	Eligibility criteria was outlined but PICO was not clearly defined (p 1170-1171)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No reference is made to a protocol, a priori design or pre-specified methods.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	The inclusion of study designs was outlined for each research question, however, rationale was not provided (p 1171)
4. Did the review authors use a comprehensive literature search strategy?	Yes	The authors searched 9 electronic bibliographic databases. (p1171) Search strings were provided
5. Did the review authors perform study selection in duplicate?	Yes	Study selection was performed in duplicate (p 1171)
6. Did the review authors perform data extraction in duplicate?	No	Not stated if data extraction was performed in duplicate
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	Full list of excluded studies not provided. The PRISMA diagram provides some indication of reasons for exclusion (Fig 1) and 5 excluded studies referenced
8. Did the review authors describe the included studies in adequate detail?	Yes	Characteristics of included studies were provided in Table 1
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Quality of the included studies was not clearly described but used the Cochrane Risk of Bias tool (p 1171 and Fig 2)

Study ID	Li 2018	
Question	**Judgement**	**Comments**
10. Did the review authors report on the sources of funding for the studies included in the review?	No	There was no mention of funding sources of included studies.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Meta-analysis was performed, heterogeneity was tested for (p 1171-1172).
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	The risk of Type 1 errors was assessed by using sequential analysis (TSA). (p 1172)
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	The major limitations due to the study quality were discussed when discussing the review (p 1178)
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Separate analysis of RCTs and observational studies was undertaken, diversity in study type was discussed (p 1178)
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Publication bias were assessed for blood loss, RBC transfusion, FFP transfusion, PLT transfusion and re-exploration in overall studies. The funnel plot of standard error versus risk ratio for RBC transfusion and re-exploration showed a symmetrical distribution that indicated no publication bias, while that for blood loss, FFP transfusion and PLT transfusion showed a relatively higher publication bias (p 1178)
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared conflict of interests (none) and funding (p 1179)
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Study ID	Roullet 2018	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	No	The inclusion criteria and PICO were not clearly defined
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No reference is made to a protocol, a priori design or pre-specified methods.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	The inclusion of study designs was not explained.

Study ID	Roullet 2018	
Question	**Judgement**	**Comments**
4. Did the review authors use a comprehensive literature search strategy?	No	The search strategy was not provided
5. Did the review authors perform study selection in duplicate?	No	The study selection process was not outlined
6. Did the review authors perform data extraction in duplicate?	No	The data extract process was not outlined
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No list of excluded studies was provided, nor referenced.
8. Did the review authors describe the included studies in adequate detail?	No	The included studies were not sufficiently outlined
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	No tools were used to assess the quality of included studies.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	There was no mention of conflict of interests of included studies.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Partial yes	No meta-analysis was performed.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Partial yes	No meta-analysis was performed.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	There was no mention of RoB when discussing the review.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Study heterogeneity was not assessed or discussed.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Quantitative synthesis was not performed.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Conflict of interest was reported but no funding declared. (p8)
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Study ID	Amgalan 2020	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Partial yes	Eligibility criteria was outlined but PICO was not clearly defined (p 1814)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No reference is made to a protocol, a priori design or pre-specified methods.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	The inclusion of study designs and rationale was not provided (p 1814)
4. Did the review authors use a comprehensive literature search strategy?	No	The authors searched Ovid Medline only (p1814). Search strings were not provided.
5. Did the review authors perform study selection in duplicate?	No	The authors did not report if study selection was performed in duplicate.
6. Did the review authors perform data extraction in duplicate?	No	Not stated if data extraction was performed in duplicate
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	Full list of excluded studies not provided. PRISMA diagram not included.
8. Did the review authors describe the included studies in adequate detail?	No	Basic characteristics (study type, sample size and inclusion criteria) were included in Table 3. However, the authors did not describe the included studies in adequate detail.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	The authors assessed included articles for bias and quality however the quality of the included studies was not clearly described. The risk of bias tool was not addressed (p1814).
10. Did the review authors report on the sources of funding for the studies included in the review?	No	There was no mention of funding sources of included studies.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No	Meta-analysis was not performed due to heterogeneity (p1833)
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Meta-analysis was not performed due to heterogeneity (p1833)
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	The major limitations due to the study quality were discussed when discussing the review (p1832)
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Study heterogeneity was noted, but reasons were not discussed (p1833)
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Publication bias was not assessed

