

Evidence summaries to support PICO questions RBC transfusion triggers

April 2018 (version 3.0) Centre for Evidence-Based Practice (CEBaP) Belgian Red Cross





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Overview responsible methodologists and Scientific Committee members

PICO question #	responsible SC member	responsible methodologist
PICO 4: Adult ICU pts. clinically stable	Erhard Seifried	Anne-Catherine Vanhove
PICO 5: Orthopedic/non-cardiac surgery	Pierre Albaladejo	Anne-Catherine Vanhove
PICO 6: Acute GI bleeding	Giancarlo Liumbruno, Giuseppe Marano, Eva Veropalumbo	Anne-Catherine Vanhove
PICO 7: Symptomatic/acute coronary heart disease	Shubha Allard	Anne-Catherine Vanhove
PICO 8: Septic shock	Erica Wood	Anne-Catherine Vanhove
PICO 9: Cardiac surgery	Jerrold Levy	Anne-Catherine Vanhove
PICO 10: Adult haematological pts.	Pierre Tiberghien	Hans van Remoortel
PICO 11: Adult pts. with solid tumours	Richard Gammon	Hans van Remoortel
PICO 12: Acute CNS injury	Marian van Kraaij	Hans van Remoortel
PICO 13: Cerebral perfusion disorders	Shubha Allard	Hans van Remoortel
PICO 14: Acutely bleeding pts.	Erica Wood, Cecile Aubron	Hans van Remoortel

Flow chart



Overview of included studies

PICO question restrictive versus liberal transfusion triggers: population of interest	Included studies from Carson review (2016/2018) ^{1,2} (34 studies)	Included studies from additional search (6 studies)
1. Critically ill but clinically stable adult intensive care patients	4 studies ³⁻⁶	none
2. Orthopaedic and non-cardiac surgery	11 studies ⁷⁻¹⁷	1 study ¹⁸
3. Acute gastrointestinal bleeding*	3 studies ¹⁹⁻²¹	none
4. Symptomatic coronary heart disease	2 studies ^{22,23}	none
5. Septic shock**	2 studies ^{24,25}	none
6. Cardiac surgery	8 studies ²⁶⁻³³	none
7. Adult haematological patients	2 studies ^{34,35}	none
8. Adult patients with solid tumours	1 study ³⁶	2 studies ^{37,38}
9. Acute central nervous system injury	none	2 studies ^{39,40}
10. Cerebral perfusion disorders	none	1 study ⁴¹
11. Acute bleeding patients	1 study ⁴²	none

* The 3 RCTs in patients with gastrointestinal bleeding were considered as a subgroup of PICO 11 (acute bleeding

** The 2 RCTs in patients with septic shock were considered as a subgroup of PICO 1 (intensive care population)

Reference list included studies

- 1. Carson JL, Stanworth SJ, Roubinian N, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev 2016;10:CD002042.
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- 4. Hebert PC, Wells G, Marshall J, et al. Transfusion requirements in critical care. A pilot study. Canadian Critical Care Trials Group. JAMA 1995;273:1439-44.
- Walsh TS, Boyd JA, Watson D, et al. Restrictive versus liberal transfusion strategies for older mechanically ventilated critically ill patients: a randomized pilot trial. Crit Care Med 2013;41:2354-63.
- Palmieri TL, Holmes JHt, Arnoldo B, et al. Transfusion Requirement in Burn Care Evaluation (TRIBE): A Multicenter Randomized Prospective Trial of Blood Transfusion in Major Burn Injury. Ann Surg 2017;266:595-602.
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- 8. Carson JL, Terrin ML, Barton FB, et al. A pilot randomized trial comparing symptomatic vs. hemoglobin-level-driven red blood cell transfusions following hip fracture. Transfusion 1998;38:522-9.
- 9. Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med 2011;365:2453-62.
- 10. Fan YX, Liu FF, Jia M, et al. Comparison of restrictive and liberal transfusion strategy on postoperative delirium in aged patients following total hip replacement: a preliminary study. Arch Gerontol Geriatr 2014;59:181-5.
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- 15. Nielsen K, Johansson PI, Dahl B, et al. Perioperative transfusion threshold and ambulation after hip revision surgery--a randomized trial. BMC Anesthesiol 2014;14:89.
- 16. Parker MJ. Randomised trial of blood transfusion versus a restrictive transfusion policy after hip fracture surgery. Injury 2013;44:1916-8.
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- 18. Markatou M, Theodoraki K, Rizos D, et al. Targeting perioperative hemoglobin in major abdominal surgery. J Anesthe Clinic Res 2012;3:1-6.
- 19. Blair SD, Janvrin SB, McCollum CN, et al. Effect of early blood transfusion on gastrointestinal haemorrhage. Br J Surg 1986;73:783-5.
- 20. Jairath V, Kahan BC, Gray A, et al. Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial. Lancet 2015;386:137-44.
- 21. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013;368:11-21.
- 22. Carson JL, Brooks MM, Abbott JD, et al. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. Am Heart J 2013;165:964-71 e1.
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- 28. Johnson RG, Thurer RL, Kruskall MS, et al. Comparison of two transfusion strategies after elective operations for myocardial revascularization. J Thorac Cardiovasc Surg 1992;104:307-14.
- 29. Murphy GJ, Pike K, Rogers CA, et al. Liberal or restrictive transfusion after cardiac surgery. N Engl J Med 2015;372:997-1008.
- 30. Shehata N, Burns LA, Nathan H, et al. A randomized controlled pilot study of adherence to transfusion strategies in cardiac surgery. Transfusion 2012;52:91-9.

- 31. Koch CG, Sessler DI, Mascha EJ, et al. A Randomized Clinical Trial of Red Blood Cell Transfusion Triggers in Cardiac Surgery. Ann Thorac Surg 2017;104:1243-50.
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- 34. DeZern AE, Williams K, Zahurak M, et al. Red blood cell transfusion triggers in acute leukemia: a randomized pilot study. Transfusion 2016;56:1750-7.
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- 39. Ngwenya LB, Suen CG, Tarapore PE, et al. Safety and cost efficiency of a restrictive transfusion protocol in patients with traumatic brain injury. J Neurosurg 2017:1-8.
- 40. McIntyre LA, Fergusson DA, Hutchison JS, et al. Effect of a liberal versus restrictive transfusion strategy on mortality in patients with moderate to severe head injury. Neurocrit Care 2006;5:4-9.
- 41. Naidech AM, Shaibani A, Garg RK, et al. Prospective, randomized trial of higher goal hemoglobin after subarachnoid hemorrhage. Neurocrit Care 2010;13:313-20.
- 42. Fisher MR, Topley E. The illness of trauma. Br J Clin Pract 1956;10:770-6.

PICO 4: RBC transfusion triggers in adult intensive care unit patients, clinically stable

Overview evidence table GRADE software (PICO 4)

			Certainty a	ssessment			Nº of pat	tients	E	ffect		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7-8 g/dL)	more liberal RBC transfusion triggers (Hb <9-10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
30-day r	nortality					•						
6	randomised trials	not serious	not serious	not serious	serious ^a	none	366/1323 (27.7%)	380/1327 (28.6%)	RR 0.97 (0.82 to 1.15)	9 fewer per 1.000 (from 43 more to 52 fewer)	⊕⊕⊕⊖ MODERATE	CRITICAL
Hospital	mortality											
3	randomised trials	not serious	not serious	not serious	serious ^a	none	263/971 (27.1%)	296/965 (30.7%)	RR 0.88 (0.76 to 1.02)	37 fewer per 1.000 (from 6 more to 74 fewer)	⊕⊕⊕⊖ MODERATE	CRITICAL
Participa	ints exposed t	to blood	transfusion									
5	randomised trials	not serious	not serious	not serious	not serious	none	726/1155 (62.9%)	1085/1150 (94.3%)	RR 0.68 (0.63 to 0.72)	302 fewer per 1.000 (from 264 fewer to 349 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Units of	blood transfu	sed										

			Certainty a	ssessment			№ of patients		E	ffect		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7-8 g/dL)	more liberal RBC transfusion triggers (Hb <9-10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	randomised trials	not serious	not serious	serious ^b	not serious	none	418	420	-	MD 3 units lower (3.64 lower to 2.36 lower)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Haemog	lobin concen	tration										
3	randomised trials	not serious	not serious	not serious	not serious	none	971	965	-	MD 1.66 lower (2.15 lower to 1.16 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Cardiac	events	•	•			•	•		•	•		
1	randomised trials	serious c	not serious	serious ^b	not serious	none	55/418 (13.2%)	88/420 (21.0%)	RR 0.63 (0.46 to 0.85)	78 fewer per 1.000 (from 31 fewer to 113 fewer)	⊕⊕⊖⊖ LOW	CRITICAL
Myocarc	lial infarction											
3	randomised trials	not serious	not serious	not serious	serious ^a	none	49/1057 (4.6%)	42/1058 (4.0%)	RR 1.01 (0.38 to 2.72)	0 fewer per 1.000 (from 25 fewer to 68 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Congest	ive heart failu	re										

			Certainty a	ssessment			Nº of patients		Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7-8 g/dL)	more liberal RBC transfusion triggers (Hb <9-10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
2	randomised trials	serious c	not serious	serious ^b	not serious	none	22/418 (5.3%)	45/420 (10.7%)	RR 0.49 (0.30 to 0.80)	55 fewer per 1.000 (from 21 fewer to 75 fewer)	⊕⊕⊖⊖ LOW	IMPORTANT
Sepsis-b	acteraemia											
1	randomised trials	serious c	not serious	serious ^b	not serious	none	30/418 (7.2%)	40/420 (9.5%)	RR 0.75 (0.48 to 1.19)	24 fewer per 1.000 (from 18 more to 50 fewer)	⊕⊕⊖⊖ LOW	IMPORTANT
Pneumo	nia							•			·	
2	randomised trials	serious c	not serious	not serious	serious ^a	none	136/586 (23.2%)	135/597 (22.6%)	RR 1.03 (0.84 to 1.27)	7 more per 1.000 (from 36 fewer to 61 more)	⊕⊕⊖⊖ LOW	IMPORTANT
Pneumo	nia or wound	infection	า									
1	randomised trials	serious c	not serious	not serious	serious ^a	none	42/418 (10.0%)	50/420 (11.9%)	RR 0.84 (0.57 to 1.24)	19 fewer per 1.000 (from 29 more to 51 fewer)	⊕⊕⊖⊖ LOW	IMPORTANT
Number	of RBC trans	fusions										

	Certainty assessment							tients	Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7-8 g/dL)	more liberal RBC transfusion triggers (Hb <9-10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	randomised trials	serious c	not serious	not serious	serious ^a	none	168	171	-	median 8 RBC transfusions lower (0 to 0)	⊕⊕⊖⊖ Low	IMPORTANT
Blood st	ream infectio	ns										
1	randomised trials	serious ^d	not serious	not serious	serious ^a	none	40/168 (23.8%)	42/177 (23.7%)	RR 1.00 (0.69 to 1.46)	0 fewer per 1.000 (from 74 fewer to 109 more)	⊕⊕⊖⊖ LOW	IMPORTANT
Wound	infections					·				<u> </u>		
1	randomised trials	serious d	not serious	not serious	serious ^a	none	20/168 (11.9%)	21/177 (11.9%)	RR 1.00 (0.56 to 1.78)	0 fewer per 1.000 (from 52 fewer to 93 more)	⊕⊕⊖⊖ LOW	IMPORTANT
Urinary t	tract infection	1						·				
1	randomised trials	serious d	not serious	not serious	serious ^a	none	24/168 (14.3%)	24/177 (13.6%)	RR 1.05 (0.62 to 1.78)	7 more per 1.000 (from 52 fewer to 106 more)	⊕⊕⊖⊖ LOW	IMPORTANT
30-day r	nortality (sub	group: le	ess severe patien	ts (APACHE-sco	ore 20 or less))							

	Certainty assessment						№ of patients		Nº of patients Effect					
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7-8 g/dL)	more liberal RBC transfusion triggers (Hb <9-10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance		
1	randomised trials	serious c	not serious	serious ^b	not serious	none	18/207 (8.7%)	35/217 (16.1%)	RR 0.54 (0.32 to 0.92)	74 fewer per 1.000 (from 13 fewer to 110 fewer)	⊕⊕⊖⊖ LOW	CRITICAL		
30-day r	30-day mortality (subgroup: younger patients (<55 years))													
1	randomised trials	serious c	not serious	serious ^b	not serious	none	10/173 (5.8%)	21/161 (13.0%)	RR 0.44 (0.22 to 0.91)	73 fewer per 1.000 (from 12 fewer to 102 fewer)	⊕⊕⊖⊖ LOW	CRITICAL		
30-day r	mortality (sub	group: ca	ardiac disease)											
1	randomised trials	serious c	not serious	not serious	serious ^a	none	31/151 (20.5%)	40/175 (22.9%)	RR 0.90 (0.59 to 1.36)	23 fewer per 1.000 (from 82 more to 94 fewer)	⊕⊕⊖⊖ LOW	CRITICAL		
30-day r	nortality (sub	group: se	evere infections a	and septic shoo	ck)									
1	randomised trials	serious c	not serious	not serious	serious ^a	none	26/114 (22.8%)	31/104 (29.8%)	RR 0.77 (0.49 to 1.20)	69 fewer per 1.000 (from 60 more to 152 fewer)	⊕⊕⊖⊖ LOW	CRITICAL		

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

a. Low number of events and/or large variability of the results; b. Lack of generaliziblity: evidence from 1 Canadian study; c. Detection bias (lack of blinding outcome assessors); d. Detection bias (lack of blinding outcome assessors) - Selection bias (allocation concealment unclear)

Detailed evidence summary (PICO 4)

Торіс	Patient Blood Management
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers
Intervention	Restrictive RBC transfusion triggers
Question (PICO)	In critically ill, but clinically stable adult intensive care patients (Population), is the use of a restrictive transfusion threshold (Intervention) not inferior to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusion threshold (Comparison)?
Search Strategy	 The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to: Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017) Identify observational studies in case no experimental studies were available.
	Databases The Cochrane Library (systematic reviews and controlled trials) using the following search strategy (from May 2016 until June 2017): #1 MeSH descriptor: [Blood Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST, Trends - TD] #2 MeSH descriptor: [Erythrocyte Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST] #3 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) near/5 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or strateg* or regimen* or criteri* or standard* or management or program*)) #4 ((h?emoglobin or h?ematocrit or HB or HCT) near/5 (polic* or practic* or protocol* or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or standard*)) #5 (blood near/3 (management or program*)) #6 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) and (critical* or intensive* or h?emorrhag* or bleed*)):ti #7 #1 or #2 or #3 or #4 or #5 or #6
	MEDLINE (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy (from 27th May 2016 until 30th June 2017): #1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI])) #2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR standard*[TI]) #3 (blood[TI] AND (management[TI] OR program*[TI]))

	#4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR
	PRBC*[11]) and (critical*[11] OR intensive*[11] OR hemorrhag*[11] OR
	naemorrnage^[II] OR bleed^[II]))
	#3 #1 OR #2 OR #3 OR #4
	Embase (via Embase com interface) using the following search strategy (from
	27 th May 2016 until 30 th June 2017):
	#1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND
	(trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR
	aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti
	OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR
	regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti))
	#2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR
	HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR
	threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR
	standard*:ti))
	#3 (blood:ti AND (management:ti OR program*:ti))
	#4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and
	(critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti))
	#5 #1 OR #2 OR #3 OR #4
	Transfusion avidence library (from 2016 until 2017)
	Pod Colls AND (trigger OP threshold OP target OP restrict OP restrictive OP
	liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit
	OR limits OR protocol OR policy OR policies OR practice OR indicator OR
	strategy OR strategies OR regimen OR criteria OR standard OR management
	OR program OR programme) OR Red Cells AND title:(critical OR critically OR
	intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging
	OR haemorrhaging OR bleed OR bleeding)
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson
	2018)
	26/01/2018 (update after latest search date Carson review)
In/Exclusion criteria	Population: Included: critically ill but clinically stable adult intensive care
	patients. Excluded: adult intensive care patients that are not
	clinically/haemodynamically stable, children or neonates.
	Intervention: the use of a restrictive transfusion threshold as a mean of
	guiding allogeneic or autologous RBC transfusion. A restrictive transfusion
	threshold most often refers to administration of blood transfusion when the
	haemoglobin level falls below / g/dL to 8 g/dL.
	Comparison: the use of a liberal transfusion threshold as a mean of guiding
	allogeneic or autologous RBC transfusion. A liberal transfusion threshold most
	often refers to administration of blood transfusion when the haemoglobin level
	falls below 9 g/dL to 10 g/dL.
	Outcomer: Primary Mortality (a.g. 20 day mortality or in bossital mortality
	during bosnital admission, at 90 days or long term) or other clinical outcomes
	including outcomes related to PPC transfusion use (i.e. preparties of
	narticipants exposed to transfusion, participants exposed to allogonais or
	autologous transfusion, units of blood transfused (in those receiving any
	transfusion) and Secondary Morbidity-related outcomes that occurred during
	hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction,

congestive heart failure, stroke, renal injury, pneumonia, septic shock,
repleeding, infection, and fatigue).
Study design: The following study designs were included: 1) (cluster)
randomized controlled trials included in the Cochrane review by Carson et al
(May 2016) or other systematic reviews identified in the update and 2) (cluster)
randomized controlled trials identified in the update. To examine the evidence
for the effect of transfusion threshold on the use of RBC transfusions and the
evidence for any change in clinical outcomes, we included randomized
controlled trials if the comparison groups were assigned on the basis of a
transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or
haematocrit level (without haemodynamic instability) that had to be reached
before a RBC transfusion was administered. We required that control group
participants had to have been either transfused with allogeneic or autologous
red blood cells, or both, at higher haemoglobin or haematocrit levels
(transfusion threshold) than the intervention group, or transfused in
accordance with current transfusion practices, which may not have included a
well-defined transfusion threshold, but involved liberal rather than restrictive
transfusion practices. We excluded trials that were not designed to include any
clinical outcomes.

Author, year, Country	Study design	Population	Comparison	Study funding, financial COI and remarks
Bergamin, 2017, Brazil	Experimental: RCT	300 adult cancer patients with septic shock in the first 6 hours of ICU admission.	Restrictive group (intervention): RBC transfusion (1 unit) if Hb <7 g/dL	Dr. Park disclosed government work. The remaining
		Restrictive group: n = 151, 84 males and 67 females,	transfusion (1 unit) if Hb <9 g/dL	disclosed that they do not have any
		age=61.4±13.5 years	HB levels assessed after IC admission, twice a day during ICU stay and after	potential conflicts of interest
		149, 70 males and 79 females.	evry transfusion.	Identified from
		age=61.6±12.9 years	Transfusion: leukodepleted RBC units	the update.
Hébert, 1995, Canada	Experimental: Randomised controlled trial	69 normovolaemic critically ill participants admitted to a tertiary level intensive care units, Hb <9.0 g/dL, randomised within 72 hours of admission (clinical specialty subgroup (Carson, 2016): critical care)	Restrictive group (intervention): transfusion if 7.0 <hb<7.5 g/dL, maintained at 7.0- 9.0 g/dL Liberal group (control): transfusion if 10.0<hb<10.5 dl,<br="" g="">maintained at 10.0-12.0 g/dL</hb<10.5></hb<7.5 	Supported by the Canadian Red Cross Society and the Physicians' Services Incorporated Foundation (charitable foundation).

Characteristics of included studies

		Restrictive group: n=33, 14 males and 19 females, age=58±15 years Liberal group: n=36, 19 males and 17 females, age=59±21 years	Transfusion: allogeneic RBC transfusions	Identified from the systematic review of Carson et al., 2016.
Hébert, 1999, Canada	Experimental: Randomised controlled trial	838 critically ill participants with euvolaemia after initial treatment admitted to ICU, Hb <9.0 g/dL, randomised within 72 hours of admission (clinical specialty subgroup (Carson, 2016): critical care) Restrictive group: n=418, 269 males and 149 females, age=57.1±18.1 years Liberal group: n=420, 255 males and	Restrictive group (intervention): transfusion if Hb <7.0 g/dL, and then maintained at 7.0-9.0 g/dL Liberal group (control): transfusion if Hb <10.0 g/dL, and then maintained at 10.0-12.0 g/dL Transfusion: RBC transfusions	Supported by federal agency. Unrestricted grant from industry (Bayer). One author received government grant. Identified from the systematic review of Carson et al., 2016.
		165 females, age=58.1±18.3 years		
Holst, 2014, Denmark	Randomised controlled trial	998 participants in Denmark, Sweden, Norway and Finland with septic shock in the ICU and haemoglobin concentration less than 9 g/dL (clinical specialty subgroup (Carson, 2016): critical care) Restrictive group: n=502, 272 males and 230 females, median age (IQR)=67 (57-73) yrs Liberal group: n=496, 259 males and 237 females, median	Restrictive group (intervention): transfusion if Hb conc ≤7.0 g/dL Liberal group (control): transfusion if Hb ≤9.0 g/dL Haemoglobin concentrations were reassessed within 3 hours after termination of the transfusion or before the initiation of another transfusion. Transfusion: single units of cross- matched, prestorage leukoreduced red cells	Research funded by hospitals, medical societies and foundations. Two authors received grant support from private industry. Identified from the systematic review of Carson et al., 2016. Two articles (one subgroup analysis and one follow-up)

		age (IQR)=67 (58-75) yrs		identified through the updated search: Rygård 2016 (follow- up) and Rygård 2017 (subgroup analysis). Relevant additional data from Rygård 2016 was extracted and included in the synthesis of findings.
Palmieri, 2017, USA	Experimental: Randomised controlled trial	Eighteen burn centers enrolled 345 patients with 20% or more total body surface area burn. Restrictive group: n=168, 79.8% males, age=41 (IQR, 27-55) Liberal group: n=177, 78.5% males, age=41 (IQR, 30-55)	Restrictive group (intervention): transfusion if Hb <7.0 g/dL, target Hb 7.0-8.0 g/dL Liberal group (control): transfusion if Hb <10.0 g/dL, target Hb 10.0-11.0 g/dL Transfusion: RBC transfusions	This study was supported by the American Burn Association and funded by USAMRMC Award W81XWH-08- 1-0760 with support from the National Center for Research Resources, National Institutes of Health, through grant UL1 RR024146, the National Center for Advancing Translational Sciences, National Institutes of Health, through grant Center for Advancing Translational Sciences, National Institutes of Health, through grant TR 000002, and the National Center for Advancing Translational Science for Advancing Translational Center for

				National Institutes of Health through grant UL1 TR001860. Identified from update systematic review of Carson et al.,
Walsh, 2013, UK	Experimental: Randomised controlled trial	ICU participants \geq 55 years, Hb <9 g/dL, mechanical ventilation for \geq 96 hours, and expected to require \geq 24 hours of further mechanical ventilation (clinical specialty subgroup (Carson, 2016): critical care) Restrictive group: n=51, 36 males and 15 females, age=67±7 years (range: 56-80) Liberal group: n=49, 24 males and 25 females, age=68±8 years (range: 55-83)	Restrictive group (intervention): transfusion if Hb <7.0 g/dL, target Hb 7.1-9.0 g/dL Liberal group (control): transfusion if Hb <9.0 g/dL, target Hb 9.1-11.0 g/dL Transfusion: RBC transfusions	Research supported by government agencies with no influence on design or conduct. Several authors received individual government grants and/or consult for industry. Identified from the systematic review of Carson et al., 2016.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Primary outcome	es			
30-day mortality	Restrictive vs liberal transfusion threshold	Not statistically significant: 366/1323 vs 380/1327 RR: 0.97, 95%CI [0.82;1.15] (p=0.75)** (Figure 1)	6, 1323 vs 1327	Bergamin 2017; Holst 2014; Hébert, 1995; Hébert ,1999; Palmieri, 2017; Walsh, 2013
30-day mortality (subgroup:		Statistically significant 18/207 vs 35/217 § RR: 0.54, 95%CI [0.32;0.92]	1, 207 vs 217	Hébert, 1999

		(~-0.02)**		
		$(p=0.02)^{n}$		
≤20)		in juvour of restrictive		
	-	transfusion threshold	1 172 1(1	اللغام منغ
			1, 173 VS 101	Hebert,
(subgroup: < 55		10/1/3 VS 21/101 9		1999
years)		RR. 0.44, 95%CI [0.22,0.91]		
		$(p=0.03)^{n}$		
		In favour of restrictive		
	-	transfusion threshold	1 1 - 1 1	l l á la la vet
30-day mortality		Not statistically significant	1, 151 VS 175	Hebert,
(subgroup:		31/151 VS 40/175 9		1999
primary or		RR: 0.90, 95%CI [0.59;1.36]		
secondary		(p=0.61)**		
diagnosis of				
cardiac disease)	-		1 114 104	l l á la a sat
30-day mortality		Not statistically significant	1, 114 VS 104	Hebert,
(subgroup: severe		20/114 VS 31/104 9		1999
soptic shock)		RR. $0.77, 95\%$ CI [$0.49, 1.20$]		
Septic Shock)	-	(p=0.24) ^{ma}		U.a.lat 2014.
			5, 971 VS 905	HOISt 2014;
		203/9/1 VS 290/905		Hebert
		(n = 0.02) ** (Figure 2)		1999, Waish,
Deuticiacasta	-	(p=0.02)** (Figure 2)		2013 Democration
Participants			5, 1155 VS 1150	Dergamin 2017: Holet
transfusion				2017, HOISU
		RR. 0.00, 95% $CI [0.05, 0.72]$		2014, Hábort
		(p<0.00001) ^{and} (Figure 5)		1005.
		transfusion threshold		Lýgy, Hóbort
				2013
Linits of blood	-	Statistically significant	1 418 vs 420	Héhert 1999
transfused		26+41 ys 56+53	1, 110 13 120	
liansiasea		MD: -3.00, 95%CI [-3.64:-2.36]		
		(p < 0.0001)* (Figure 4)		
		In favour of restrictive		
		transfusion threshold		
Number of RBC		Statistically significant	1 168 vs 171	Palmieri
transfusions		7 (IOR: 2-19) vs 15 (IOR: 7-31)	1, 100 13 1, 1	2017
		Median difference: -8		2017
		$(n < 0.001)^*$		
		In favour of restrictive		
		transfusion threshold		
Secondary outcor	nes			
Haemoglobin	Restrictive vs liberal	Statistically significant	3, 971 vs 965	Holst 2014:
concentration	transfusion	MD: -1.66, 95%CI [-2.15:-1.16]	,	Hébert
	threshold	$(p < 0.00001)^{**}$ (Figure 5)		1999: Walsh.
	-			2013
Cardiac events	1	Statistically significant	1, 418 vs 420	Hébert 1999
		55/418 vs 88/420 §		
		RR: 0.63, 95%CI [0.46;0.85]		

	$(p=0.003)^*$ (
	Restrictive Liber	ő	
	Study or Subgroup Events Total Events	-	
	Total (95% CI) 418 Total events 55 88		
	Heterogeneity: Not applicable		
	Test for overall effect: Z = 2.96 (P = 0.003)		
	Risk of bias legend		
	 (A) Random sequence generation (selection bi (B) Allocation concealment (selection bias) 	1	
	(C) Blinding of participants and personnel (perf	c	
	(E) Incomplete outcome data (attrition bias)		
	(F) Selective reporting (reporting bias)		
	Figure 6)		
	In favour of restrictive		
	transfusion threshold		
Myocardial	Not statistically significant:	3, 1057 vs 1058	Bergamin
infarction	49/1057 vs 42/1058 §		2017; Holst
	RR: 1.01, 95%CI [0.38;2.72]		2014;
	(p=0.98)* (Figure 7)		Hébert 1999
Congestive heart	Statistically significant	2, 906 vs 909	Holst 2014;
failure	22/906 vs 45/909 §		Hébert 1999
	RR: 0.49, 95%CI [0.30;0.80]		
	(p=0.005)* (Fout!		
	Verwijzingsbron niet		
	gevonden.)		
	In favour of restrictive		
	transfusion threshold		
Sepsis/bacteraemi	Not statistically significant:	1, 418 vs 420	Hébert 1999
а	30/418 vs 40/420 §		
	RR: 0.75, 95%CI [0.48;1.19] ¥		
	(p=0.22)* (Figure 8)		
Pneumonia or	Not statistically significant:		
wound infection	42/418 vs 50/420 §		
	RR: 0.84, 95%CI [0.57;1.24] ¥		
	(p=0.39)* (Figure 0)		
Pneumonia	Not statistically significant:	2, 586 vs 597	Hébert
	136/586 vs 135/597 §		1999,
	RR: 1.03, 95%CI [0.84;1.27] ¥		Palmieri
	(p=0.78)* (Figure 911)		2017
Blood stream	Not statistically significant:	1, 168 vs 177	Palmieri
infections	40/168 vs 42/177 §	,	2017
	RR: 1.00, 95%CI [0.69:1.46] ¥		-
	(p=0.99)* (Figure 912)		
Wound infections	Not statistically significant:	1, 168 vs 177	Palmieri
	20/168 vs 21/177 §	_,	2017
	RR: 1.00. 95%CI [0.56:1.78] ¥		
	(p=0.99)* (Figure 913)		
Urinary tract	Not statistically significant	1, 168 vs 177	Palmieri
infections	24/168 vs 24/177 §	_, _ 00 10 1/ ,	2017
	RR: 1.05.95%CI [0.62:1.78] ¥		
	(p=0.85)* (Figure 914)		
		L	L

Mean ± SD (unless otherwise indicated)

CI: confidence interval, RR: relative risk, MD: mean difference

* Calculations (p-value) done by the reviewer(s) using Review Manager software

** Calculations (RR or MD, 95% CI and p-value) done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events

Forest plots

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Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias)

(F) Selective reporting

(G) Other bias

Figure 1: Forest plot of outcome: 30-day mortality.



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 2: Forest plot of outcome: Hospital mortality.

	Restrictive Liberal			Risk Ratio	Risk R	Ratio	Risk of Bias		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Rando	m, 95% Cl	ABCDEFG
Bergamin 2017	62	151	91	149	6.9%	0.67 [0.53, 0.85]	+		
Holst 2014	326	502	490	496	37.9%	0.66 [0.62, 0.70]	•		$\bullet \bullet ? \bullet \bullet \bullet \bullet$
Hébert 1995	18	33	35	36	3.9%	0.56 [0.41, 0.77]	-		?????+++
Hébert 1999	280	418	420	420	36.8%	0.67 [0.63, 0.72]	•		
Walsh 2013	40	51	49	49	14.5%	0.79 [0.68, 0.91]	-		••??••
Total (95% CI)		1155		1150	100.0%	0.68 [0.63, 0.72]	•		
Total events	726		1085						
Heterogeneity: Tau ² =	= 0.00; Chi	² = 6.20), df = 4 (l	P = 0.1	9); I ² = 35'	%		10 100	
Test for overall effect	Z=11.94	(P < 0.	00001)				Favours restrictive	Favours liberal	
Risk of bias legend									

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 3: Forest plot of outcome: Participants exposed to blood transfusion.

	Restrictive Liberal				Mean Difference	Mean Difference	Risk of Bias			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
Hébert 1999	2.6	4.1	418	5.6	5.3	420	100.0%	-3.00 [-3.64, -2.36]		••?••
Total (95% CI)			418			420	100.0%	-3.00 [-3.64, -2.36]	•	
Heterogeneity: Not ap	plicable									_
Test for overall effect: Z = 9.17 (P < 0.00001) Favours restrictive Favours liberal										
Risk of bias legend										
(A) Random sequenc	e genera	ation	(selecti	ion bias)					
(B) Allocation conceal	ment (s	electi	on bias)						
(C) Blinding of participants and personnel (performance bias)										
(D) Blinding of outcom	ne asses	ssme	nt (dete	ection b	ias)					
E) Incomplete outcome data (attrition bias)										

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 4: Forest plot of outcome: Units of blood transfused.



(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 5: Forest plot of outcome: Haemoglobin concentration.



(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 6: Forest plot of outcome: Cardiac events.



(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 7: Forest plot of outcome: Myocardial infarction.



(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 8: Forest plot of outcome: Congestive heart failure.

	Restrictive Liberal				Risk Ratio	Risk Ratio	Risk of Bias		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG	
Hébert 1999	30	418	40	420	100.0%	0.75 [0.48, 1.19]	-	••?••	
Total (95% CI)		418		420	100.0%	0.75 [0.48, 1.19]	◆		
Total events	30		40						
Heterogeneity: Not ap	plicable							<u>_</u>	
Test for overall effect:	Z=1.22 (P = 0.2	2)				Favours restrictive Favours libera	00 I	
Risk of bias legend									
(A) Random sequence generation (selection bias)									
(B) Allocation concealment (selection bias)									
(C) Plinding of participants and personnal (performance bias)									

(C) Blinding of participants and personnel (performance bia

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 8: Forest plot of outcome: Sepsis/bacteraemia.



(F) Selective reporting (reporting bias)

(G) Other bias

Figure 10: Forest plot of outcome: Pneumonia or wound infection.

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio	Risk of Bias	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG	
Hébert 1999	87	418	86	420	61.4%	1.02 [0.78, 1.33]	•		
Palmieri 2017	49	168	49	177	38.6%	1.05 [0.75, 1.47]	+		
Total (95% CI)		586		597	100.0%	1.03 [0.84, 1.27]	•		
Total events	136		135						
Heterogeneity: Tau ² =	= 0.00; Chi	ř = 0.03	3, df = 1 (I	P = 0.87	7); I² = 0%)			
Test for overall effect:	Z=0.28 (P = 0.7	8)				Favours restrictive Favours liberal	0	
Risk of bias legend									
(A) Random sequence generation (selection bias)									
(B) Allocation concealment (selection bias)									

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 91: Forest plot of outcome: Pneumonia.

	Restrictive Liberal				Risk Ratio	Risk Ratio	Risk of Bias			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG		
Palmieri 2017	40	168	42	177	100.0%	1.00 [0.69, 1.46]				
Total (95% CI)		168		177	100.0%	1.00 [0.69, 1.46]	•			
Total events	40		42							
Heterogeneity: Not ap	Heterogeneity: Not applicable									
Test for overall effect:	Test for overall effect: Z = 0.02 (P = 0.99) 0.01 0.1 1 10 100 Favours restrictive Favours liberal									
Risk of bias legend										
(A) Random sequenc	e generat	tion (se	lection bi	as)						
(B) Allocation conceal	ment (sel	ection	bias)							
(C) Blinding of participants and personnel (performance bias)										
(D) Blinding of outcom	(D) Blinding of outcome assessment (detection bias)									
(E) Incomplete outcome data (attrition bias)										

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 102: Forest plot of outcome: Blood stream infections.



(F) Selective reporting (reporting bias)

(G) Other bias

Figure 113: Forest plot of outcome: Wound infections.



(F) Selective reporting (reporting bias)

(G) Other bias

Figure 124: Forest plot of outcome: Urinary tract infections.

Quality of evidence

Author, Year	Lack of allocation concealment and random sequence generation (selection bias)	Lack of blinding (performance bias)	Incomplete accounting of outcome events (attrition bias)	Selective outcome reporting (reporting bias)	Other limitations
Bergamin , 2017	Randomization: no, an internet-based system was used Allocation concealment: no internet-based system concealed assignments	Personnel and participants: no, physicians and nurses of the ICU were aware, patients and investigators were blinded	No, no exclusions after randomizatio n or loss to follow-up	No Pre- registration of study protocol @ ClinicalTrials. Gov (NCT0164894 6)	No
		Outcome assessment: no, 2 blinded investigators assessed outcomes			
Hébert, 1995	Randomization: Unclear, assigned to 1 of 2 groups by consecutive allocation from a random listing stratified by centre and disease severity. Allocation concealment: Unclear, no information.	Participants and personnel: Unclear, blinding was not feasible but unlikely to be important. Outcome assessors: Unclear, not specified.	No	Yes No pre- registration of study protocol	No
Hébert, 1999	Randomization: No, computer generated randomization. Allocation concealment: No, sealed opaque envelopes prepared by data co-ordinating centre, opened sequentially in ICU to determine participants assignment	Participants and personnel: Unclear, unfeasible to blind personnel. Patients were in ICU. Outcome assessors: No for mortality (primary outcome), Yes for cardiac events, myocardial infarction, heart failure, sepsis.	No	Yes No pre- registration of study protocol	No definitions provided for cardiac events, myocardial infarction, heart failure, sepsis, pneumonia and wound infection

		pneumonia and			
		wound infection			
Holst, 2014	Randomization: No, a centralised computer generated the assignment sequence. Allocation concealment: No, use of a centralised computer ensured allocation concealment.	vound infection Participants and personnel: Unclear, clinicians were not blinded. Outcome assessors: No, the investigators assessing mortality (the DSMB) and the trial statistician were blinded.	main study (Holst 2014): No, near complete follow-up. follow-up study (Rygård 2016 identified in search update): Unclear, considerable loss to follow-up for health survey questionnair e. Responders are older and suffered more often had a pulmonary source of sepsis. Among responders, baseline characteristic s were similar in the two	No Pre- registration of study protocol @ ClinicalTrials. Gov (NCT0148531 5)	No
			groups.		
Palmieri, 2017	Randomization: adaptive random allocation procedure was used + "biased coin" procedure. Allocation concealment: Unclear, no information.	Participants and personnel: yes Outcome assessors: yes Investigators were informed of treatment group by calling the randomization center, which used the computer- generated	No lost to follow-up in both groups, Discontinued intervention: n=10 in restrictive group, n=19 in liberal group. Intention-to- treat analysis	No Study protocol registered @ ClinicalTrials. Gov (NCT0107924 7)	No

		scheme described	was		
		above to provide	performed.		
		treatment			
		assignments.			
Walsh,	Randomization: No,	Participants and	No, good	Yes	No
2013	minimisation by centre	personnel:	follow-up.		
	and the presence of	Unclear, clinicians		No pre-	
	ischaemic heart	not blinded. Most		registration	
	disease, including	surviving		of study	
	a random element, was	participants were		protocol	
	used	unaware of			
		allocation.			
	Allocation				
	concealment: No,	Outcome			
	telephone	assessors:			
	randomisation.	Unclear,			
		researchers			
		administering			
		questionnaires			
		were blinded, but			
		assessment of			
		clinical outcomes			
		was not			
		documented to			
		have been done			
		blindly.			

Certainty of the body of evidence: see GRADE evidence tables

Conclusion	See Evidence-to-Decision template							
	Articles							
	Bergamin 2017							
	Bergamin FS, Almeida JP, Landoni G, Galas FRBG, Fukushima JT, Fominskiy E, Park							
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	Hébert 1995							
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	Palmieri TL, Holmes, JH, Arnoldo B, Peck, M, Potenza B, Cochran A, King BT,
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	liberal transfusion strategies for older mechanically ventilated critically ill patients: a
	randomized pilot trial. Crit Care Med 2013, 41(10): 2354–2363.
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	Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC.
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	Coodman SG, Rao SV, Doree C, Hebert PC, <i>Clinical trials evaluating red blood coll</i>
	transfusion thresholds: an undated systematic review and with additional focus on
	nations with cardiovascular disease. In peer-review (February 2018)
	parents man caratorascalar discuse. In peer review [rebradry 2010].
	*Indicates the major publication for the study
Evidence used for	Consensus meeting PBM
Project	PBM
Reviewer(s)	Anne-Catherine Vanhove

PICO 5: RBC transfusion triggers in adult orthopaedic/non-cardiac surgery patients

Overview evidence table GRADE software (PICO 5)

	Certainty assessment			№ of patients		Effect						
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <8-9 g/dL)	more liberal RBC transfusion triggers (Hb <10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
30-day r	nortality (ove	rall)										
7	randomised trials	not serious	not serious	not serious	serious ^a	none	79/1467 (5.4%)	72/1463 (4.9%)	RR 1.18 (0.75 to 1.85)	9 more per 1.000 (from 12 fewer to 42 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
30-day r	nortality (sub	group: ortl	hopaedic surgery	/)	•	•	•		•	•	•	•
6	randomised trials	not serious	not serious	not serious	serious ^a	none	75/1417 (5.3%)	68/1414 (4.8%)	RR 1.27 (0.72 to 2.25)	13 more per 1.000 (from 13 fewer to 60 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
30-day r	mortality (sub	group: vas	cular surgery)									
1	randomised trials	serious ^b	not serious	serious ^c	serious ^a	none	4/50 (8.0%)	4/49 (8.2%)	RR 0.98 (0.26 to 3.70)	2 fewer per 1.000 (from 60 fewer to 220 more)	⊕○○○ VERY LOW	CRITICAL
Hospital	mortality (ov	erall)										

Certainty assessment				Nº of patients		Effect						
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <8-9 g/dL)	more liberal RBC transfusion triggers (Hb <10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
4	randomised trials	serious ^d	not serious	not serious	serious ^a	none	14/1369 (1.0%)	25/1272 (2.0%)	RR 0.55 (0.25 to 1.25)	9 fewer per 1.000 (from 5 more to 15 fewer)	⊕⊕⊖⊖ LOW	CRITICAL
Hospital mortality (subgroup: orthopaedic surgery)												
3	randomised trials	not serious	not serious	not serious	serious ^a	none	14/1344 (1.0%)	23/1245 (1.8%)	RR 0.45 (0.09 to 2.28)	10 fewer per 1.000 (from 17 fewer to 24 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Hospital	mortality (su	bgroup: ab	dominal surgery)								
1	randomised trials	serious ^d	not serious	serious ^e	serious ^f	none	0/25 (0.0%)	2/27 (7.4%)	RR 0.22 (0.01 to 4.28)	58 fewer per 1.000 (from 73 fewer to 243 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL
90-day r	nortality (orth	nopaedic su	urgery)					·				
2	randomised trials	not serious	not serious	serious ^g	serious ^a	none	51/244 (20.9%)	40/240 (16.7%)	RR 1.25 (0.87 to 1.81)	42 more per 1.000 (from 22 fewer to 135 more)	⊕⊕⊖⊖ LOW	CRITICAL
Patients	exposed to R	BC transfu	sion (overall)									