Study ID	Amgalan 2020	
Question	**Judgement**	**Comments**
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No	The authors declared no conflicts of interest or financial interest (p1833). The sources of funding for the included studies was not addressed.
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Study ID	Bugaev 2020	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	PICO was clearly described (p1000)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No reference is made to a protocol, a priori design or pre-specified methods.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	The inclusion of study designs was outlined for each research question, however, rationale was not provided (p1000)
4. Did the review authors use a comprehensive literature search strategy?	Yes	The authors searched PubMed, EMBASE, Cochrane Library, Web of Science and Ovid Medline. The search was performed using MeSH terms including: haemorrhage, blood loss, bleeding, theromboelastography, thromboelastograph, thromboelastometry, ROTEM and TEG (full search string attached in Appendix 1) (p1000)
5. Did the review authors perform study selection in duplicate?	Yes	Study selection was performed in duplicate (p 1000). Disagreements between the reviewers were adjudicated by discussion and consensus among the individuals. When consensus was not reached, a third reviewer was involved as an arbitrator.
6. Did the review authors perform data extraction in duplicate?	No	Not stated if data extraction was performed in duplicate
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	Full list of excluded studies not provided. The PRISMA diagram provides some indication of reasons for exclusion (Fig 1)
8. Did the review authors describe the included studies in adequate detail?	Yes	Characteristics of included studies were provided in Table 1
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Quality of the included studies was described using GRADE methodology (p1001). Details provided in Appendix 2.
10. Did the review authors report on the sources of funding for the studies included in the review?	No	There was no mention of funding sources of included studies.
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Meta-analysis was performed, heterogeneity was tested for (p 1005-1006).

Study ID	Bugaev 2020	
Question	**Judgement**	**Comments**
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Meta-analysis was performed and assessed the level of evidence as very low. As such, the authors assessed the impact of RoB in the individual studies (p1002)
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	The major limitations due to the study quality were discussed when discussing the review (p 1002)
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Study heterogeneity was assessed but reasons were not discussed (p1005-1006)
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Publication bias was addressed as a limitation due to the mainly positive published results (p1013)
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Partial yes	The authors declared no conflicts of interest however did not report on sources of funding (p1016)
Overall methodological quality of the review	***Moderate***	***More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.***

Randomised controlled trials

Study ID	Baksaas-Aasen 2021	
Domain	**Judgement**	**Description**
Random sequence generation (selection bias)	Low	Patients were randomised in a 1:1 ratio. Randomisation codes were generated and secured by an independent statistician (p51).
Allocation concealment (selection bias)	Low	Group allocation was by study personnel opening the numbered opaque sealed envelope in sequence taken from a stack held by each study site (p51).
Blinding of participants and personnel (performance bias)	Low	Research personnel collecting safety and outcome data were blinded to group allocation. The trial was unblinded-to the treating clinical teams (p51).
Blinding of outcome assessment (detection bias)	High	The treating clinical teams were un-blinded (p51).
Incomplete outcome data addressed (attrition bias)	Low	15 patients withdrew consent and did not complete the study. Missing data for a measure were excluded from statistical comparisons regarding that measure (p52).
Selective reporting (reporting bias)	Low	All outcomes were reported on (p55-57).
Other sources of bias*	Low	Funding was provided. No details on whether the trial was peer-reviewed however all authors reviewed and commented on the manuscript (p57).
Overall risk of bias	***High***	***The study has plausible bias that seriously weakens confidence in the results.***