	Certainty assessment				Nº of patients		Effect					
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <8-9 g/dL)	more liberal RBC transfusion triggers (Hb <10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
12	randomised trials	not serious	not serious ^h	not serious	not serious	none	809/2026 (39.9%)	1659/2032 (81.6%)	RR 0.50 (0.38 to 0.67)	408 fewer per 1.000 (from 269 fewer to 506 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Patients exposed to RBC transfusion (subgroup: orthopaedic surgery)												
10	randomised trials	not serious	not serious ^h	not serious	not serious	none	760/1951 (39.0%)	1597/1956 (81.6%)	RR 0.50 (0.38 to 0.67)	408 fewer per 1.000 (from 269 fewer to 506 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Patients	exposed to R	BC transfu	sion (subgroup:	vascular surger	y)							
1	randomised trials	not serious	not serious	serious ^c	serious ^f	none	40/50 (80.0%)	43/49 (87.8%)	RR 0.91 (0.77 to 1.08)	79 fewer per 1.000 (from 70 more to 202 fewer)	⊕⊕⊖⊖ LOW	IMPORTANT
Patients	exposed to R	BC transfu	sion (subgroup:	abdominal surg	gery)							•
1	randomised trials	not serious	not serious	serious ^e	serious ^f	none	9/25 (36.0%)	19/27 (70.4%)	RR 0.51 (0.29 to 0.91)	345 fewer per 1.000 (from 63 fewer to 500 fewer)	⊕⊕⊖⊖ LOW	IMPORTANT
RBC unit	s transfused	(overall)										

	Certainty assessment Nº of patients Effect											
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <8-9 g/dL)	more liberal RBC transfusion triggers (Hb <10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
2	randomised trials	serious ⁱ	not serious	serious ^j	not serious	none	349	353	_	MD 0.23 units lower (0.85 lower to 0.39 higher)	⊕⊕⊖⊖ LOW	IMPORTANT
RBC unit	RBC units transfused (subgroup: orthopaedic surgery)											
1	randomised trials	serious ⁱ	not serious	serious ^k	not serious	none	299	304	_	MD 0.08 units lower (0.32 lower to 0.16 higher)	⊕⊕⊖⊖ LOW	IMPORTANT
RBC unit	s transfused	(subgroup:	vascular surgery	/)								
1	randomised trials	serious ⁱ	not serious	serious ^c	serious ^a	none	50	49	_	MD 0.9 units lower (2.2 lower to 0.4 higher)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
RBC unit	s transfused	(subgroup:	abdominal surg	ery)	·			·				
1	randomised trials	serious ⁱ	not serious	serious ^e	serious ¹	none	25	27	-	median 1 unit lower (0 to 0)	⊕○○○ VERY LOW	IMPORTANT
Haemog	lobin concen	tration (ov	erall)			·		·	·	·		·
			Certainty as	sessment			Nº of p	oatients	Effect			
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Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <8-9 g/dL)	more liberal RBC transfusion triggers (Hb <10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
6	randomised trials	not serious	not serious	not serious	not serious	none	1532	1534	_	MD 0.99 lower (1.53 lower to 0.45 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Haemoglobin concentration (subgroup: orthopaedic surgery)												
4	randomised trials	not serious	not serious	not serious	not serious	none	1457	1458	_	MD 0.9 units lower (1.6 lower to 0.2 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Haemog	lobin concen	tration (sul	bgroup: vascular,	/abdominal sur	rgery)							
2	randomised trials	not serious	not serious	not serious	serious ¹	none	75	76	-	MD 1.2 units lower (1.57 lower to 0.83 lower)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Cardiac	events (overa)										
4	randomised trials	not serious	not serious	not serious	not serious	none	116/1420 (8.2%)	87/1425 (6.1%)	RR 1.32 (1.01 to 1.72)	20 more per 1.000 (from 1 more to 44 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Cardiac	events (subgr	oup: ortho	paedic surgery)									

			Certainty as	sessment			Nº of p	patients	Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <8-9 g/dL)	more liberal RBC transfusion triggers (Hb <10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
3	randomised trials	not serious	not serious	not serious	not serious	none	108/1370 (7.9%)	79/1376 (5.7%)	RR 1.36 (1.03 to 1.80)	21 more per 1.000 (from 2 more to 46 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Cardiac events (subgroup: vascular surgery)												
1	randomised trials	serious ^d	not serious	not serious	serious ^a	none	8/50 (16.0%)	8/49 (16.3%)	RR 0.98 (0.40 to 2.40)	3 fewer per 1.000 (from 98 fewer to 229 more)	⊕⊕⊖⊖ LOW	CRITICAL
Myocard	lial infarction	(overall)										
6	randomised trials	not serious	not serious	not serious	serious ^a	none	41/1384 (3.0%)	27/1382 (2.0%)	RR 1.50 (0.93 to 2.42)	10 more per 1.000 (from 1 fewer to 28 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Myocard	lial infarction	(subgroup	: orthopaedic su	rgery)								
5	randomised trials	not serious	not serious	not serious	serious ^a	none	40/1334 (3.0%)	25/1333 (1.9%)	RR 1.58 (0.97 to 2.56)	11 more per 1.000 (from 1 fewer to 29 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Myocard	Myocardial infarction (subgroup: vascular surgery)											

			Certainty as	sessment			Nº of p	oatients	Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <8-9 g/dL)	more liberal RBC transfusion triggers (Hb <10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	randomised trials	serious ^d	not serious	not serious	serious ^f	none	1/50 (2.0%)	2/49 (4.1%)	RR 0.49 (0.05 to 5.23)	21 fewer per 1.000 (from 39 fewer to 173 more)	⊕⊕⊖⊖ LOW	CRITICAL
Congest	Congestive heart failure (subgroup: orthopaedic surgery)											
4	randomised trials	not serious	not serious	not serious	serious ^a	none	39/1263 (3.1%)	30/1263 (2.4%)	RR 1.28 (0.80 to 2.05)	7 more per 1.000 (from 5 fewer to 25 more)	⊕⊕⊕⊖ MODERATE	IMPORTANT
CVA-stro	oke (subgroup	: orthopae	edic surgery)									
5	randomised trials	serious ^d	not serious	not serious	serious ^a	none	5/1305 (0.4%)	13/1301 (1.0%)	RR 0.43 (0.16 to 1.13)	6 fewer per 1.000 (from 1 more to 8 fewer)	⊕⊕⊖⊖ LOW	CRITICAL
Sepsis-b	acteraemia (s	ubgroup: c	orthopaedic surg	ery)								
2	randomised trials	serious ^d	not serious	not serious	serious ^a	none	2/399 (0.5%)	2/404 (0.5%)	RR 0.96 (0.14 to 6.55)	0 fewer per 1.000 (from 4 fewer to 27 more)	⊕⊕⊖⊖ LOW	IMPORTANT
Pneumo	nia (subgroup	: orthopae	edic surgery)									

			Certainty as	sessment			Nº of p	patients	Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <8-9 g/dL)	more liberal RBC transfusion triggers (Hb <10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
8	randomised trials	not serious	not serious	not serious	serious ^a	none	84/1778 (4.7%)	105/1778 (5.9%)	RR 0.83 (0.63 to 1.09)	10 fewer per 1.000 (from 5 more to 22 fewer)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Pneumonia or wound infection (subgroup: orthopaedic surgery)												
4	randomised trials	not serious	not serious	not serious	serious ^a	none	182/1512 (12.0%)	209/1511 (13.8%)	RR 0.76 (0.50 to 1.16)	33 fewer per 1.000 (from 22 more to 69 fewer)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Thromb	oembolism (s	ubgroup: c	orthopaedic surg	ery)								
6	randomised trials	not serious	not serious	not serious	serious ^a	none	12/1604 (0.7%)	17/1605 (1.1%)	RR 0.71 (0.34 to 1.47)	3 fewer per 1.000 (from 5 more to 7 fewer)	⊕⊕⊕⊖ MODERATE	CRITICAL
Renal fa	ilure (subgrou	ıp: orthopa	edic surgery)									
2	randomised trials	serious ^m	not serious	not serious	serious ^a	none	2/194 (1.0%)	3/192 (1.6%)	RR 0.73 (0.14 to 3.84)	4 fewer per 1.000 (from 13 fewer to 44 more)	⊕⊕⊖⊖ LOW	CRITICAL
Mental o	confusion (sub	ogroup: or	thopaedic surger	y)								

			Certainty as	ssessment			Nº of patients E		Ef	ffect		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <8-9 g/dL)	more liberal RBC transfusion triggers (Hb <10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
6	randomised trials	serious ^m	not serious	not serious	serious ^a	none	61/668 (9.1%)	66/676 (9.8%)	RR 0.92 (0.65 to 1.30)	8 fewer per 1.000 (from 29 more to 34 fewer)	⊕⊕⊖⊖ LOW	IMPORTANT
Inability	Inability to walk or death at 30 days (subgroup: orthopaedic surgery)											
1	randomised trials	not serious	not serious	serious ^c	not serious	none	481/1000 (48.1%)	459/995 (46.1%)	RR 1.04 (0.95 to 1.14)	18 more per 1.000 (from 23 fewer to 65 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Inability	to walk or de	ath at 60 d	lays (subgroup: c	orthopaedic su	rgery)							
1	randomised trials	not serious	not serious	serious ^c	not serious	none	347/1001 (34.7%)	351/998 (35.2%)	RR 0.99 (0.87 to 1.11)	4 fewer per 1.000 (from 39 more to 46 fewer)	⊕⊕⊕⊖ MODERATE	CRITICAL
Lower ex	tremity physi	ical activiti	es of daily living	at 30 days (sub	group: orthop	aedic surgery)						
1	randomised trials	not serious	not serious	serious ^c	not serious	none	507	472	-	MD 0.2 points higher (0.26 lower to 0.66 higher)	⊕⊕⊕⊖ MODERATE	IMPORTANT

			Certainty as	sessment			Nº of p	oatients	Ef	fect		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <8-9 g/dL)	more liberal RBC transfusion triggers (Hb <10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Lower ex	Lower extremity physical activities of daily living at 60 days (subgroup: orthopaedic surgery)											
1	randomised trials	not serious	not serious	serious ^c	not serious	none	553	523	_	MD 0 points (0.51 lower to 0.51 higher)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Instrumental activities of daily living at 30 days (subgroup: orthopaedic surgery)												
1	randomised trials	not serious	not serious	serious ^c	not serious	none	450	437	-	MD 0 points (0.06 lower to 0.06 higher)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Instrume	ental activities	s of daily liv	ving at 60 days (s	subgroup: orth	opaedic surger	y)						
1	randomised trials	not serious	not serious	serious ^c	not serious	none	411	389	-	MD 0 points (0.12 lower to 0.12 higher)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Energy/f	atigue at 30 d	days (subg	roup: orthopaed	ic surgery)								
1	randomised trials	not serious	not serious	serious ^c	not serious	none	459	456	-	MD 0.1 lower (1.09 lower to 0.89 higher)	⊕⊕⊕⊖ MODERATE	IMPORTANT

			Certainty as	sessment			Nº of p	oatients	Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <8-9 g/dL)	more liberal RBC transfusion triggers (Hb <10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Energy/f	Energy/fatigue at 60 days (subgroup: orthopaedic surgery)											
1	randomised trials	not serious	not serious	serious ^c	not serious	none	525	544	-	MD 0.5 points higher (0.38 lower to 1.38 higher)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Timed u	Timed up and go test (subgroup: orthopaedic surgery)											
1	randomised trials	not serious	not serious	not serious	serious ¹	none	25	28	-	MD 6 seconds higher (0 to 0)	⊕⊕⊕⊖ MODERATE	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

a. Large variability in results; b. Selection bias (randomization + allocation concealment unclear), performance bias (lack of blinding unclear), reporting bias (no pre-registration study protocol); c. Lack of generalizibility: Single centre study conducted in the USA; d. Detection bias and reporting bias; e. Lack of generalizibility: Single centre study conducted in Greece; f. Low number of events, limited sample size and/or large variability in results; g. Lack of generalizibility: 2 small single centre studies form UK and Denmark; h. Decision not to downgrade by reviewer(s) although point estimates vary, CIs show minimal or no overlap, tests for heterogeneity show a low p-value and I2>75%. This large inconsistency or variability is, however, not considered important as the direction of effect is the same for all studies which is most relevant for this outcome; i. Detection bias unclear, no pre-registration of study protocol; j. Lack of generalizibility: 1 (old) small study from USA + 1 study conducted in The Netherlands; k. Lack of generalizibility: one study conducted in The Netherlands; l. Low number of events and/or limited sample size; m. Detection bias and selection bias.

Detailed evidence summary (PICO 5)

Торіс	Patient Blood Management
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers
Intervention	Restrictive RBC transfusion triggers
Question (PICO)	In elderly high risk (cardiovascular) patients undergoing orthopaedic or non- cardiac surgery (Population), is the use of a restrictive transfusion threshold (Intervention) not inferior to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusion threshold (Comparison)?
Search Strategy	 The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to: Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017) Identify observational studies in case no experimental studies were available.
	Databases The Cochrane Library (systematic reviews and controlled trials) using the following search strategy (from May 2016 until June 2017): #1 MeSH descriptor: [Blood Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST, Trends - TD] #2 MeSH descriptor: [Erythrocyte Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST] #3 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) near/5 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or strateg* or regimen* or criteri* or standard* or management or program*)) #4 ((h?emoglobin or h?ematocrit or HB or HCT) near/5 (polic* or practic* or protocol* or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or standard*)) #5 (blood near/3 (management or program*)) #6 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) and (critical* or intensive* or h?emorrhag* or bleed*)):ti #7 #1 or #2 or #3 or #4 or #5 or #6
	MEDLINE (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy (from 27th May 2016 until 30th June 2017): #1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI])) #2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR standard*[TI])) #3 (blood[TI] AND (management[TI] OR program*[TI]))

PREC(TIII) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR PREC(TIII) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR #aemorrhage*[TI] OR bleed*[TI]]) #5 #1 OR #2 OR #3 OR #4 Embase (via Embase.com interface) using the following search strategy (from 27 th May 2016 until 30 th June 2017): #1 ((transfus*ti OR red cell*ti OR red blood cell*ti OR RBC*ti OR PREC*) AND (trigger*ti OR threshold*ti OR angagetexit*ti OR prophylatic*ti OR strateg*ti OR regime*ti OR conservative*ti OR prophylatic*ti OR strateg*ti OR program*ti)) #2 ((hemoglobinti OR hemoglobinti OR hematocritti OR strateg*ti OR program*ti)) #2 ((hemoglobinti OR hemoglobinti OR hemothag*ti OR program*ti)) #3 (bloodti AND (managementti OR program*ti)) #3 (bloodti AND (managementti OR program*ti)) #4 ((transfus*ti OR red cell*ti OR ned blood cell*ti OR RBC*ti OR PRBC*ti) and (critical*ti OR intensive*ti OR hemorrhag*ti OR hemorrhage*ti OR liberad*ti)) #5 #1 OR #2 OR #3 OR #4 Transfusion evidence library (from 2016 until 2017) Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive) OR policies OR practice OR indicator OR strategy: OR strategies OR regime OR restrict OR indicator OR strategy OR strategies OR regime OR restrica OR standard OR management OR program OR program OR programme) OR Red Cells AND title/critical OR critically OR intensive/ OR hemorrhagio R hemorrhaging OR hemorrhaging OR bleed OR bleeding) Search date 13/11/2017 (Cochrane review 2016 + updated/unpublished revi		#4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RRC*[TI] OR
Field (1) and (fittig (1) (1) (1) (1) (1) (1) (1) (1) (1) (1)		PPRC*[TI]) and (critical*[TI] OP intensive*[TI] OP homorrhag*[TI] OP
#5 #10 R#20 R#3 0 R#4 #5 #10 R#20 R#3 0 R#4 Embase (via Embase.com interface) using the following search strategy (from 27 th May 2016 until 30 th June 2017): #1 ((transfus*ti) OR red cell*ti) OR red blood cell*ti OR RBC*ti OR PRBC*) AND (trigger*ti) OR Reschold*ti OR parept*ti OR Restrict*ti OR limit*ti OR protocol*ti OR policyti OR policyti OR policyti OR protocol*ti OR indicat*ti OR protocol*ti OR protocol*ti OR protocol*ti OR redict*ti OR nanagementti OR program*ti)) #2 (hemoglobinti OR haemoglobinti OR haemoglobi OR protocol OR policy OR policics OR practice OR Indicator OR strategy OR strategies OR regimen OR riteria OR standard OR management OR program. Vin Program OR programme) OR Red Cells AND title/critical OR cellical OR attagies OR regimen OR riteria OR standard OR management OR program. Vin OR Dimorrhagi OR haemorrhage OR hemorrhagi OR haemoglobin level faltest search date Carson review) Intextentio		hasmorrhage*[T] OR blood*[T])
*** FLOR #2 OK #3 OK #4 Embase (via Embase.com interface) using the following search strategy (from 27 th May 2016 until 30 th June 2017): #1 (transfust ti OR red cell*ti OR red blood cell*ti OR RBC*ti OR PRBC*) AND (trigger*ti OR conservative via TOR prophylactic*ti OR liberal*ti OR protocol*ti OR policyti OR policyti OR policyti OR practic*ti OR indicat*ti OR strateg*ti OR regimen*ti OR criteri*ti OR strateg*ti OR managementti OR program*ti) #2 ((hemoglobinti OR haematocritit OR haematocritit OR haematocritit OR HB:ti OR HCT:ti) AND (polic*ti OR practic*ti OR protocol*ti OR haematocriti OR HB:ti OR HCT:ti) AND (polic*ti OR program*ti)) #3 (bloodti AND (managementti OR program*ti)) #3 (bloodti AND (managementti OR program*ti)) #4 (transfust*ti OR red cell*ti OR red blood cell*ti OR RBC*ti OR PRBC*ti) and (critical*ti OR intensive*ti OR hemorrhag*ti OR haemorrhage*ti OR bloed*ti)) #3 (bloodti AND (managementti OR program*ti)) #4 (transfust*ti OR red cell*ti OR red blood cell*ti OR RBC*ti) OR PRBC*ti) and (critical*ti OR intensive*ti OR hemorrhag*ti OR haemorrhage*ti OR alpet*ti)) #4 (transfust*ti OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR aggime OR cell*ti AND title/critical OR critical OR crital*sti OR BPOgutalon*tin CRC*tera OR BAD title/critical OR critic		
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participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and <i>Secondary</i> : Morbidity-related outcomes that occurred during		including outcomes related to RBC transfusion use (i.e. proportion of
autologous transfusion, units of blood transfused (in those receiving any transfusion)) and <i>Secondary</i> : Morbidity-related outcomes that occurred during		participants exposed to transfusion, participants exposed to allogeneic or
transfusion)) and <i>Secondary</i> : Morbidity-related outcomes that occurred during		autologous transfusion, units of blood transfused (in those receiving any
		transfusion)) and Secondary: Morbidity-related outcomes that occurred during
hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction.		hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction.

congestive heart failure, stroke, renal injury, pneumonia, septic shock, rebleeding, infection, and fatigue).
Study design: Systematic reviews (+ meta-analyses) of experimental studies (RCT's). If systematic reviews (published within 5 years of the search date) are not available, we will search for individual experimental studies (RCT's). To examine the evidence for the effect of transfusion threshold on the use of RBC transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or haematocrit level (without hemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic or autologous red blood cells, or both, at higher haemoglobin or haematocrit levels (transfusion threshold) than the intervention group, or transfused in accordance with current transfusion practices, which may not have included a well-defined transfusion threshold, but involved liberal rather than restrictive transfusion practices. We excluded trials that were not designed to include any clinical outcomes.
ciffical outcomes.

Characteristics of included studies

Studies also labeled according to age of the population:

- Elderly: all participants ≥65 years old
- Older: mean age of participants ≥64 years old
- Younger: participants of all ages

Author, year, Country	Study design	Population	Comparison	Study funding, financial COI and
				remarks
Bush, 1997,	Randomised	99 participants undergoing	Restrictive group	No information
USA	controlled	elective aortic or	(intervention):	available on study
	trial	infrainguinal arterial	transfusion if Hb < 9.0	funding or
		reconstruction	g/dL	financial COI.
		(clinical specialty subgroup		
		(Carson, 2016): vascular	Liberal group	Identified from
		surgery)	(control):	the systematic
			Hb maintained ≥10.0	review of Carson
		Restrictive group:	g/dL	et al., 2016.
		n=50, 32 males and 18		
		females, age=66±10 years	Transfusion:	
			Predonated	
		Liberal group:	autologous blood	
		n=49, 41 males and 8	(restrictive group:	
		females, age=64±11 years	n=1, liberal group:	
			n=3) if available or	
		Age of population: older	allogeneic blood	
Carson, 1998,	Randomised	84 hip fracture participants	Restrictive group	No information
USA	controlled	(in USA and Scotland)	(intervention):	available on study
	trial	undergoing surgical repair	transfusion permitted	funding or
		with postoperative	if symptoms of	financial COI.
		Hb<10.0 g/dL	anemia or Hb<8g/dL;	

		 (clinical specialty subgroup (Carson, 2016): orthopaedic surgery) Restrictive group: n=42, 11 males and 31 females, age=83.3±10.8 years Liberal group: n=42, 9 males and 33 females, age=81.3±8.1 years Age of population: older 	1 unit at a time until symptoms disappeared or Hb increased >8 g/dL Liberal group (control): immediately transfuse 1 unit after randomisation (Hb < 10 g/dL) and transfuse enough blood to maintain Hb > 10 g/dL Transfusion: units of packed RBC (allogeneic)	Identified from the systematic review of Carson et al., 2016.
Carson, 2011, USA	Randomised controlled trial	2016 participants (> 50 years, in USA and Canada) undergoing surgical repair of a hip fracture with Hb<10.0 g/dL who had clinical evidence of cardiovascular disease or cardiovascular risk factors (clinical specialty subgroup (Carson, 2016): orthopaedic surgery) Restrictive group: n=1009, 239 males and 770 females, age=81.5±9.0 years Liberal group: n=1007, 250 males and 757 females, age=81.8±8.8 years Age of population: older	Restrictive group (intervention): transfusion permitted if symptoms of anaemia or Hb<8g/dL; 1 unit at a time until symptoms disappeared or Hb increased >8 g/dL Liberal group (control): immediately transfuse 1 unit after randomisation (Hb<10 g/dL) and transfuse enough blood to maintain Hb>10 g/dL Transfusion: units of packed RBC	Study partly funded by National Heart, Lung and Blood Institute. Research institute does receive grant support from industry. Several authors also work with industry. Identified from the systematic review of Carson et al., 2016.
Fan, 2014, China	Randomised controlled trial	186 participants (>65 years) undergoing elective unilateral total hip replacement (clinical specialty subgroup (Carson, 2016): orthopaedic surgery) Restrictive group: n=94, 30 males and 64 females, age=73±7 years	Restrictive group (intervention): transfusion if symptoms of anemia or Hb<8g/dL Liberal group (control): transfuse enough blood to maintain Hb>10 g/dL	Research funded by government grants. No conflicts of interest stated. Identified from the systematic review of Carson et al., 2016.

		Liberal group: n=92, 33 males and 59 females, age=75±6 years	Transfusion: units of blood	
Foss, 2009, Denmark	Randomised controlled trial	120 hip fracture participants (>65 years) (clinical specialty subgroup (Carson, 2016): orthopaedic surgery) Restrictive group: n=60, 14 males and 46 females, age=81±7.3 years Liberal group: n=60, 114 males and 46 females, age=81±6.8 years Age of population: elderly	Restrictive group (intervention): transfusion with RBC if Hb conc <8.0 g/dL (7.2 g/dL <hb<8 g/dL: 1 unit of RBC; 5.6 g/dL<hb<math>\leq7.2 g/dL: 2 units of RBC; Hb<5.6 g/dL: 3 units of RBC; all transfusions followed by control of Hb) Liberal group (control): transfusion with RBC if Hb <10.0 g/dL (8.8 g/dL<hb<10 1<br="" dl:="" g="">unit of RBC; 7.2 g/dL<hb<math>\leq8.8 g/dL: 2 units of RBC; Hb<7.2 g/dL: 3 units of RBC, all transfusions followed by control of Hb) Transfusion: RBC unit</hb<math></hb<10></hb<math></hb<8 	Research support by private foundation (IMK Almene Fond). No conflict of interest declared. Identified from the systematic review of Carson et al., 2016.
Gregersen, 2015, Denmark	Randomised controlled trial	284 participants (≥65 years) undergoing hip fracture surgery with postoperative 9.7 g/dL <hb 11.3 g/dL (clinical specialty subgroup (Carson, 2016): orthopaedic surgery) Restrictive group: n=144, 36 males and 108 females, age=86±6.8 years Liberal group: n=140, 34 males and 106 females, age=88±6.9 years Age of population: elderly</hb 	Restrictive group (intervention): transfusion if Hb<9.7 g/dL until target achieved with max 2 units per day Liberal group (control): transfusion if Hb<11.3 g/dL until target achieved with max 2 units per day Transfusion: 1 RBC unit	Research supported by university and foundation established at university. No conflict of interest declared. Identified from the systematic review of Carson et al., 2016.

Grover, 2006, UK	Randomised controlled trial	260 participants undergoing elective lower limb joint replacement surgery (clinical specialty subgroup (Carson, 2016): orthopaedic surgery) Restrictive group: n=109, 48 males and 61 females, age=70.7±7.1 years Liberal group: n=109, 55 males and 54 females, age 71.5±7.6 years Age of population: older	Restrictive group (intervention): transfusion if Hb < 8.0 g/dL, Hb conc maintained at 8.0-9.5 g/dL Liberal group (control): transfusion if Hb < 10.0 g/dL, Hb conc maintained at 10.0-12.0 g/dL Transfusion: RBC unit	Study funded by government grant (NHS). Identified from the systematic review of Carson et al., 2016.
Lotke, 1999, USA	Randomised controlled trial	152 participants undergoing primary total knee arthroplasty (TKA) (clinical specialty subgroup (Carson, 2016): orthopaedic surgery) Restrictive group: n=62, 20 males and 42 females, mean age=68.7 years Liberal group: n=65, 19 males and 46 females, mean age=69.7 years Age of population: older [an additional 25 participants did not predonate blood and were not included in the	Restrictive group (intervention): transfusion of the 2 units of autologous blood if Hb <9.0 g/dL Liberal group (control): transfusion of the 2 units of autologous blood immediately after surgery in the recovery room Transfusion: preoperatively donated autologous blood [patients who did not donate prior to surgery, excluded from systematic	No information available on study funding or financial COI. Identified from the systematic review of Carson et al., 2016.
Markatou, 2012, Greece	Randomised controlled trial	52 participants scheduled for elective upper major abdominal surgery Restrictive group: n=25, 13 males and 12 females, mean age=58.2±11.7 years Liberal group:	Restrictive group (intervention): transfusion if Hb <7.7 g/dL, target Hb 7.7- 9.9 g/dL Liberal group (control): transfusion if Hb <9.9 g/dL, target Hb >10 g/dL	No information available on study funding or financial COI. Identified from the systematic review of Hovaguimian and Myles, 2016.

		n=27, 16 males and 11 females, mean age=63.4±11.3 years	Transfusion: RBC unit	
Nielsen, 2014, Denmark	Randomised controlled trial	66 participants (>18 years) scheduled for elective hip revision surgery (clinical specialty subgroup (Carson, 2016): orthopaedic surgery) Restrictive group: n=33, 16 males and 17 females, median age (5%- 95% range)=68 (43-86) years Liberal group: n=33, 20 males and 13 females, median age (5%- 95% range)=72 (53-89) years	Restrictive group (intervention): transfusion if Hb <7.3 g/dL with target range of 7.3-8.9 g/dL Liberal group (control): transfusion if Hb <8.9 g/dL with target >8.9 g/dL Transfusion: allogeneic RBC	Research funded by foundation from insurance company, but foundation was not involved in study design, data analysis or manuscript approval. No conflict of interest declared. Identified from the systematic review of Carson et al., 2016.
Parker, 2013, UK	Randomised controlled trial	Age of population: older 200 participants (>60 years) with hip fracture, 8.0 g/dL <hb<9.5 dl<br="" g="">(clinical specialty subgroup (Carson, 2016): orthopaedic surgery) Restrictive group: n=100, 15 males and 85 females, mean age (range)=84.2 (60-97) years Liberal group: n=100, 17 males and 83 females, mean age (range)=84.4 (60-104) years Age of population: older</hb<9.5>	Restrictive group (intervention): transfusion only if definite symptoms of anemia Liberal group (control): transfusion of at least 1 unit of blood and then maintained >10.0 g/dL Transfusion: units of blood	No external funding. No conflict of interest. Identified from the systematic review of Carson et al., 2016.
So-Osman, 2013, The Netherlands	Randomised controlled trial	603 participants in 3 hospitals undergoing elective orthopaedic surgery (clinical specialty subgroup (Carson, 2016): orthopaedic surgery) Restrictive group:	This is a post-hoc analysis of an earlier randomized controlled trial (So- Osman 2010) which is re-analyzed to create Restrictive group (intervention):	Study fully supported by grant from participating hospital. No conflicts of interest declared. Identified from the systematic

n=299, 109 males and 190	according to new	review of Carson
females, age=70.2±10.3	protocol hospital 1	et al., 2016.
years	and 2 and to the	
	standard protocol in	Re-analysis of So-
Liberal group:	hospital 3	Osman (2010) by
n=304, 93 males and 211		pooling the
females,, age=70.7±9.6	Liberal group	patients who were
years	(control): according	randomised to
	to standard protocol	the most
Age of population: older	in hospital 1 and 2	restrictive trigger
	and to new protocol	to a restrictive
	in hospital 3	policy group and
		the patients who
	Hb threshold values	were randomised
	were based on age	to the most liberal
	and comorbidities,	transfusion policy
	details are provided	to a liberal policy
	in Appendix paper	group, thereby
	So-Osman et al.	respecting the
	(2013)	randomised
		nature of the
	Transfusion:	data.
	pre-storage	
	leucocyte-depleted	
	RBC units	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, #	Reference
			participants	
Primary outcome	es			
30-day mortality	Restrictive vs liberal transfusion threshold	Overall: Not statistically significant: 79/1467 vs 72/1463 RR: 1.18, 95%CI [0.75;1.85] ¥ (p=0.48)* (Figure 13)	7, 1467 vs 1463	Carson, 1998; Carson, 2011; Foss, 2009; Gregersen, 2015; Lotke, 1999; Parker, 2013; Bush, 1997 (vascular)
		Subgroup orthopaedic surgery: Not statistically significant: 75/1417 vs 68/1414 RR: 1.27, 95%CI [0.72;2.25] ¥ (p=0.41) (Figure 13)	6, 1417 vs 1414	Carson, 1998; Carson, 2011; Foss, 2009; Gregersen, 2015; Lotke, 1999; Parker, 2013
		Subgroup other surgery:	1, 50 vs 49	Bush, 1997

	Not statistica 4/50 vs 4/49 RR: 0.98, 95% (p=0.98) (Fig	ally significant: § 6CI [0.26;3.70] ¥ Jure 13)		(vascular)
Hospital mortality	<i>Overall:</i> Not statistica 14/1369 vs 2 RR: 0.55, 95% (p=0.16)* (Fig	ally significant: 5/1272 6CI [0.25;1.25] ¥ gure 14)	4, 1369 vs 1272	
	<i>Subgroup ort</i> Not statistica 14/1344 vs 2 RR:0.45 , 95% (p=0.33)* (Fig	<i>hopaedic surgery:</i> ally significant: 3/1245 6CI [0.09;2.28] ¥ gure 14)	3, 1344 vs 1245	Carson, 1998; Carson, 2011; So- Osman, 2013
	<i>Subgroup oth</i> Not statistica 0/25 vs 2/27 RR: 0.22, 95% (p=0.31)* (Fig	ner surgery: ally significant: § 6CI [0.01;4.28] ¥ gure 14)	1, 25 vs 27	Markatou, 2012 (abdominal)
90-day mortality	Orthopaedic Not statistica 51/244 vs 40 RR: 1.25, 95% (p=0.23)* (Fig	<i>surgery:</i> ally significant: //240 6CI [0.87;1.81] ¥ gure 15)	2, 244 vs 240	Gregersen, 2015; Parker, 2013
Participants exposed to blood transfusion	<i>Overall:</i> <u>Statistically s</u> 809/2026 vs RR: 0.53, 959 (p<0.00001) ³ In favour of r transfusion th	ignificant: 1659/2032 6CI [0.41;0.69] * (Figure 16) restrictive hreshold	12, 2026 vs 2032	
	Subgroup ort Statistically s 760/1951 vs RR: 0.50, 959 (p<0.00001) In favour of r transfusion th	hopaedic surgery: ignificant: 1597/1956 6CI [0.38;0.67] (Figure 16) restrictive hreshold	10, 1951 vs 1956	Carson, 1998; Carson, 2011; Fan, 2014;Foss, 2009; Gregersen, 2015; Grover, 2006 Lotke, 1999; Nielsen, 2014; Parker, 2013; So- Osman, 2013
	Subgroup oth (vascular): Not statistica 40/50 vs 43/- RR: 0.91, 959	ner surgery ally significant: 49 § 6CI [0.77;1.08] ¥	1, 50 vs 49	Bush, 1997 (vascular);

		(p=0.30)* (Figure 16)		
		Subgroup other surgery	1, 25 vs 27	Markatou,
		(abdominal):		2012
		Statistically significant:		(abdominal)
		9/25 vs 19/27 §		(,
		RR: 0.51, 95%CI [0.77;1.08] ¥		
		(p=0.02)* (Figure 16)		
		In favour of restrictive		
		transfusion threshold		
Units of blood	1	Overall:	2, 349 vs 353	
transfused		Not statistically significant:	[
		MD: -0.23, 95%CI [-0.85:0.39]		
		$(p=0.47)^*$ (Figure 17)		
		Subaroup orthopaedic suraery:	1, 299 vs 304	So-Osman.
		Not statistically significant:	_,	2013
		0.78 ± 1.4 vs 0.86 ± 1.6		2010
		MD: -0.08 95%CI [-0.32:0.16]		
		(p=0.51)* (Figure 17)		
		Subaroup other surgery:	1 50 vs 49 8	Bush 1997
		Not statistically significant	1, 50 15 15 5	(vascular)
		28+31 yrs 37+35		(vascalar)
		$MD = -0.90, 95\%CI = 2.200, 401 \times 10^{-2}$		
		(n=0.18)** (Figure 17)		
		(p=0.10) (figure 17) Subaroup other surgery:	1 25 vs 27 8	Markatou
		Statistically significant:	1, 25 V3 27 3	2012
		median [IOR]: 0 [0 2] vs 1 [0 3]		(abdominal)
		(n=0.013)		(abaonina)
Secondary outcor	nes	(° · · · · · · · · · · · · · · · · · · ·		
Haemoglobin	Restrictive vs liberal	Overall:	6, 1532 vs 1534	
concentration	transfusion	Statistically significant:		
	threshold	MD: -0.99, 95%CI [-1.53;-0.45]		
		(p=0.0003)* (Figure 18)		
		Subaroup orthopaedic suraery:	4, 1457 vs 1458	Carson.
		Statistically significant:	,	1998:
		MD: -0.90, 95%CI [-1.60:-0.20]		Carson.
		$(p=0.01)^*$ (Figure 18)		2011
		(p 0.01) (l'igare 10)		Grover
				2006: 50-
				Osman
				2013
		Subaroup other surgery:	2, 75 vs 76 §	Bush, 1997
		Statistically significant:	2,75 45 76 5	(vascular):
		MD: -1 20, 95% CI [-1 57:-0 83]		Markatou
				i i la
		(p < 0.0001)* (Figure 18)		2012
		(p<0.00001)* (Figure 18)		2012 (abdominal)
Cardiac events	-	(p<0.00001)* (Figure 18)	4. 1420 vs 1425	2012 (abdominal)
Cardiac events	-	(p<0.00001)* (Figure 18)	4, 1420 vs 1425	2012 (abdominal)
Cardiac events	-	(p<0.00001)* (Figure 18) <i>Overall:</i> <u>Statistically significant:</u> 116/1420 vs 87/1425	4, 1420 vs 1425	2012 (abdominal)
Cardiac events		(p<0.00001)* (Figure 18) Overall: <u>Statistically significant:</u> 116/1420 vs 87/1425 RR: 1.32, 95%CI [1 01:1 72]	4, 1420 vs 1425	2012 (abdominal)
Cardiac events	-	(p<0.00001)* (Figure 18) <i>Overall:</i> <u>Statistically significant:</u> 116/1420 vs 87/1425 RR: 1.32, 95%CI [1.01;1.72] (p=0.04)* (Figure 19)	4, 1420 vs 1425	2012 (abdominal)
Cardiac events		(p<0.00001)* (Figure 18) <i>Overall:</i> <u>Statistically significant:</u> 116/1420 vs 87/1425 RR: 1.32, 95%CI [1.01;1.72] (p=0.04)* (Figure 19) Subgroup orthongedic surgery:	4, 1420 vs 1425 3.1370 vs 1376	2012 (abdominal) Carson
Cardiac events		(p<0.00001)* (Figure 18) Overall: Statistically significant: 116/1420 vs 87/1425 RR: 1.32, 95%CI [1.01;1.72] (p=0.04)* (Figure 19) Subgroup orthopaedic surgery: Statistically significant:	4, 1420 vs 1425 3,1370 vs 1376	2012 (abdominal) Carson, 2011: Lotke
Cardiac events		(p<0.00001)* (Figure 18) <i>Overall:</i> <u>Statistically significant:</u> 116/1420 vs 87/1425 RR: 1.32, 95%CI [1.01;1.72] (p=0.04)* (Figure 19) <i>Subgroup orthopaedic surgery:</i> <u>Statistically significant:</u> 108/1370 vs 79/1376	4, 1420 vs 1425 3,1370 vs 1376	2012 (abdominal) Carson, 2011; Lotke, 1999: So-

	RR: 1.36, 95%CI	[1.03;1.80]	Osman,
	(p=0.03)^ (Figur	<u>e 19)</u>	2013
	Subgroup other	<i>surgery:</i> 1, 50 vs 4	¹⁹ Bush, 1997
	Not statistically	significant:	(vascular)
	8/50 vs 8/49 §		
	RR: 0.98, 95%CI	[0.40;2.40] ¥	
	(p=0.96)** (Figu	ire 19)	
Myocardial	Overall:	6, 1384 v	/s 1382
infarction	Not statistically	significant:	
	41/1384 vs 27/1	1382	
	RR: 1.50, 95%CI	[0.93;2.42] ¥	
	(p=0.09)* (Figur	e 20)	
	Subgroup ortho	baedic surgery: 5, 1334 v	/s 1333 Carson,
	Not statistically	significant:	2011; Fan,
	40/1334 vs 25/1	1333	2014; Foss,
	RR: 1.58, 95%CI	[0.97;2.56] ¥	2009;
	(p=0.07)* (Figur	e 20)	Grover,
			2006; Lotke,
			1999
	Subgroup other	<i>surgery</i> : 1, 50 vs 4	49 Bush, 1997
	Not statistically	significant:	(vascular)
	1/50 vs 2/49 §	5	
	RR: 0.49, 95%CI	[0.05;5.23] ¥	
	(p=0.55)** (Figu	ire 20)	
Congestive heart	Orthopaedic sur		/s 1263 Carson,
failure	Not statistically	significant:	2011; Fan,
	39/1263 vs 30/1	263	2014; Foss,
	RR: 1.28, 95%CI	[0.80;2.05] ¥	2009;
	(p=0.30)* (Figur	e 21)	Parker, 2013
Cerebrovascular	Orthopaedic sur	<i>gery</i> : 5, 1305 v	vs 1301 Carson,
accident (CVA) -	Not statistically	significant:	1998;
stroke	5/1305 vs 13/13	301	Carson,
	RR: 0.43, 95%CI	[0.16;1.13] ¥	2011; Fan,
	(p=0.09)* (Figur	e 22)	2014; Foss,
			2009; Parker
			2013
Sepsis/bacteraemi	Orthopaedic sur	gery: 2, 399 vs	404 Parker,
а	Not statistically	significant:	2013;
	2/399 vs 2/404		So-Osman,
	RR: 0.96, 95%CI	[0.14;6.55] ¥	2013
	(p=0.97)* (Figur	e 23)	
Pneumonia	Orthopaedic sur	rgery: 8, 1778 v	rs 1778 Carson,
	Not statistically	significant:	1998;
	84/1778 vs 105,	/1778	Carson,
	RR: 0.83, 95%CI	[0.63;1.09] ¥	2011; Fan,
	(p=0.18)* (Figur	[.] e 24)	2014; Foss,
			2009;
			Gregersen,
			2015;
			Nielsen,
			2014;
			Parker,
			2013; So-