Observational /cohort studies

Study ID	Wang 2017	
Domain	**Judgement**	**Description**
Bias due to failure to develop and apply appropriate eligibility criteria	Critical	Patients were prospectively enrolled in a trauma registry. All study data was prospectively collected, except for TEG results and transfused blood type which were retrospectively abstracted. Treatment groups were determined retrospectively with knowledge of the outcomes. Patients whose did not follow strict protocol based on TEG-results (ie received unnecessary blood components) were placed in the non-TEG guided group. Bias in favour of TEG is likely due to the way patients were allocated to treatment groups. p. 434
Bias due to flawed measurement of both exposure and outcome	Serious	Outcomes are objective and are unlikely changed by blinding. Intervention was not given blindly. It is unclear if outcome assessment was carried out blindly. p. 435
Bias due to failure to adequately control confounding	Moderate	Possible confounding. Patient demographics appear similar between both arms however, patients in non-TEG group tended to be older, had lower initial systolic blood pressure, and more severe injury severity. Multivariate regression analysis tested to analyse potential factors.
Bias due to incomplete or inadequately short follow-up	Low	Length of follow-up was not stated, presumably until hospital discharge. Follow up was likely long enough for outcomes to occur. p. 436
Overall risk of bias	***Critical***	***The study is too problematic to provide any useful evidence on the effectiveness of the intervention for the outcome of interest.***

D9 Cell salvage (Question 9)

Systematic review of observational /cohort studies

Study ID	Shantikumar 2011	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	Eligible studies included those which included data on the use of cell salvage in abdominal-aortic-aneurysm repairs.
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial yes	Not explicitly stated. However, the authors noted using pre-prepared data extraction sheets
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Study type was neither an inclusion nor an exclusion criterion.
4. Did the review authors use a comprehensive literature search strategy?	Yes	The authors searched PubMed Cochrane and Embase. The key search words used were (AAA or aneurysm) AND (cell salvage or cell saver or autotransfusion).
5. Did the review authors perform study selection in duplicate?	Yes	The titles and relevant abstracts were screened by 2 authors (SS and SP), with any discrepancy resolved by mutual discussion. In addition, the references of eligible articles were screened for further relevant studies.
6. Did the review authors perform data extraction in duplicate?	No	Not explicitly stated
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	Parameters such as data concerning procedures for aorto-occlusive disease and trials, which combined CS with another technique were excluded from this analysis. No list of excluded studies. PRIMSA flow shows studies as irrelevant, but no justification provided.
8. Did the review authors describe the included studies in adequate detail?	Yes	Tables included information for each included trial.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	Study risk of bias not mentioned in the review
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Not stated
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Where possible, data were pooled in a meta-analysis, using a random-effects model, given the heterogeneity of included studies.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	No Risk of bias accounted for
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	Risk of bias not accounted for in the review
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partial yes	Authors acknowledged that differing results may be due to study heterogeneity but did not discuss in detail

Study ID	Shantikumar 2011	
Question	**Judgement**	**Comments**
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Partial yes	The magnitude of this effect was similar when only the 3 relevant RCTs were analysed.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared that there we no conflict of interest and no funding received.
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Study ID	Meybohm 2016	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	All elements of PICO were included (p2).
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	The study was registered in PROSPERO; registration number CRD42016035726
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	To be eligible for inclusion, studies had to include patients undergoing surgery randomized to cell salvage or to a control group that did not receive cell salvage (p2).
4. Did the review authors use a comprehensive literature search strategy?	Yes	Medline, Cochrane Library and grey literature and reference lists were searched using the search terms outlined in p2
5. Did the review authors perform study selection in duplicate?	Yes	Two independent authors screened the abstracts of identified studies (AW, PM)
6. Did the review authors perform data extraction in duplicate?	No	Not explicit statement regarding this
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes	List of excluded studies not provided but reasons shown in PRISMA flow (fig.1)
8. Did the review authors describe the included studies in adequate detail?	Partial yes	Brief descriptions including patient numbers were mentioned for some studies. Table 1 shows all included studies including patient numbers, year, country, and surgical discipline
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Risk of bias assessed: including the domains of random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and 'other' (p2)
10. Did the review authors report on the sources of funding for the studies included in the review?	Partial yes	No statements regarding how included studies were funded. It is noted however that the authors rated "other" bias as unclear, which typically includes funding and potential conflicts of interest.