			Osman, 2013
Pneumonia or wound infection	<i>Orthopaedic surgery:</i> Not statistically significant: 182/1512 vs 209/1511 RR: 0.76, 95%CI [0.50;1.16] ¥ (p=0.20)* (Figure 25)	4, 1512 vs 1511	Carson, 2011; Foss, 2009; Gregersen, 2015; So- Osman, 2013
Thromboembolism	<i>Orthopaedic surgery:</i> Not statistically significant: 12/1604 vs 17/1605 RR: 0.71, 95%CI [0.34;1.47] ¥ (p=0.36)* (Figure 26)	6, 1604 vs 1605	Carson, 1998; Carson, 2011; Fan, 2014; Foss, 2009; Parker, 2013; So- Osman, 2013
Renal failure	<i>Orthopaedic surgery:</i> Not statistically significant: 2/194 vs 3/192 RR: 0.73, 95%CI [0.14;3.84] ¥ (p=0.71)* (Figure 27)	2, 194 vs 192	Fan, 2014; Parker, 2013
Mental confusion	<i>Orthopaedic surgery:</i> Not statistically significant: 61/668 vs 66/676 RR: 0.92, 95%CI [0.65;1.30] ¥ (p=0.65)* (Figure 28)	6, 668 vs 676	Carson, 2011; Fan, 2014; Foss, 2009; Lotke, 1999; Parker, 2013; So- Osman, 2013
Inability to walk or death at 30 days	<i>Orthopaedic surgery:</i> Not statistically significant: 481/1000 vs 459/995 RR: 1.04, 95%CI [0.95;1.14] (p=0.38)** (Figure 29)	1, 1000 vs 995	Carson, 2011
Inability to walk or death at 60 days	<i>Orthopaedic surgery:</i> Not statistically significant: 347/1001 vs 351/998 RR: 0.99, 95%CI [0.87;1.11] (p=0.81)** (Figure 30)_	1, 1001 vs 998	Carson, 2011
Lower extremity physical activities of daily living at 30 days	<i>Orthopaedic surgery:</i> Not statistically significant: 7.4±3.7 vs 7.2±3.6 MD: 0.20, 95%CI [-0.26;0.66] (p=0.39)** (Figure 31)	1, 507 vs 472	Carson, 2011
Lower extremity physical activities of daily living at 60 days	Orthopaedic surgery: Not statistically significant: 5.1±4.3 vs 5.1±4.2 MD: 0.00, 95%CI [-0.51;0.51] (p=1.00)** (Figure 32)	1, 553 vs 523	Carson, 2011

Instrumental	Orthopaedic surgery:	1, 450 vs 437	Carson,
activities of daily	Not statistically significant:		2011
living at 30 days	3.9±0.4 vs 3.9±0.5		
	MD: 0.00, 95%CI [-0.06;0.06]		
	(p=1.00)** (Figure 33)		
Instrumental	Orthopaedic surgery:	1, 411 vs 389	Carson,
activities of daily	Not statistically significant:		2011
living at 60 days	3.7±0.9 vs 3.7±0.8		
	MD: 0.00, 95%CI [-0.12;0.12]		
	(p=1.00)** (Figure 34)		
Energy/fatigue at	Orthopaedic surgery:	1, 459 vs 456	Carson,
30 days	Not statistically significant:		2011
	38.6±7.6 vs 38.7±7.7		
	MD: -0.1, 95%CI [-1.09;0.89]		
	(p=0.84)** (Figure 35)		
Energy/fatigue at	Orthopaedic surgery:	1, 525 vs 544	Carson,
60 days	Not statistically significant:		2011
	42.3±7.4 vs 41.8±7.3		
	MD: 0.50, 95%CI [-0.38;1.38]		
	(p=0.27)** (Figure 36)		
'Timed up and go'	Orthopaedic surgery:	1, 25 vs 28 §	Nielsen,
test	Not statistically significant:		2014
	36±0 vs 30±0		
	Not estimable (Figure 37)		

Mean ± SD (unless otherwise indicated)

CI: confidence interval, RR: relative risk, MD: mean difference, IQR: interquartile range

* Calculations (MD or RR, 95%CI and p-value) done by the reviewer using Review Manager software

** Calculations (p-value) done by the reviewer using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Forest plots

Libera	al		Risk Ratio	Risk Ratio	Risk of Bias
Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1	42	2.6%	1.00 [0.06, 15.47]		
52	1007	47.5%	0.83 [0.56, 1.22]		
0	60	2.4%	11.00 [0.62, 194.63]	+	\bullet ? \bullet \bullet ? \bullet \bullet
12	140	28.3%	1.70 [0.87, 3.32]	+	$\bullet \bullet ? \bullet \bullet \bullet \bullet$
0	65		Not estimable		
3	100	9.1%	1.67 [0.41, 6.79]		? 🕂 ? ? ? 🕂 🕂
	1414	89.9%	1.27 [0.72, 2.25]	•	
68					
: 4 (P = 0.1	7); I² =	38%			
	40	10.1%	0.00 (0.06, 0.70)		2222888
4	49	10.1%	0.98 [0.20, 3.70]		
4	45	10.170	0.00 [0.20, 0.10]		
4					
	1463	100.0%	1.18 [0.75, 1.85]	◆	
72					
5 (P = 0.2	6); I ² =	23%			
				Eavours restrictive Eavours liberal	
df = 1 (P =	0.72), I	²=0%			
on bias)					
performan	ice bias	5)			
	Liber: 1 Events 2 1 3 52 0 0 4 12 2 0 3 3 68 4 (P = 0.1 4 4 4 7 72 = 5 (P = 0.2 df = 1 (P = on bias) (performan	Liberal <u>I Events Total</u> 2 1 42 3 52 1007 0 0 60 1 12 140 2 0 65 3 100 7 1414 68 = 4 (P = 0.17); P= 4 4 7 1463 72 = 5 (P = 0.26); P= df = 1 (P = 0.72), I on bias) (performance bias	Liberal <u>I Events</u> Total Weight 2 1 42 2.6% 3 52 1007 47.5% 0 0 60 2.4% 1 12 140 28.3% 2 0 65 3 100 9.1% 7 1414 89.9% 68 4 (P = 0.17); I^2 = 38% 1 449 10.1% 4 49 10.1% 5 (P = 0.26); I^2 = 23% df = 1 (P = 0.72), I^2 = 0% on bias) (performance bias)	Liberal Risk Ratio I Events Total Weight M-H, Random, 95% CI 2 1 42 2.6% 1.00 [0.06, 15.47] 3 52 1007 47.5% 0.83 [0.56, 1.22] 0 60 2.4% 11.00 [0.62, 194.63] 1 12 140 28.3% 1.70 [0.87, 3.32] 2 0 65 Not estimable 3 100 9.1% 1.67 [0.41, 6.79] 7 1414 89.9% 1.27 [0.72, 2.25] 68 - 4 (P = 0.17); P = 38% 0 4 49 10.1% 0.98 [0.26, 3.70] 4 4 10.1% 0.98 [0.26, 3.70] 4 4 10.1% 0.98 [0.26, 3.70] 4 4 10.1% 0.98 [0.26, 3.70] 4 5 (P = 0.26); P = 23% 118 [0.75, 1.85] 72 5 (P = 0.72), P = 0% 0 91 0.93 1.18 [0.75, 1.85] 0 <	Liberal Risk Ratio Risk Ratio $M-H$, Random, 95% CI 2 1 42 2.6% 1.00 [0.06, 15.47] 3 52 1007 47.5% 0.83 [0.56, 1.22] 3 0 60 2.4% 11.00 [0.62, 194.63] 12 140 28.3% 1.70 [0.87, 3.32] 2 0 65 Not estimable 3 3 100 9.1% 1.67 [0.41, 6.79] 1414 89.9% 1.27 [0.72, 2.25] 68 4 (P = 0.17); P = 38% 1.27 [0.72, 2.25] 68 4 (P = 0.17); P = 38% 1.27 [0.75, 1.85] 72 5 (P = 0.26); P = 23% 1.18 [0.75, 1.85] 72 5 (P = 0.26); P = 23% 1.18 [0.75, 1.85] 72 5 (P = 0.72), P = 0% 1.18 [0.75, 1.85] 72 5 (P = 0.72), P = 0% 1.18 [0.75, 1.85] 72 5 (P = 0.72), P = 0% 1.18 [0.75, 1.85]

(D) Blinding of outcome assessment (detection bias)
 (E) Incomplete outcome data (attrition bias)
 (F) Selective reporting (reporting bias)

(G) Other bias

Figure 13: Forest plot of outcome: 30-day mortality.

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.2.1 Orthopaedic								
Carson 1998 (older)	0	42	0	42		Not estimable		
Carson 2011 (older)	14	1003	20	999	85.5%	0.70 [0.35, 1.37]		
So-Osman 2013 (older)	0	299	3	204	7.3%	0.10 [0.01, 1.88]	← - – – – –	••••?••
Subtotal (95% CI)		1344		1245	92.8%	0.45 [0.09, 2.28]		
Total events	14		23					
Heterogeneity: Tau ² = 0.77;	Chi² = 1.0	85, df =	1 (P = 0.)	20); I ² =	39%			
Test for overall effect: Z = 0.	.97 (P = 0	.33)						
1.2.2 Other								
Markatou 2012 (vounger)	0	25	2	27	7.2%	0.22 (0.01, 4.28)		? • • ? • • •
Subtotal (95% CI)		25		27	7.2%	0.22 [0.01, 4.28]		
Total events	0		2					
Heterogeneity: Not applical	ble							
Test for overall effect: Z = 1.	.01 (P = 0	.31)						
Total (95% CI)		1360		1272	100.0%	0.55 [0.25, 1.25]		
Total events	1.4	1000	25		1001070	000 [0120, 1120]	-	
Hotorogonoity: Tou ² – 0.08:	⊂hi≅ – 2 :	13 df-	2/P = 0	34) - 12	6%			
Tect for overall effect: 7 = 1	A2 (P = 0)	16) 16)	2 (1 - 0.	547,1 -	0.0		0.01 0.1 1 10 100	
Test for subgroup difference	.+2 (i = 0. :es: Chi²=	:018 c	if = 1 (P =	: 0.67)	I² = 0%		Favours restrictive Favours liberal	
Risk of bias legend		0.10,0		0.017,				
(A) Random sequence der	neration (s	electio	n bias)					
(B) Allocation concealment	(B) Allocation concealment (selection bias)							
(C) Blinding of participants and personnel (performance bias)								
(D) Blinding of outcome as	sessmen	t (detec	tion bias)				
(E) Incomplete outcome da	ta (attritio	n bias)						

(F) Selective reporting (reporting bias) (G) Other bias

Figure 14: Forest plot of outcome: Hospital mortality.



(A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias)

(G) Other bias

Figure 15: Forest plot of outcome: 90-day mortality.

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio	Risk of Bias			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI	ABCDEFG			
1.4.1 Orthopaedic											
Carson 1998 (older)	19	42	41	42	8.5%	0.46 [0.33, 0.65]	-				
Carson 2011 (older)	415	1009	974	1007	9.7%	0.43 [0.39, 0.46]	•				
Fan 2014 (elderly)	41	96	52	96	8.7%	0.79 [0.59, 1.06]		• ? ? ? • • •			
Foss 2009 (elderly)	22	60	44	60	8.3%	0.50 [0.35, 0.72]	-	\bullet ? \bullet \bullet ? \bullet \bullet			
Gregersen 2015 (elderly)	109	144	140	140	9.7%	0.76 [0.69, 0.83]	•				
Grover 2006 (older)	37	109	46	109	8.4%	0.80 [0.57, 1.13]					
Lotke 1999 (older)	16	62	65	65	7.9%	0.26 [0.17, 0.40]	-				
Nielsen 2014 (older)	11	30	16	33	6.6%	0.76 [0.42, 1.36]					
Parker 2013 (older)	11	100	100	100	6.9%	0.11 [0.07, 0.20]	- -	? + ? ? ? + +			
So-Osman 2013 (older)	79	299	119	304	9.1%	0.67 [0.53, 0.85]					
Subtotal (95% CI)		1951		1956	83.9%	0.50 [0.38, 0.67]	•				
Total events	760		1597								
Heterogeneity: Tau ² = 0.18;	Chi ^z = 16	9.52, di	f= 9 (P <	0.0000	1); P = 959	6					
Test for overall effect: Z = 4.	77 (P ≤ 0.	00001)									
1.4.2 Other											
Bush 1997 (older)	40	50	43	49	9.4%	0.91 [0.77, 1.08]	+	?????			
Markatou 2012 (younger)	9	25	19	27	6.7%	0.51 [0.29, 0.91]		? 🖢 🛑 ? 🖶 🖶 🖢			
Subtotal (95% CI)		75		76	16.1%	0.72 [0.38, 1.37]	-				
Total events	49		62								
Heterogeneity: Tau ² = 0.17;	Chi² = 4.6	69, df=	1 (P = 0.0	03); I ² =	79%						
Test for overall effect: Z = 1.	01 (P = 0.	31)									
		2026		2022	400.08	0.53.50.44.0.601					
Total (95% CI)		2020		2032	100.0%	0.55 [0.41, 0.69]	•				
lotal events	809		1659		~ ~ ~ ~	~~~					
Heterogeneity: Tau* = 0.19;	Chi# = 21	2.06, di	r= 11 (P	< 0.000	01); F= 95)%	0.01 0.1 1 10 100				
Test for overall effect: $Z = 4$.	68 (P < 0.	00001)					Favours restrictive Favours liberal				
Test for subgroup difference	es: Chif=	1.02, 0	t= 1 (P =	0.31),	F= 2.3%						
Risk of bias legend											
(A) Random sequence generation (selection bias)											
(B) Allocation concealment	(selection	i bias)									
(C) Blinding of participants	and perso	onnel (p	erformar	nce bia	s)						
(D) Blinding of outcome ass	sessmen	t (detec	tion bias)							
(E) Incomplete outcome dat	to (ottritio)	hine)									

(E) Incomplete or

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 16: Forest plot of outcome: Participants exposed to blood transfusion.

	Res	trictiv	/e	Li	beral			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
1.5.1 Orthopaedic										
So-Osman 2013 (older) Subtotal (95% Cl)	0.78	1.4	299 299	0.86	1.6	304 304	81.8% 81.8%	-0.08 [-0.32, 0.16] - 0.08 [-0.32, 0.16]	•	•••?•••
Heterogeneity: Not applica	ble									
Test for overall effect: Z = 0).65 (P =	0.51))							
1.5.2 Other										
Bush 1997 (older)	2.8	3.1	50	3.7	3.5	49	18.2%	-0.90 [-2.20, 0.40]		?????+++
Subtotal (95% CI)			50			49	18.2%	-0.90 [-2.20, 0.40]		
Heterogeneity: Not applica	ble									
Test for overall effect: Z = 1	.35 (P =	0.18))							
Total (95% CI)			349			353	100.0%	-0.23 [-0.85, 0.39]	🕈	
Heterogeneity: Tau ² = 0.11	; Chi²=	1.47,	df=1 (P = 0.23	3); I 2 =	= 32%			-4 -2 0 2 4	-
Test for overall effect: Z = 0).72 (P =	0.47))						Favours restrictive Favours liberal	
Test for subgroup differen	ces: Chi	² = 1.4	47, df =	1 (P = 0	0.23),	l² = 32	.0%			
Risk of bias legend										
(A) Random sequence ge	neration	(sele	ection b	ias)						
(B) Allocation concealment	t (select	ion bi	as)							
(C) Blinding of participants	and pe	rsonn	el (per	formand	ce bia	as)				
(D) Blinding of outcome as	sessm	ent (d	etectior	n bias)						
(E) Incomplete outcome da	ata (attrit	ion bi	as)							
(F) Selective reporting (rep	orting bi	as)								
(G) Other bias										

Figure 17: Forest plot of outcome: Units of blood transfused.



(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias)

(F) Selective re (G) Other bias

Figure 18: Forest plot of outcome: Haemoglobin concentration.

	Restric	ctive	Liber	al		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.7.1 Orthopaedic								
Carson 2011 (older)	76	1009	52	1007	61.2%	1.46 [1.04, 2.05]	₩	
Lotke 1999 (older)	2	62	0	65	0.8%	5.24 [0.26, 106.98]		• ? ? • • • •
So-Osman 2013 (older) Subtotal (95% CI)	30	299 1370	27	304 1376	29.2%	1.13 [0.69, 1.85] 1.36 [1.03, 1.80]	-	
Total events	108	1010	79	1010	011170	nee [nee, nee]	•	
Heterogeneity: Tau ² = 0.00	l; Chi² = 1	.47, df=	= 2 (P = 0	.48); I²	= 0%			
Test for overall effect: Z = 2	2.15 (P = 0	0.03)						
1.7.2 Other								
Bush 1997 (older)	8	50	8	49	8.9%	0.98 [0.40, 2.40]		?????
Subtotal (95% CI)		50		49	8.9%	0.98 [0.40, 2.40]		
Total events	8		8					
Heterogeneity: Not applica	ible							
Test for overall effect: Z = 0).04 (P = (0.96)						
Total (95% CI)		1420		1425	100.0%	1.32 [1.01, 1.72]	•	
Total events	116		87					
Heterogeneity: Tau ² = 0.00	i; Chi ² = 1	.94, df=	= 3 (P = 0	.58); I²	= 0%			
Test for overall effect: Z = 2	2.04 (P = 0	0.04)					Eavours restrictive Eavours liberal	
Test for subgroup differen	ces: Chi²	= 0.46,	df=1 (P	= 0.50)	, I² = 0%			
Risk of bias legend								
(A) Random sequence ge	neration ((selection	on bias)					
(B) Allocation concealmen	t (selectio	on bias)) 		>			
(C) Blinding of participants	and pers	sonnei (periorma ction bio	ance bi	as)			
(E) Incomplete outcome da	ata (attriti	ni (uele on biae'		>)				
(E) Selective reporting (rep	ortina bia	us)	,					
(G) Other bias	orang bio	,						
·								

Figure 19: Forest plot of outcome: Cardiac events

	Restrictive Liberal					Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	ABCDEFG
1.8.1 Orthopaedic								
Carson 2011 (older)	38	1009	23	1007	87.0%	1.65 [0.99, 2.75]		
Fan 2014 (elderly)	0	94	1	92	2.2%	0.33 [0.01, 7.91]		
Foss 2009 (elderly)	1	60	0	60	2.2%	3.00 [0.12, 72.20]		
Grover 2006 (older)	0	109	1	109	2.2%	0.33 [0.01, 8.09]		
Lotke 1999 (older)	1	62	0	65	2.2%	3.14 [0.13, 75.72]		• • • • • •
Subtotal (95% CI)		1334		1333	96.0%	1.58 [0.97, 2.56]	-	
Total events	40		25					
Heterogeneity: Tau ² = I	0.00; Chi*	= 2.22,	df = 4 (P	= 0.70); I* = 0%			
l est for overall effect: 2	Z = 1.83 (F	' = 0.07)					
1.8.2 Other								
Bush 1997 (older)	1	50	2	49	4.0%	0.49 [0.05, 5.23]		?????+++
Subtotal (95% CI)		50		49	4.0%	0.49 [0.05, 5.23]		
Total events	1		2					
Heterogeneity: Not app	plicable							
Test for overall effect: 2	Z = 0.59 (F	° = 0.55)					
Total (95% CI)		1384		1382	100.0%	1.50 [0.93, 2.42]	•	
Total events	41		27					
Heterogeneity: Tau ² = I	0.00; Chi ^z	= 3.12,	df = 5 (P	= 0.68); I ² = 0%			
Test for overall effect: 2	Z = 1.68 (F	9 = 0.09) .				U.U1 U.1 1 1U 1UU Eavoure restrictive Eavoure liberal	
Test for subgroup diffe	erences: C	;hi ² = 0.	90, df = 1	(P = 0	.34), I ² = 0)%	Favouis lestilcuve Favouis liberal	
Risk of bias legend								
(A) Random sequence	e generati	on (sele	ection bia	as)				
(B) Allocation concealr	ment (sele	ection b	ias)					
(C) Blinding of particip	ants and p	personr	nel (perfo	rmanc	e bias)			
(D) Blinding of outcom	e assess	ment (d	letection	bias)				
(E) Incomplete outcom	ne data (at	trition b	ias)					
(F) Selective reporting	(reporting	bias)						
(G) Other bias								

Figure 20: Forest plot of outcome: Myocardial infarction

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	ABCDEFG
Carson 2011 (older)	35	1009	27	1007	90.7%	1.29 [0.79, 2.12]		
Fan 2014 (elderly)	1	94	1	96	2.9%	1.02 [0.06, 16.09]		••••
Foss 2009 (elderly)	2	60	0	60	2.4%	5.00 [0.25, 102.00]		\bullet ? \bullet \bullet ? \bullet \bullet
Parker 2013 (older)	1	100	2	100	3.9%	0.50 [0.05, 5.43]		? 🛨 ? ? ? 🛨 🛨
Total (95% CI) Total events	39	1263	30	1263	100.0%	1.28 [0.80, 2.05]	+	
Heterogeneity: Tau ² = 0 Test for overall effect: Z).00; Chi² (= 1.03 (F	= 1.41, P = 0.30	df = 3 (P)	= 0.70)); I ^z = 0%		0.01 0.1 1 10 100 Favours restrictive Favours liberal	

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 21: Forest plot of outcome: Congestive heart failure



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 22: Forest plot of outcome: Cerebrovascular accident (CVA) - stroke



Figure 23: Forest plot of outcome: Sepsis/bacteraemia

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Carson 1998 (older)	0	42	2	42	0.8%	0.20 [0.01, 4.04]	·	
Carson 2011 (older)	48	1009	60	1007	54.9%	0.80 [0.55, 1.16]		
Fan 2014 (elderly)	3	94	3	92	3.0%	0.98 [0.20, 4.72]		••••
Foss 2009 (elderly)	1	60	2	60	1.3%	0.50 [0.05, 5.37]		\bullet ? \bullet \bullet ? \bullet \bullet
Gregersen 2015 (elderly)	30	144	28	140	35.5%	1.04 [0.66, 1.65]	+	
Nielsen 2014 (older)	0	30	4	33	0.9%	0.12 [0.01, 2.17]	←	
Parker 2013 (older)	2	100	5	100	2.9%	0.40 [0.08, 2.01]		? + ? ? ? + +
So-Osman 2013 (older)	0	299	1	304	0.7%	0.34 [0.01, 8.29]		
Total (95% CI)		1778		1778	100.0%	0.83 [0.63, 1.09]	•	
Total events	84		105					
Heterogeneity: Tau ² = 0.00;	Chi ² = 4.9	94, df =	7 (P = 0.6	67); I ^z =	0%			
Test for overall effect: $Z = 1.3$	33 (P = 0.	18)					Favours restrictive Favours liberal	

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias) (E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

(u) Other bias

Figure 24: Forest plot of outcome: Pneumonia



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 25: Forest plot of outcome: Pneumonia or wound infection

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Carson 1998 (older)	1	42	0	42	5.2%	3.00 [0.13, 71.61]		
Carson 2011 (older)	8	1009	12	1007	66.0%	0.67 [0.27, 1.62]		
Fan 2014 (elderly)	1	94	2	92	9.2%	0.49 [0.05, 5.30]		••???
Foss 2009 (elderly)	1	60	2	60	9.3%	0.50 [0.05, 5.37]		• ? • • ? • •
Parker 2013 (older)	1	100	0	100	5.1%	3.00 [0.12, 72.77]		? 🛨 ? ? ? 🛨 🛨
So-Osman 2013 (older)	0	299	1	304	5.1%	0.34 [0.01, 8.29]		
Total (95% CI)		1604		1605	100.0%	0.71 [0.34, 1.47]	•	
Total events	12		17					
Heterogeneity: Tau ² = 0.00	i; Chi² = 1	.98, df=	= 5 (P = 0	.85); I²∶	= 0%			ų.
Test for overall effect: Z = 0).92 (P = I	D.36)					Eavours restrictive Eavours liberal	J

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 26: Forest plot of outcome: Thromboembolism

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Fan 2014 (elderly)	2	94	2	92	73.0%	0.98 [0.14, 6.80]		• ? ? ? • • •
Parker 2013 (older)	0	100	1	100	27.0%	0.33 [0.01, 8.09]		?•???••
Total (95% CI)		194		192	100.0%	0.73 [0.14, 3.84]		
Total events	2		3					
Heterogeneity: Tau ² =	0.00; Chi	² = 0.32	, df = 1 (F	P = 0.57	7); I 2 = 0%			1
Test for overall effect:	Z=0.37 (P = 0.7	1)				Favours restrictive Favours liberal	
Disk of his stand								

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 27: Forest plot of outcome: Renal failure



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 28: Forest plot of outcome: Mental confusion



(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 29: Forest plot of outcome: Inability to walk or death at 30 days



(G) Other bias

Figure 30: Forest plot of outcome: Inability to walk or death at 60 days



Figure 31: Forest plot of outcome: Lower extremity physical activities of daily living at 30 days



Figure 32: Forest plot of outcome: Lower extremity physical activities of daily living at 60 days

	Res	trictiv	/e	Li	beral			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	ABCDEFG
Carson 2011 (older)	3.9	0.4	450	3.9	0.5	437	100.0%	0.00 [-0.06, 0.06]		
Total (95% CI)			450			437	100.0%	0.00 [-0.06, 0.06]		
Heterogeneity: Not app	olicable									
Test for overall effect: 2	Z = 0.00 ((P = 1	.00)						Favours restrictive Favours liberal	
Risk of bias legend (A) Random sequence (B) Allocation concealr (C) Blinding of particip (D) Blinding of outcom (E) Incomplete outcom (F) Selective reporting (G) Other bias	e genera ment (se ants and e asses: ne data (a (reportin	tion (s lectio pers smen attritio g bias	selectic n bias) onnel (nt (detec n bias) s)	on bias) perform ction bia	iance is)	bias)				



	Res	trictiv	e	Li	bera	I		Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	ABCDEFG
Carson 2011 (older)	3.7	0.9	411	3.7	0.8	389	100.0%	0.00 [-0.12, 0.12]		
Total (95% CI) Heterogeneity: Not app Test for overall effect: 7	olicable 7 = 0 00 j	(P = 1	411			389	100.0%	0.00 [-0.12, 0.12]	-100 -50 0 50 100	I
	- 0.00	() — I	.00,						Favours restrictive Favours liberal	
Risk of bias legend										
(A) Random sequence	e genera	tion (s	selectio	on bias))					
(B) Allocation concealr	nent (se	lectio	n bias)							
(C) Blinding of participa	ants and	l pers	onnel (perform	nance	bias)				
(D) Blinding of outcom	e asses	smen	t (dete	ction bia	as)					
(E) Incomplete outcom	e data (a	attritio	n bias))						
(F) Selective reporting	(reportin	g bias	3)							
(G) Other bias										

Figure 34: Forest plot of outcome: Instrumental activities of daily living at 60 days



Figure 35: Forest plot of outcome: Energy/fatigue at 30 days

	Res	tricti	ve	Li	beral			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	ABCDEFG
Carson 2011 (older)	42.3	7.4	525	41.8	7.3	544	100.0%	0.50 [-0.38, 1.38]		
Total (95% CI)			525			544	100.0%	0.50 [-0.38, 1.38]		
Heterogeneity: Not ap	plicable									
Test for overall effect: 2	Z=1.11	(P = 0).27)						Favours restrictive Favours liberal	
Risk of bias legend										
(A) Random sequence	e genera	tion (selectio	on bias)						
(B) Allocation conceal	ment (se	lectio	n bias)							
(C) Blinding of particip	ants and	l pers	onnel (perform	ance	bias)				
(D) Blinding of outcom	e asses	smer	nt (dete	ction bia	as)					
(E) Incomplete outcom	ne data (a	attritio	n bias))						
(F) Selective reporting	(reportin	g bia	s)							
(C) Other biog		-								

(G) Other bias

Figure 36: Forest plot of outcome: Energy/fatigue at 60 days

	Rest	trictiv	e	Lil	beral	I		Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	ABCDEFG
Nielsen 2014 (older)	36	0	25	30	0	28		Not estimable		•••
Total (95% CI)			25			28		Not estimable		
Heterogeneity: Not app	licable									
Test for overall effect: N	lot applic	able							Favours restrictive Favours liberal	
Risk of bias legend										
(A) Random sequence	generat	ion (s	electio	n bias)						
(B) Allocation conceal	nent (sel	ectior	n bias)							
(C) Blinding of participa	ants and	perso	onnel (perform	ance	bias)				
(D) Blinding of outcome	e assess	ment	t (deteo	tion bia	s)					
(E) Incomplete outcom	e data (a	ttritior	n bias)							
(F) Selective reporting (reporting	g bias	;)							
(G) Other bias										

Figure 37: Forest plot of outcome: 'Timed up and go' test

Quality of evidence

Author,	Lack of	Lack of blinding	Incomplete	Selective	Other
Year	allocation	(performance bias)	accounting	outcome	limitat
	concealment and		of outcome	reporting	ions
	random		events	(reporting bias)	
	sequence		(attrition		
	generation		bias)		
Puch	(selection bias)	Darticipants and	No outcomo	Voc	No
1007			data appears	res	INO
1997	information	Uncloar both surgoons	to bo	No pro-	
	nrovided	and anaesthesiologists	complete	registration of	
	provided.	were informed of the	complete.	study protocol	
	Allocation	aroun of randomisation			
	concealment.	group of randomisation.			
	Unclear sealed	Outcome assessors:			
	envelopes were	Unclear no information			
	chosen at random	provided			
	for participant	provided.			
	assignment				
Carson.	Randomization:	Participants and	No. minimal	Yes	No
1998	No,	personnel:	missing data.		
	randomisation	Yes, no blinding of	5	No pre-	
	schedules were	participants or		registration of	
	stratified by	personnel.		study protocol	
	clinical site and				
	cardiovascular	Outcome assessors:			
	disease state. The	No, primary outcome of			
	randomisation	mortality allowed a			
	was designed in	judgement of low risk of			
	blocks of 2 to 8	bias. Although function			
	participants to	was assessed blinded,			
	avoid imbalance	the morbidity outcomes			
	within a site.	were not assessed			
		blindly.			
	Allocation				
	concealment:				
	No, study				
	personnel at the				
	clinical sites				
	randomly				
	assigned				
	participants by				
	contacting the				
	uata co-				
	contro's 24 hour				
	automated				
	telephone service				
Carson	Randomization:	Participants and	No. nearly	Νο	No
2011	No, data co-	personnel:	complete		
	ordinating centre	Yes, after random	reportina	Pre-registration of	
	staff prepared	allocation, clinical site	data for	study protocol @	

	randomisation schedules for each site using randomly ordered block sizes of 2, 4, 6, or 8. Allocation concealment: No, trial used an automated telephone randomisation system.	staff, clinicians, and participants were not blinded to treatment assignment. Outcome assessors: No, primary and secondary outcomes were assessed blinded to treatment assignment.	primary outcomes and most secondary outcomes.	ClinicalTrials.gov (NCT00071032)	
Fan, 2014	Randomization: No, trial used a random number table. Allocation concealment: Unclear, trial used a sealed envelope technique.	Participants and personnel: Unclear, no information provided. Outcome assessors: Unclear, no information provided.	No, low rate of missing data.	Yes No pre- registration of study protocol	No
Foss, 2009	Randomization: No, a computer- generated list was used. Allocation concealment: Unclear, sealed envelopes were used.	Participants and personnel: No, participants were blinded. Outcome assessors: No, physiotherapist who performed ambulation assessment was blinded	Unclear, 13 of 100 participants did not have ambulation assessment.	No Pre-registration of study protocol @ ClinicalTrials.gov (NCT00162617)	No
Gregersen , 2015	Randomization: No, random sequence generation was not specifically stated, but it was likely since a clinical trial support system was used. Allocation concealment: No, web-based randomisation system with allocation concealment was used.	Participants and personnel: Unclear, participants were blinded but not the clinicians. Outcome assessors: No, assessor was blinded.	No, outcome data appeared to be complete.	No Pre-registration of study protocol @ ClinicalTrials.gov (NCT01102010)	No

Grover, 2006	Randomization: No, random numbers table was used. Allocation concealment: Unclear, sealed envelopes were used.	Participants and personnel: Yes, anaesthetists and surgical team responsible for treatment were aware of allocation. Outcome assessors: No, outcome assessment was blind.	Unclear, of a recruited 260 participants, outcome data were presented for 218. The missing 42 participants did not have analysable tape recordings.	Yes No pre- registration of study protocol	No
Lotke, 1999	Randomization: No, trial used a computer random number generator. Allocation concealment: Unclear, no information provided.	Participants and personnel: Unclear, no information provided. Outcome assessors: No, assessments were made by a person blind to the group to which the participant was assigned.	No, outcome data appear to have been complete.	Yes No pre- registration of study protocol	No
Markatou, 2012	Randomization: Unclear, randomization was done by means of sealed opaque envelopes containing odd and even numbers. Allocation concealment: No, sealed opaque envelopes were used.	Participants and personnel: Yes, the surgical team and the anesthesiologist responsible for the patient were aware of the study protocol and group assignment. Outcome assessors: Unclear, no information provided.	No, no loss to follow-up reported.	Yes No pre- registration of study protocol	No
Nielsen, 2014	Randomization: No, a dedicated computer program (Idefix) was used after entering participants' baseline data. The allocation was written on a form, which was kept in the investigator's office, and the allocation could	Participants and personnel: Yes, the allocation and Hb during the testing period were concealed from the participants but the investigator, the staff in the operating room, and the staff at the ward could not be blinded. Outcome assessors:	No	No Pre-registration of study protocol @ ClinicalTrials.Gov (NCT00906295)	No

	only be accessed by the investigator in charge of administrating red blood cells. Allocation concealment: No, only 1 investigator had access to the programme. Investigators at the other hospital had to call this investigator to randomise.	Unclear, the physiotherapist testing the participant was blinded, but it was not stated who reviewed medical records for other outcomes.			
Parker, 2013	Randomization: Unclear, no information provided. Allocation concealment: No, trial used opaque numbered envelopes.	Participants and personnel: Unclear, no information provided. Outcome assessors: Unclear, no information provided.	Unclear, mobility score was missing for 94 of 200 participants.	No Pre-registration of study protocol (ISRCTN61328173)	No
So- Osman, 2013	Randomization: No, post-hoc analysis of an earlier randomized trial in which patients were stratified (using blocks of variable length) according to hospital, type of surgery and risk group. Randomization was achieved using a uniform distribution for a pregenerated list of sufficient length. Allocation concealment:	Participants and personnel: Yes, clinicians caring for the participants were aware of allocation status. There was no blinding information on participants. Outcome assessors: Unclear, no information provided.	No	Yes No pre- registration of study protocol	No

No, research		
nurse opened		
sealed opaque		
envelopes.		

Certainty of the body of evidence: see GRADE evidence tables

Conclusion	See Evidence-to-Decision template
	Articles
	Bush 1997
	Bush RL, Pevec WC, Holcroft JW. A prospective, randomized trial limiting
	perioperative red blood cell transfusions in vascular patients. Am J Surg 1997,
	174(2):143–148.
	Carson 1998
	Carson JL, Terrin ML, Barton FB, Aaron R, Greenburg AG, Heck DA, et al. A pilot
	randomized trial comparing symptomatic vs. hemoglobin-level-driven red blood cell
	transfusions following hip fracture. Transfusion 1998, 38(6): 522–529.
	Carson 2011
	Carson JL, Sieber F, Cook DR, Hoover DR, Noveck H, Chaitman BR, et al. Liberal
	versus restrictive blood transfusion strategy: 3-year survival and cause of death
	results from the FOCUS randomised controlled trial. Lancet 2015, 385(99/4):1183–9.
	^Carson JL, TerriniviL, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, et al.
	2011 265(26):2452–2462
	2011, 303(20).2433-2402. Gruber-Baldini Al, Marcantonio E, Onwig D, Magaziner I, Terrin M, Barr E, et al.
	Delirium outcomes in a randomized trial of blood transfusion thresholds in
	hospitalized older adults with hip fracture 1 Am Geriatr Soc 2013 61(8):1286–95
	Fan 2014
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	*Indicates the major publication for the study
Evidence used for	Consensus meeting PBM
Project	РВМ
Reviewer(s)	Anne-Catherine Vanhove
PICO 6: RBC transfusion triggers in adult acute (gastrointestinal) bleeding patients

Overview evidence table GRADE software (PICO 6)

	Certainty assessment				Nº of patients		Effect					
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7-8 g/dL)	more liberal RBC transfusion triggers (Hb <9-10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
30-day r	mortality											
3	randomised trials	serious ^a	not serious	not serious	serious ^b	none	33/699 (4.7%)	61/823 (7.4%)	RR 0.65 (0.43 to 0.97)	26 fewer per 1.000 (from 2 fewer to 42 fewer)	⊕⊕⊖⊖ LOW	CRITICAL
Hospital	mortality										·	
1	randomised trials	serious ^a	not serious	serious ^c	serious ^b	none	0/26 (0.0%)	2/24 (8.3%)	RR 0.19 (0.01 to 3.67)	68 fewer per 1.000 (from 82 fewer to 222 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Patients	exposed to R	BC transfu	sion					·				
4	randomised trials	serious ^a	not serious	not serious	not serious	none	365/885 (41.2%)	665/1012 (65.7%)	RR 0.55 (0.41 to 0.75)	296 fewer per 1.000 (from 164 fewer to 388 fewer)	⊕⊕⊕⊖ MODERATE	IMPORTANT
RBC unit	ts transfused											

	Certainty assessment					Nº of patients		Effect				
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7-8 g/dL)	more liberal RBC transfusion triggers (Hb <9-10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
3	randomised trials	serious ^a	not serious	not serious	not serious	none	873	1002	_	MD 1.79 units lower (3 lower to 0.58 lower)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Haemog	lobin concen	tration										
3	randomised trials	serious ^a	not serious	not serious	serious ^b	none	647	725	-	MD 0.89 lower (1.01 lower to 0.77 lower)	⊕⊕⊖⊖ LOW	IMPORTANT
Myocard	lial infarction	ł							ł			
1	randomised trials	serious ^d	not serious	not serious	serious ^b	none	8/444 (1.8%)	13/445 (2.9%)	RR 0.62 (0.26 to 1.47)	11 fewer per 1.000 (from 14 more to 22 fewer)	⊕⊕⊖⊖ LOW	CRITICAL
Congest	ive heart failu	re			·							
1	randomised trials	serious ^d	not serious	not serious	serious ^b	none	12/444 (2.7%)	21/445 (4.7%)	RR 0.57 (0.29 to 1.15)	20 fewer per 1.000 (from 7 more to 34 fewer)	⊕⊕⊖⊖ LOW	IMPORTANT
CVA-stro	oke											

	Certainty assessment			Nº of patients		Effect						
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7-8 g/dL)	more liberal RBC transfusion triggers (Hb <9-10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	randomised trials	serious ^d	not serious	not serious	serious ^b	none	3/444 (0.7%)	6/445 (1.3%)	RR 0.50 (0.13 to 1.99)	7 fewer per 1.000 (from 12 fewer to 13 more)	⊕⊕⊖⊖ LOW	CRITICAL
Rebleed	ing						·					
3	randomised trials	serious ^a	not serious	not serious	serious ^b	none	55/727 (7.6%)	104/852 (12.2%)	RR 0.54 (0.31 to 1.99)	56 fewer per 1.000 (from 84 fewer to 121 more)	⊕⊕⊖⊖ LOW	IMPORTANT
Pneumo	nia	1	<u> </u>	I	·		·		1	1	1	L
1	randomised trials	serious ^d	not serious	not serious	very serious	none	43/444 (9.7%)	48/445 (10.8%)	RR 0.90 (0.61 to 1.33)	11 fewer per 1.000 (from 36 more to 42 fewer)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
Pneumo	nia or wound	infection			·		·					
2	randomised trials	serious ^a	not serious	not serious	serious ^b	none	186/701 (26.5%)	227/828 (27.4%)	RR 0.96 (0.79 to 1.17)	11 fewer per 1.000 (from 47 more to 58 fewer)	⊕⊕⊖⊖ LOW	IMPORTANT
Renal fa	ilure											

			Certainty as	sessment			Nº of p	oatients	Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7-8 g/dL)	more liberal RBC transfusion triggers (Hb <9-10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	randomised trials	serious ^d	not serious	not serious	serious ^b	none	78/444 (17.6%)	97/445 (21.8%)	RR 0.81 (0.62 to 1.05)	41 fewer per 1.000 (from 11 more to 83 fewer)	⊕⊕⊖⊖ LOW	CRITICAL
Function	Function and fatigue (EQ-5D)											
1	randomised trials	serious ^a	not serious	not serious	serious ^b	none	176	139	-	MD 0.07 points higher (0 to 0.14 higher)	⊕⊕⊖⊖ LOW	IMPORTANT
30-day r	nortality (sub	group: pati	ents with cirrhos	is)								
1	randomised trials	not serious	not serious	not serious	very serious	none	15/139 (10.8%)	25/138 (18.1%)	RR 0.60 (0.33 to 1.08)	72 fewer per 1.000 (from 14 more to 121 fewer)	⊕⊕⊖⊖ LOW	CRITICAL
Rebleed	ing (subgroup	o: patients v	with cirrhosis)									
1	randomised trials	not serious	not serious	not serious	very serious	none	16/139 (11.5%)	31/138 (22.5%)	RR 0.51 (0.29 to 0.89)	110 fewer per 1.000 (from 25 fewer to 159 fewer)	⊕⊕⊖⊖ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; a. see risk of bias items in forest plots or quality of evidence table; b. Limited sample size, low number of events and/or large variability of the results; c. study from the 1980s, not generalizible to the 2018 context; d. Detection bias (outcome assessors were not blinded)

Detailed evidence summary (PICO 6)