Study ID	Meybohm 2016	
Question	**Judgement**	**Comments**
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	The meta-analysis was done in line with recommendations from the Preferred Reporting Items for Systemic reviews and Meta-Analyses (PRISMA statement).
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Partial yes	The authors noted limitations regarding the pooled analysis. In our meta-analysis we found that most of the studies were of limited methodological quality and risk of bias could not be fully judged in any of the included trials
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Bias was discussed but not at the level of individual studies
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partial yes	Heterogeneity was analysed but not discussed in detail
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Investigation of publication bias by generating funnel plots showed no obvious deviations from symmetry excluding the possibility of potential publication bias.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Disclosure of conflict was reported, and it is stated that "No pharmaceutical company funded the presented study".
Overall methodological quality of the review	***High***	***No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.***

Study ID	Nayar 2017	
Question	**Judgement**	**Comments**
1. Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	Systematic search using the key words, "blood conservation," "orthopedics," and "trauma" to major databases (p45)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	Not stated
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Keywords were searched in major databases to identify original research and review articles published in the last 3 decades (p45).
4. Did the review authors use a comprehensive literature search strategy?	Yes	Authors searched PubMed, Embase, The Cochrane Library, Scopus, Global Health, and World Health Organization Global Health Library and Regional Libraries
5. Did the review authors perform study selection in duplicate?	Partial yes	The abstracts were manually reviewed by the first author, yielding 61 that were also reviewed by the senior author and incorporated into this review (p45)
6. Did the review authors perform data extraction in duplicate?	No	Not stated

Study ID	Nayar 2017	
Question	**Judgement**	**Comments**
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	Not explicitly stated
8. Did the review authors describe the included studies in adequate detail?	Yes	Each discussion of a trial/study began with a brief description including information on number of patients, population, setting and main findings
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	Bias not mentioned in study
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Not stated
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Partial yes	No meta-analysis performed
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Partial yes	No meta-analysis performed
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	Risk of bias not accounted for in the review
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partial yes	Authors acknowledged that differing results may be due to the different types of surgery
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	No quantitative synthesis performed. No discussion of publication bias.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The authors declared that they had nothing to disclose
Overall methodological quality of the review	***Critically low***	***More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.***

Randomised controlled trials

No studies found.

Observational /cohort studies

Study ID	Banghu 2012	
Domain	**Judgement**	**Comments**
Bias due to failure to develop and apply appropriate eligibility criteria	Low risk	All patients admitted with combat-related injuries requiring surgery were prospectively identified for intraoperative blood salvage (IBS) during one month in 2011. IBS was performed for all adult patients who were judged by the attending military surgeon (DB) to be likely to require massive blood transfusion, arbitrarily defined for the purpose of this study as likely to require at least 10 units of RBCs in the first 12 hours after injury
Bias due to flawed measurement of both exposure and outcome	Moderate risk	All outcomes were objective in nature and easily measurable and unlikely to be influenced by blinding, however the decision to use the cell salvage and transfuse was at the surgeon's discretion which may have introduced bias.
Bias due to failure to adequately control confounding	Serious risk	Patient demographics were not reported for patients where cell salvage was successful vs. not given. No comparative information reported.
Bias due to incomplete or inadequately short follow-up	Low risk	Although not reported, follow-up was sufficient to assess the outcomes
Overall risk of bias	***Serious***	***The study has some important problems and cannot provide reliable evidence on the effectiveness of the intervention.***