Торіс	Patient Blood Management
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers
Intervention	Restrictive RBC transfusion triggers
Question (PICO)	In patients with an acute gastrointestinal bleeding (Population), is the use of a restrictive transfusion threshold (Intervention) not inferior to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusion threshold (Comparison)?
Search Strategy	 The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to: Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017) Identify observational studies in case no experimental studies were available.
	Databases The Cochrane Library (systematic reviews and controlled trials) using the following search strategy (from May 2016 until June 2017): #1 MeSH descriptor: [Blood Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST, Trends - TD] #2 MeSH descriptor: [Erythrocyte Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST] #3 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) near/5 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or strateg* or regimen* or criteri* or standard* or management or program*)) #4 ((h?emoglobin or h?ematocrit or HB or HCT) near/5 (polic* or practic* or protocol* or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or standard*)) #5 (blood near/3 (management or program*)) #6 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) and (critical* or intensive* or h?emorrhag* or bleed*)):ti #7 #1 or #2 or #3 or #4 or #5 or #6
	MEDLINE (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy (from 27th May 2016 until 30th June 2017): #1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI])) #2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR standard*[TI]) #3 (blood[TI] AND (management[TI] OR program*[TI]))

	#4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR
	PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR
	haemorrhage*[TI] OR bleed*[TI]))
	#5 #1 OR #2 OR #3 OR #4
	Embase (via Embase.com interface) using the following search strategy (from
	27 th May 2016 until 30 th June 2017):
	#1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND
	(trigger*:ti OR threshold:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR
	angressive*ti OB concernative*ti OB prophyloctic*ti OB limit*ti OB protocol*ti
	regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti))
	#2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR
	HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR
	threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR
	standard*:ti))
	#3 (blood:ti AND (management:ti OR program*:ti))
	#4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and
	(critical*ti OR intensive*ti OR hemorrhag*ti OR haemorrhage*ti OR bleed*ti))
	Transfusion ovidence library (from 2016 until 2017)
	Pad Calls AND (triager OB threshold OB target OB restrict OB restrictive OB
	the real OD expressive OD expressively OD expressively OD expressive OD expressively OD expres
	liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit
	OR limits OR protocol OR policy OR policies OR practice OR indicator OR
	strategy OR strategies OR regimen OR criteria OR standard OR management
	OR program OR programme) OR Red Cells AND title:(critical OR critically OR
	intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging
	OR haemorrhaging OR bleed OR bleeding)
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson
	2018)
	26/01/2018 (update after latest search date Carson review)
In/Exclusion criteria	Population: Included: patients with an acute gastrointestinal bleeding.
	Intervention: the use of a restrictive transfusion threshold as a mean of
	quiding allogeneic or autologous RBC transfusion. A restrictive transfusion
	threshold most often refers to administration of blood transfusion when the
	happeneolobin loval falls balow 7 a/dL to 8 a/dL
	Thernoglobilitievel fails below 7 g/ul to 8 g/ul.
	Comparison the use of a liberal transfusion threshold as a mean of quiding
	Comparison: the use of a liberal transitision threshold as a filean of guiding
	allogeneic or autologous RBC transfusion. A liberal transfusion threshold most
	often refers to administration of blood transfusion when the haemoglobin level
	falls below 9 g/dL to 10 g/dL
	Outcomes: <i>Primary</i> : Mortality (30-day mortality or in-hospital mortality, during
	hospital admission, at 90 days or long term) or other clinical outcomes
	including outcomes related to RBC transfusion use (i.e. proportion of
	participants exposed to transfusion, participants exposed to allogeneic or
	autologous transfusion, units of blood transfused (in those receiving any
	transfusion)) and Secondary: Morbidity-related outcomes that occurred during
	hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction
	congestive heart failure stroke renal injury pneumonia sentic shock
	congestive neure failure, stroke, renar injury, preamona, septie snock,
	rebleeding, infection, and fatigue

1	
	Study design: The following study designs were included: 1) (cluster) randomized controlled trials included in the Cochrane review by Carson et al (May 2016) or other systematic reviews identified in the update and 2) (cluster) randomized controlled trials identified in the update. To examine the evidence for the effect of transfusion threshold on the use of RBC transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or haematocrit level (without hemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic or autologous red blood cells, or both, at higher haemoglobin or haematocrit levels (transfusion threshold) than the intervention group, or transfused in accordance with current transfusion practices, which may not have included a well-defined transfusion threshold, but involved liberal rather than restrictive
	well-defined transfusion threshold, but involved liberal rather than restrictive transfusion practices. We excluded trials that were not designed to include any clinical outcomes

Author, year, Country	Study design	Population	Comparison	Study funding, financial COI and remarks
Blair, 1986, UK	Randomised controlled trial	50 consecutive participants with severe upper gastrointestinal haemorrhage (clinical specialty subgroup (Carson, 2016): acute blood loss/trauma) Restrictive group: n=26, male/female ratio=2:1, age=60±17.8 years Liberal group: n=24, male/female ratio=2:1, age=64±17.6 years	Restrictive group (intervention): not transfused unless the Hb <8.0 g/dL or shock persisted after initial resuscitation with Haemaccel Liberal group (control): at least 2 units of red blood cells during their first 24 hours in hospital Transfusion: units of blood	Financial assistance from Crawley and Jersey Research Fund. Identified from the systematic review of Carson et al., 2016.
Fisher, 1956, United Kingdom	Experimental: randomised controlled trial	 22 trauma participants were randomly allocated to 1 of 2 groups: Liberal group: n = 10 Restrictive group: n = 12 NB: no demographic data were reported. 	Restrictive RBC transfusion trigger: an attempt was made to leave the RBC volume at the end of resuscitation at 70% to 80% of normal. Liberal RBC transfusion trigger: the aim was to achieve 100% or more of the RBC volume at	The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Characteristics of included studies

			the end of resuscitation.	
Jairath, 2015, UK	Cluster- randomised controlled trial	936 participants with upper gastrointestinal bleeding in 6 hospitals (clinical specialty subgroup (Carson, 2016): acute blood loss/trauma) Restrictive group: n=403, 244 males and 159 females, age=58.0±20.3 years Liberal group: n=533, 322 males and 211 females, age=60.4±20.0 years	Restrictive group (intervention): transfusion if Hb <8 g/dL, post-transfusion target of 8.1–10.0 g/dL Liberal group (control): transfusion if Hb <10 g/dL threshold, post- transfusion Hb target of 10.1–12.0 g/dL Transfusion: RBC tranfusion	Government funded and run clinical trial. Identified from the systematic review of Carson et al., 2016.
Villanueva, 2013, Spain	Randomised controlled trial	889 participants with haematemesis and/or melena due to upper GI bleeding (clinical specialty subgroup (Carson, 2016): acute blood loss/trauma) Restrictive group: n=444, 291 males and 154 females, age=66±15 years Liberal group: n=445, 314 males and 130 females, age=64±16 years	Restrictive group (intervention): transfusion if Hb <7 g/dL target range for the post- transfusion Hb level of 7- 9 g/dL Liberal group (control): transfusion if Hb <9 g/dL target range for the post- transfusion Hb level of 9-11 g/dL Transfusion: prestorage leukocyte reduced units of red cells	Research funded by foundation connected to hospital. One author divulged receiving consulting fees from industry. Identified from the systematic review of Carson et al., 2016.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Primary outcome	25			
30-day mortality	Restrictive vs liberal transfusion threshold	Statistically significant: 33/699 vs 61/823 § RR: 0.65, 95%CI [0.43;0.97] (p=0.037) (Figure 38) In favour of restrictive transfusion threshold	3, 699 vs 823	Blair, 1986; Jairath, 2015; Villanueva, 2013

30-day mortality (subgroup: patients with cirrhosis)		Not Statistically significant: 15/139 vs 25/138 § RR: 0.60, 95%CI [0.33;1.08] (p=0.09)	1, 139 vs 138	Villanueva, 2013
Hospital mortality		Not statistically significant: 0/26 vs 2/24 § RR: 0.19, 95%CI [0.01;3.67] ¥ (p=0.27)* (Figure 39)	1, 26 vs 24	Blair, 1996
Participants exposed to blood transfusion		<u>Statistically significant:</u> 365/885 vs 665/1012 RR: 0.58, 95%CI [0.45;0.75] (p<0.0001)** (Figure 40) In favour of restrictive transfusion threshold	4, 885 vs 1012	Blair, 1986; Fisher 1956; Jairath, 2015; Villanueva, 2013
Units of blood transfused		Statistically significant: MD: -1.79; 95%CI [-3.00; -0.58] (p=0.004)** (Figure 41) In favour of restrictive transfusion threshold		
Secondary outcor	nes			
Haemoglobin concentration	Restrictive vs liberal transfusion threshold	<u>Statistically significant:</u> MD: -0.89; 95%CI [-1.01;-0.77] (p<0.00001)** (Figure 42)	3, 647 vs 725	Blair, 1986; Jairath, 2015; Villanueva, 2013
Myocardial infarction		Not statistically significant: 8/444 vs 13/445 § RR: 0.62, 95%CI [0.26;1.47] ¥ (p=0.28)* (Figure 43)	1, 444 vs 445	Villanueva, 2013
Congestive heart failure		Not statistically significant: 12/444 vs 21/445 § RR: 0.57, 95%CI [0.29;1.15] ¥ (p=0.12)* (Figure 44)		
Cerebrovascular accident (CVA) - stroke		Not statistically significant: 3/444 vs 6/445 § RR: 0.50, 95%CI [0.13;1.99] ¥ (p=0.33)* (Figure 45)		
Rebleeding		Statistically significant: 55/727 vs 104/852 § RR: 0.54, 95%CI [0.31;0.93] (p=0.03)** (Figure 46) In favour of restrictive transfusion threshold	3, 727 vs 852	Blair, 1986; Jairath, 2015; Villanueva, 2013
Rebleeding (subgroup: patients with cirrhosis)		Statistically significant: 16/139 vs 31/138 § RR: 0.51, 95%CI [0.29;0.89] (p=0.02) In favour of restrictive transfusion threshold	1, 139 vs 138	Villanueva 2013
Pneumonia		Not statistically significant: 43/444 vs 48/445 § RR: 0.90, 95%CI [0.61;1.33] ¥ (p=0.59)* (Figure 47)	1, 444 vs 445	Villanueva, 2013

Pneumonia or	Not statistically significant:	2, 701 vs 828	Jairath,
wound infection	186/701 vs 227/828		2015;
	RR: 0.96, 95%CI [0.79;1.17]		Villanueva,
	(p=0.69)** (Figure 48)		2013
Renal failure	Not statistically significant:	1, 444 vs 445	Villanueva,
	78/444 vs 97/445 §		2013
	RR: 0.81, 95%CI [0.62;1.05] ¥		
	(p=0.11)* (Figure 49)		
Function and	Statistically significant:	1, 176 vs 139 §	Jairath, 2015
fatigue (EuroQol	0.76±0.27 vs 0.69±0.32		
(EQ-5D))	MD: 0.07, 95%CI [0.00;0.14]		
	(p=0.04)* (Figure 50)		
	In favour of restrictive		
	transfusion threshold		

Mean ± SD (unless otherwise indicated)

CI: confidence interval, RR: relative risk, MD: mean difference

* Calculations (p-value) done by the reviewer(s) using Review Manager software

** Calculations (RR or MD, 95%CI and p-value) done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Forest plots

	Restric	tive	Liberal			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Blair 1986	0	26	2	24	1.9%	0.19 [0.01, 3.67]	←	?????+
Jairath 2015	14	257	25	382	41.6%	0.83 [0.44, 1.57]		••••?•
Villanueva 2013	19	416	34	417	56.5%	0.56 [0.32, 0.97]		$\bullet \bullet ? \bullet \bullet \bullet \bullet$
Total (95% CI)		699		823	100.0%	0.65 [0.43, 0.97]	•	
Total events	33		61					
Heterogeneity: Tau ² =	: 0.00; Chi	r = 1.55	i, df = 2 (i	P = 0.46	6); I ² = 0%	1		1
Test for overall effect:	Z=2.08 (P = 0.0	4)				Favours restrictive Favours liberal	
Dick of bice learned								

Risk of blas legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias) (E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 38: Forest plot of outcome: 30-day mortality.



(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 39: Forest plot of outcome: Hospital mortality.

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	ABCDEFG
Blair 1986	5	26	24	24	8.8%	0.21 [0.10, 0.44]		????•••
Fisher 1956	8	12	10	10	19.1%	0.68 [0.45, 1.04]		? 🗣 ? ? 🗣 🖶 🗣
Jairath 2015	133	403	247	533	34.2%	0.71 [0.60, 0.84]	-	•••?•?•
Villanueva 2013	219	444	384	445	37.8%	0.57 [0.52, 0.63]	•	$\bullet \bullet ? \bullet \bullet \bullet \bullet$
Total (95% CI)		885		1012	100.0%	0.58 [0.45, 0.75]	•	
Total events	365		665					
Heterogeneity: Tau ² =	= 0.04; Chi	≈ =13.0)9, df = 3	(P = 0.0	004); I ^z = 7	'7%		<u>_</u>
Test for overall effect	Z= 4.20 (P < 0.0	001)				Favours restrictive Favours liberal	UU
Risk of bias legend			1					

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 40: Forest plot of outcome: Participants exposed to blood transfusion.



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 41: Forest plot of outcome: Units of blood transfused.



(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 42: Forest plot of outcome: Haemoglobin concentration.

	Restric	tive	Liberal Risk Ratio Risk Ratio			Risk of Bias		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Villanueva 2013	8	444	13	445	100.0%	0.62 [0.26, 1.47]		
Total (95% CI)		444		445	100.0%	0.62 [0.26, 1.47]		
Total events Heterogeneity: Not ap Test for overall effect:	8 plicable Z = 1.09 ((P = 0.2	13 8)				0.01 0.1 1 10 1 Favours restrictive Favours liberal	
<u>Risk of bias legend</u>								

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 43: Forest plot outcome: Myocardial infarction.



(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 44: Forest plot of outcome: Congestive heart failure.



(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 45: Forest plot of outcome: Cerebrovascular accident (CVA) - Stroke.

	Restrictive Liberal					Diale Datia	Biok Batio	Dials of Diag			
	Restric	uve	Liber	al		RISK RAUO	RISK RAUO	RISK OF BIAS			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	ABCDEFG			
Blair 1986	1	26	9	24	6.9%	0.10 [0.01, 0.75]		????? ++ +			
Jairath 2015	9	257	24	383	32.1%	0.56 [0.26, 1.18]		••••?•?•			
Villanueva 2013	45	444	71	445	61.0%	0.64 [0.45, 0.90]		$\bullet \bullet ? \bullet \bullet \bullet \bullet$			
Total (95% CI)		727		852	100.0%	0.54 [0.31, 0.93]	•				
Total events	55		104								
Heterogeneity: Tau ² =	= 0.10; Chi	² = 3.22	2, df = 2 (F	P = 0.21	0); I ² = 38 ⁴	%		- H			
Test for overall effect:	Z= 2.23 (P = 0.0	3)				Favours restrictive Favours liberal	U			
Risk of bias legend											
(A) Random sequen	(A) Random sequence generation (selection bias)										
(B) Allocation concea	Iment (sel	ection	bias)								

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 46: Forest plot of outcome: Rebleeding.



(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 47: Forest plot of outcome: Pneumonia.



(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 48: Forest plot of outcome: Pneumonia or wound infection.

	Restrictive Liberal			al		Risk Ratio	Risk Ratio	Risk of Bias			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG			
Villanueva 2013	78	444	97	445	100.0%	0.81 [0.62, 1.05]					
Total (95% CI)		444		445	100.0%	0.81 [0.62, 1.05]	•				
Total events	78		97								
Heterogeneity: Not ap	plicable							100			
Test for overall effect:	Z=1.58 (P = 0.1	1)				Favours restrictive Favours liber	al			
Risk of bias legend											
(A) Random sequend	(A) Random sequence generation (selection bias)										

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 49: Forest plot of outcome: Renal failure.



(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 50: Forest plot of outcome: Function and fatigue - EuroQol (EQ-5D).

Quality of evidence

Author, Year	Lack of allocation concealment and random sequence generation (selection bias)	Lack of blinding (performance bias)	Incomplete accounting of outcome events (attrition bias)	Selective outcome reporting (reporting bias)	Other limitations
Blair, 1986,	Randomization: Unclear, no information. Allocation concealment: Unclear, no information.	Participants and personnel: Unclear, no information. Outcome assessors: Unclear, no information.	No, no missing data.	No	No
Jairath, 2015,	Randomization: No, hospital was randomized, not the individual participant. Allocation concealment: Yes, hospital was randomized, so everyone knew which arm the participants were in.	Participants and personnel: Yes, trial was not blinded. Outcome assessors: Unclear, mortality allows low risk of bias but assessment of other clinical outcomes was unblended.	Yes, high percentage of missing data.	Unclear, no reporting bias was apparent.	Yes, differential enrolment by treatment arms.
Villanueva , 2013	Randomization: No, random sequence generation by computer. Allocation concealment: No, use of sealed consecutively numbered, opaque envelopes.	Participants and personnel: Unclear, clinicians and participants were not blinded. Outcome assessors: No, mortality was primary outcome. Assessors of other outcomes were not documented to be blinded.	No, good follow-up.	No, complete reporting.	No

Certainty of the body of evidence: see GRADE evidence tables

Conclusion	See Evidence-to-Decision template							
	Articles							
	Blair 1986							
	Blair SD, Janvrin SB, McCollum CN, Greenhalgh RM. Effect of early blood transfusion							
	on gastrointestinal haemorrhage. Br J Surg 1986, 73(10):783–5.							
Reference(s)	Jairath 2015							
	Jairath V, Kahan BC, Gray A, Doré CJ, Mora A, James MW, et al. Restrictive versus							
	liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a							
	pragmatic, open-label, cluster randomised feasibility trial. Lancet 2015,							
	386(9989):137–44.							

	Villanueva 2013
	Colomo A, Hernandez-Gea V, Muniz-Diaz E, Madoz P, Aracil C, Alvarez-Urturi C.
	Transfusion strategies in patients with cirrhosis and acute gastrointestinal bleeding.
	Hepatology 2008, 48(4(Suppl)):413A.
	*Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, et al.
	Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013,
	368(1):11–21.
	Systematic reviews
	Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC.
	Transfusion thresholds and other strategies for guiding allogeneic red blood cell
	transfusion. Cochrane Database Syst Rev 2016, 10:CD002042.
	Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ,
	Goodman SG, Rao SV, Doree C, Hebert PC. Clinical trials evaluating red blood cell
	transfusion thresholds: an updated systematic review and with additional focus on
	patients with cardiovascular disease. In peer-review [February 2018].
	* Indicates the major publication for the study
Evidence used for	Consensus meeting PBM
Project	PBM
Reviewer(s)	Anne-Catherine Vanhove

PICO 7: RBC transfusion triggers in adult patients with symptomatic/acute coronary heart disease

Overview evidence table GRADE software (PICO 7)

			Certainty as	sessment			Nº of p	oatients	Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <8 g/dL)	more liberal RBC transfusion triggers (Hb <10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
30-day r	nortality											
2	randomised trials	not serious	not serious	not serious	very serious ª	none	9/78 (11.5%)	0.0%	RR 3.88 (0.83 to 18.13)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕⊕⊖⊖ LOW	CRITICAL
Hospital	mortality											
1	randomised trials	not serious	not serious	not serious	very serious ^a	none	2/24 (8.3%)	1/21 (4.8%)	RR 1.75 (0.17 to 17.95)	36 more per 1.000 (from 40 fewer to 807 more)	⊕⊕⊖⊖ LOW	CRITICAL
Participa	ints exposed t	to RBC trar	sfusion		·	·						
2	randomised trials	not serious	not serious ^b	not serious	very serious ª	none	28/79 (35.4%)	76/76 (100.0%)	RR 0.40 (0.19 to 0.82)	600 fewer per 1.000 (from 180 fewer to 810 fewer)	⊕⊕⊖⊖ LOW	IMPORTANT
RBC unit	s transfused											

			Certainty as	sessment			Nº of p	oatients	Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <8 g/dL)	more liberal RBC transfusion triggers (Hb <10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	randomised trials	not serious	not serious	not serious	very serious ª	none	24	21	-	MD 0.9 units lower (1.87 lower to 0.07 higher)	⊕⊕⊖⊖ LOW	IMPORTANT
Haemog	Haemoglobin concentration											
1	randomised trials	not serious	not serious	not serious	very serious ^a	none	55	55	-	MD 1.52 lower (1.79 lower to 1.25 lower)	⊕⊕⊖⊖ LOW	IMPORTANT
Myocard	dial infarction				·		·	·				
2	randomised trials	not serious	not serious	not serious	very serious ª	none	7/77 (9.1%)	6/74 (8.1%)	RR 1.20 (0.43 to 3.34)	16 more per 1.000 (from 46 fewer to 190 more)	⊕⊕⊖⊖ LOW	CRITICAL
Congest	ive heart failu	re										
2	randomised trials	not serious	serious ^c	not serious	very serious ª	none	9/78 (11.5%)	10/76 (13.2%)	RR 0.87 (0.06 to 13.46)	17 fewer per 1.000 (from 124 fewer to 1.000 more)	⊕○○○ VERY LOW	CRITICAL
CVA-stro	oke											

			Certainty as	sessment			Nº of p	oatients	Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <8 g/dL)	more liberal RBC transfusion triggers (Hb <10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	randomised trials	not serious	not serious	not serious	very serious ª	none	0/54 (0.0%)	1/55 (1.8%)	RR 0.34 (0.01 to 8.15)	12 fewer per 1.000 (from 18 fewer to 130 more)	⊕⊕⊖⊖ LOW	CRITICAL
Sepsis-b	Sepsis-bacteraemia											
1	randomised trials	not serious	not serious	not serious	very serious ª	none	0/54 (0.0%)	0/55 (0.0%)	not estimable		⊕⊕⊖⊖ LOW	IMPORTANT
Pneumo	nia											
1	randomised trials	not serious	not serious	not serious	very serious ª	none	2/54 (3.7%)	0/55 (0.0%)	RR 5.09 (0.25 to 103.64)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕⊕⊖⊖ LOW	IMPORTANT
Pneumo	Pneumonia or wound infection											
1	randomised trials	not serious	not serious	not serious	very serious ª	none	2/54 (3.7%)	0/55 (0.0%)	RR 5.09 (0.25 to 103.64)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕⊕⊖⊖ LOW	IMPORTANT
Thrombo	pembolism											

			Certainty as	sessment			Nº of patients		Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <8 g/dL)	more liberal RBC transfusion triggers (Hb <10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	randomised trials	not serious	not serious	not serious	very serious ª	none	0/54 (0.0%)	1/55 (1.8%)	RR 0.34 (0.01 to 8.15)	12 fewer per 1.000 (from 18 fewer to 130 more)	⊕⊕⊖⊖ LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

a. Low number of events, limited sample size and/or large variability in results

b. Decision not to downgrade by reviewer(s) although point estimates vary, CIs show minimal overlap, test for heterogeneity shows a low p-value and I2>75%. This large inconsistency or variability is, however, not considered important as the direction of effect is the same for all studies which is most relevant for this outcome.
c. Decision to downgrade by reviewer(s) since point estimates vary, CIs show minimal overlap, test for heterogeneity shows a low p-value and I2>75%. Moreover, the point estimates point to different directions of effect.

Detailed evidence summary (PICO 7)

Торіс	Patient Blood Management
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers
Intervention	Restrictive RBC transfusion triggers
Question (PICO)	In patients with symptomatic coronary heart disease (Population), is the use of a restrictive transfusion threshold (Intervention) effective to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusion threshold (Comparison)?
Search Strategy	 The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to: Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017) Identify observational studies in case no experimental studies were available.
	Databases The Cochrane Library (systematic reviews and controlled trials) using the following search strategy (from May 2016 until June 2017): #1 MeSH descriptor: [Blood Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST, Trends - TD] #2 MeSH descriptor: [Erythrocyte Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST] #3 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) near/5 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or strateg* or regimen* or criteri* or standard* or management or program*)) #4 ((h?emoglobin or h?ematocrit or HB or HCT) near/5 (polic* or practic* or protocol* or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or standard*)) #5 (blood near/3 (management or program*)) #6 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) and (critical* or intensive* or h?emorrhag* or bleed*)):ti #7 #1 or #2 or #3 or #4 or #5 or #6
	MEDLINE (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy (from 27th May 2016 until 30th June 2017): #1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI])) #2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR standard*[TI]) #3 (blood[TI] AND (management[TI] OR program*[TI]))

	#4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR
	PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR
	haemorrhage*[TI] OR bleed*[TI]))
	#5 #1 OR #2 OR #3 OR #4
	Embase (via Embase.com interface) using the following search strategy (from
	27 th May 2016 until 30 th June 2017):
	#1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND
	(trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR
	aggressive*ti OP concentrative*ti OP prophyloctic*ti OP limit*ti OP protocol*ti
	Aggressive OK conservative OK propriyactic OK innit OK protocor
	regimen^:ti OR criteri^:ti OR standard^:ti OR management:ti OR program^:ti))
	#2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR
	HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR
	threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR
	standard*:ti))
	#3 (blood:ti AND (management:ti OR program*:ti))
	#4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and
	(critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti))
	#5 #1 OR #2 OR #3 OR #4
	Transfusion evidence library (from 2016 until 2017)
	Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR
	liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit
	OR limits OR protocol OR policy OR policies OR practice OR indicator OR
	strategy OR strategies OR regimen OR criteria OR standard OR management
	OR program OR programme) OR Red Cells AND title:(critical OR critically OR
	intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging
	OD have a when size a OD have d OD have dive a)
	OR naemorrhaging OR bleed OR bleeding)
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018)
Search date	OR haemorrhaging OR bleed OR bleeding)13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson2018)26/01/2018 (update after latest search date Carson review)
Search date In/Exclusion criteria	OR haemorrhaging OR bleed OR bleeding) 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease.
Search date In/Exclusion criteria	OR haemorrhaging OR bleed OR bleeding) 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease.
Search date In/Exclusion criteria	OR haemorrhaging OR bleed OR bleeding) 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease. Intervention: the use of a restrictive transfusion threshold as a mean of
Search date In/Exclusion criteria	OR haemorrhaging OR bleed OR bleeding) 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease. Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion
Search date In/Exclusion criteria	OR haemorrhaging OR bleed OR bleeding) 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease. Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the
Search date In/Exclusion criteria	OR haemorrhaging OR bleed OR bleeding) 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease. Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the baemoglobin level falls below 7 g/dL to 8 g/dL.
Search date In/Exclusion criteria	OR haemorrhaging OR bleed OR bleeding) 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease. Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL.
Search date In/Exclusion criteria	OR haemorrhaging OR bleed OR bleeding) 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease. Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion threshold as a mean of guiding
Search date In/Exclusion criteria	OR haemorrhaging OR bleed OR bleeding) 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease. Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold most often refers to a g/dL to 8 g/dL.
Search date In/Exclusion criteria	 OR haemorrhaging OR bleed OR bleeding) 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease. Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous restrictive transfusion threshold as a mean of guiding allogeneic or autologous restrictive transfusion threshold as a mean of guiding allogeneic or autologous restrictive transfusion threshold as a mean of guiding allogeneic or autologous restrictive transfusion threshold as a mean of guiding allogeneic or autologous restrictive transfusion threshold as a mean of guiding allogeneic or autologous restrictive transfusion threshold as a mean of guiding allogeneic or autologous restrictive transfusion threshold as a mean of guiding allogeneic or autologous restrictive transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion threshold most often refers to administration of blood transfusion threshold most often refers to administration of blood transfusion threshold most often refers to administration of blood transfusion threshold most often refers to administration of blood transfusion threshold most often refers to administration of blood transfusion threshold most often refers to administration of blood transfusion threshold most often refers to administration of blood transfusion threshold most often refers to administration of blood transfusion thres
Search date In/Exclusion criteria	 OR haemorrhaging OR bleed OR bleeding) 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease. Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold most often refers to administration threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold most often refers to administration threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL
Search date In/Exclusion criteria	 OR haemorrhaging OR bleed OR bleeding) 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease. Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion threshold most often refers to a g/dL to 8 g/dL.
Search date In/Exclusion criteria	 OR naemorrhaging OR bleed OR bleeding) 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease. Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL. Outcomes: Primary: Mortality (30-day mortality or in-hospital mortality, during the second transfusion threshold mortality.
Search date In/Exclusion criteria	 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease. Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion threshold most often refers to administration. A liberal transfusion threshold most often refers to administration of blood transfusion threshold most often refers to administration. A liberal transfusion threshold most often refers to administration of blood transfusion threshold most often refers to administration of blood transfusion threshold most often refers to administration of blood transfusion threshold most often refers to administration of blood transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL. Outcomes: Primary: Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes
Search date In/Exclusion criteria	 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease. Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold most often refers to administration of blood transfusion threshold most often refers to a g/dL. Comparison: the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL. Outcomes: Primary: Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of
Search date In/Exclusion criteria	 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease. Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL. Outcomes: Primary: Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion participants exposed to transfusion participants exposed to transfusion.
Search date In/Exclusion criteria	 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease. Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL. Outcomes: Primary: Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion units of blood transfused (in those receiving any participants exposed to transfusion).
Search date In/Exclusion criteria	 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease. Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL. Outcomes: Primary: Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion) and Secondary. Morthidity-related outcomes that occurred during
Search date In/Exclusion criteria	 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease. Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold most often refers to administration of blood transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL. Outcomes: Primary: Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and Secondary: Morbidity-related outcomes that occurred during hospitalisation (i.e. cardiac events non-fatal and fatal myocardial infarction
Search date In/Exclusion criteria	 OK haemorrhaging OK bleed OK bleeding) 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease. Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL. Outcomes: <i>Primary:</i> Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and <i>Secondary:</i> Morbidity-related outcomes that occurred during hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction, capacity on both to participants exposed.
Search date In/Exclusion criteria	 OK haemorrhaging OK bleed OK bleeding) 13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review) Population: Included: patients with symptomatic coronary heart disease. Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL. Outcomes: <i>Primary:</i> Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and <i>Secondary:</i> Morbidity-related outcomes that occurred during hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction, congestive heart failure, stroke, renal injury, pneumonia, septic shock, reholement of participants exposed to transfusion)

Study design: The following study designs were included: 1) (cluster) randomized controlled trials included in the Cochrane review by Carson et al (May 2016) or other systematic reviews identified in the update and 2) (cluster) randomized controlled trials identified in the update. To examine the evidence for the effect of transfusion threshold on the use of RBC transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or haematocrit level (without hemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic or autologous red blood cells, or both, at higher haemoglobin or transfusion threshold) than the intervention group, or transfused in
red blood cells, or both, at higher haemoglobin or haematocrit levels (transfusion threshold) than the intervention group, or transfused in
accordance with current transfusion practices, which may not have included a well-defined transfusion threshold, but involved liberal rather than restrictive
transfusion practices. We excluded trials that were not designed to include any clinical outcomes.

Author year	Study docion	Deputation	Comparison/Bick factor	Ctudy
Author, year,	Study design	Population	Comparison/ Kisk factor	Study
Country				financial COL
Correct 2012	Developsional	110 menticinente with	Destrictive energy	
Carson, 2013,	Randomised		Restrictive group	Research
USA	controlled trial	acute myocardiai	(Intervention):	supported by
		infarction or	transfusion permitted if	government
		undergoing cardiac	symptoms of anemia or	grant from
		catheterisation with	Hb<8 g/dL; 1 unit at a time	National
		Hb<10 g/dL	until symptoms	Heart Lung
		(clinical specialty	disappeared or Hb	and Blood
		subgroup (Carson,	increased >8 g/dL	Institute.
		2016): acute		
		myocardial infarction)	Liberal group (control):	Identified
			immediately transfuse 1	from the
		Restrictive group:	unit after randomisation	systematic
		n=55, 27 males and	(Hb<10 g/dL) and	review of
		28 females,	transfuse enough blood to	Carson et al.,
		age=74.3±11.1 years	maintain Hb>10 g/dL	2016.
		Liberal group:	Transfusion:	
		n=55, 28 males and	RBC units	
		27 females,		
		age=67.3±13.6 years		
Cooper, 2011,	Randomised	45 participants with	Restrictive group	Study was
USA	controlled trial	acute myocardial	(intervention):	supported by
		infarction and	transfusion with RBC if	the
		haematocrit less than	haematocrit <24%; target	Cardiovascular
		30%	haematocrit: 24-27% (Hb:	Research
		(clinical specialty	8-9 g/dL)	Institute of
		subgroup (Carson,		the
		2016): acute	Liberal group (control):	Washington
		mvocardial infarction)		

Characteristics of included studies

	transfusion with RBC if	Hospital
Restrictive group:	haematocrit <30%; target	Center.
n=24, 13 males and	haematocrit: 30-33% (Hb:	
11 females,	10-11 g/dL)	Identified
age=70.3±14.3 years		from the
	Transfusion:	systematic
Liberal group:	Leukocyte-depleted	review of
n=21, 10 males and	packed RBC	Carson et al.,
11 females,		2016.
age=76.4±13.5 years		

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, #	Reference
			participants	
Primary outcome	S	•		
30-day mortality	Restrictive vs liberal	Not statistically significant:	2, 78 vs 76	Carson,
	transfusion	9/78 vs 2/76 §		2013;
	threshold	RR: 3.88, 95%CI [0.83;18.13] ¥		Cooper,
		(p=0.085) (Figure 51)		2011
Hospital mortality		Not statistically significant:	1, 24 vs 21	Cooper,
		2/24 vs 1/21 §		2011
		RR: 1.75, 95%CI [0.17;17.95] ¥		
		(p=0.64)* (Figure 52)		
Participants		Statistically significant:	2, 79 vs 76	Carson,
exposed to blood		28/79 vs 76/76 §		2013;
transfusion		RR: 0.40, 95%CI [0.19;0.82]		Cooper,
		(p=0.012) (Figure 53)		2011
		In favour of restrictive		
		transfusion threshold		
Units of blood		Not statistically significant:	1, 24 vs 21 §	Cooper,
transfused		1.6±2.0 vs 2.5±1.3		2011
		MD: -0.90, 95%CI [-1.87;0.07] ¥		
		(p=0.07)* (Figure 54)		
Secondary outcor	nes			
Haemoglobin	Restrictive vs liberal	Statistically significant:	1, 55 vs 55 §	Carson,
concentration	transfusion	9.12±0.75 vs 10.64±0.71		2013
	threshold	MD: -1.52, 95%CI [-1.79;-1.25]		
		(p<0.00001)* (Figure 55)		
Myocardial		Not statistically significant:	2, 77 vs 74	Carson,
infarction		7/77 vs 6/74 §		2013;
		RR: 1.20, 95%CI [0.43;3.34] ¥		Cooper,
		(p=0.73)** (Figure 56)		2011
Congestive heart		Not statistically significant:	2, 78 vs 76	
failure		9/78 vs 10/76 §		
		RR: 0.87, 95%CI [0.06;13.46] ¥		
		(p=0.92)** (Figure 57)		
Cerebrovascular		Not statistically significant:	1, 54 vs 55	Carson,
accident (CVA) -		0/54 vs 1/55 §		2013
Stroke		RR: 0.34, 95%CI [0.01; 8.15] ¥		
		(p=0.51)* (Figure 58)	1	
Sepsis/bacteraemi		0/54 vs 0/55 §		
а		RR: not estimable (Figure 59)		

Pneumonia	Not statistically significant: 2/54 vs 0/55 § RR: 5.09, 95%CI [0.25;103.64] ¥
	(p=0.29)* (Figure 60)
Pneumonia or	Not statistically significant:
wound infection	2/54 vs 0/55 §
	RR: 5.09, 95%CI [0.25;103.64] ¥
	(p=0.29)* (Figure 61)
Thromboembolism	Not statistically significant:
	0/54 vs 1/55 §
	RR: 0.34, 95%CI [0.01; 8.15] ¥
	(p=0.51)* (Figure 62)

Mean ± SD (unless otherwise indicated)

* Calculations (p-value) done by the reviewer(s) using Review Manager software

** Calculations (RR, 95%CI and p-value) done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Forest plots

	Restrictive Liberal		Risk Ratio		Risk Ratio	Risk of Bias		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Carson 2013	7	55	1	55	56.0%	7.00 [0.89, 55.01]		$\bullet \bullet ? \bullet \bullet \bullet \bullet$
Cooper 2011	2	23	1	21	44.0%	1.83 [0.18, 18.70]		? • ? ? • • •
Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	78 76 9 2 = 0.00; Chi [≈] = 0.74, df = 1 (P = 0.3 t Z = 1.72 (P = 0.09)		76 P = 0.3	100.0% 9); I ² = 0%	3.88 [0.83, 18.13]	0.01 0.1 1 10 100 Favours restrictive Favours liberal	1	

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 51: Forest plot of outcome: 30-day mortality.



(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 52: Forest plot of outcome: Hospital mortality.



(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 53: Forest plot of outcome: Participants exposed to blood transfusion.

	Restrictive Liberal			Mean Difference	Mean Difference	Risk of Bias				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	ABCDEFG
Cooper 2011	1.6	2	24	2.5	1.3	21	100.0%	-0.90 [-1.87, 0.07]	-8-	? • ? ? • • •
Total (95% CI)			24			21	100.0%	-0.90 [-1.87, 0.07]	•	
Heterogeneity: Not applicable										
Test for overall effect:	Z = 1.81	(P =	0.07)						Favours restrictive Favours liberal	
<u>Risk of bias legend</u>	Risk of bias legend									
(A) Random sequend	e genera	ation	(select	ion bias	5)					
(B) Allocation concealment (selection bias)										
(C) Blinding of participants and personnel (performance bias)										
(D) Blinding of outcon	(D) Blinding of outcome assessment (detection bias)									
and the second state of the second										

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 54: Forest plot of outcome: Units of blood transfused.



(G) Other bias

Figure 55: Forest plot of outcome: Haemoglobin concentration.



(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 56: Forest plot of outcome: Myocardial infarction.

	Restrictive Liberal		Risk Ratio		Risk Ratio	Risk of Bias		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Carson 2013	7	54	2	55	49.5%	3.56 [0.78, 16.40]		
Cooper 2011	2	24	8	21	50.5%	0.22 [0.05, 0.92]		?•??••
Total (95% CI)		78		76	100.0%	0.87 [0.06, 13.46]		
Total events	9		10					
Heterogeneity: Tau ² = 3.33; Chi ² = 6.83, df = 1 (P = 0.009); l ² = 85%							100	
Test for overall effect: Z = 0.10 (P = 0.92) Favours restrictive Favours liberal					eral			
Risk of bias legend								

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 57: Forest plot of outcome: Congestive heart failure.



(G) Other bias

Figure 58: Forest plot of outcome: Cerebrovascular (CVA) - stroke.



(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 59: Forest plot of outcome: Sepsis/bacteraemia.



(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 60: Forest plot of outcome: Pneumonia.



(F) Selective reporting (reporting bias)

(G) Other bias

Figure 61: Forest plot of outcome: Pneumonia or wound infection.



(F) Selective reporting (reporting bias)

(G) Other bias

Figure 62: Forest plot of outcome: Thromboembolism.

Quality of evidence

Author, Year	Lack of allocation concealment and random sequence generation (selection bias)	Lack of blinding (performance bias)	Incomplete accounting of outcome events (attrition bias)	Selective outcome reporting (reporting bias)	Other limitations
Carson, 2013, USA	Randomization: No, computer programme generated allocation sequence Allocation concealment: No, central telephone randomization	Participants and personnel: Unclear, not blinded but unlikely to affect outcome assessors: No, all primary and most secondary outcomes assessed blindly	No, only 1 of 110 participants lost to follow-up	No Pre- registration of study protocol (NCT01167 582)	No
Cooper, 2011, USA	Randomization: Unclear, no information provided Allocation concealment: No, use of consecutively numbered opaque envelopes	Participants and personnel: Unclear, not blinded Outcome assessors: Unclear, local investigator determined outcomes	No, complete in-hospital follow-up. 3 of 45 participants lost to follow-up at 30 days.	No Pre- registration of study protocol (NCT00126 334)	No

Certainty of the body of evidence: see GRADE evidence tables

Conclusion	See Evidence-to-Decision template
Reference(s)	 Articles Carson JL, Brooks MM, Abbott JD, Chaitman B, Kelsey SF, Triulzi DJ, et al. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. Am Heart J 2013;165(6):964–71. Cooper HA, Rao SV, Greenberg MD, Rumsey MP, Mckenzie M, Alcorn KW, et al. Conservative versus liberal red cell transfusion in acute myocardial infarction (the CRIT randomized pilot study). Am J Cardiol 2011;108(8):1108–11. Systematic reviews Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC. Transfusion. Cochrane Database Syst Rev. 2016, 10:CD002042. Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, Goodman SG, Rao SV, Doree C, Hebert PC. Clinical trials evaluating red blood cell transfusion thresholds: an updated systematic review and with additional focus on patients with cardiovascular disease. In peer-review [February 2018].
Evidence used for	Consensus meeting PBM
Reviewer(s)	Anne-Catherine Vanhove

PICO 8: RBC transfusion triggers in adult patients with septic shock

Overview evidence table GRADE software (PICO 8)

Certainty assessment							№ of patients		Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7 g/dL)	more liberal RBC transfusion triggers (Hb <9 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
28-30-d	ay mortality											
2	randomised trials	not serious	not serious	not serious	serious ^a	none	252/653 (38.6%)	242/645 (37.5%)	RR 1.07 (0.83 to 1.39)	26 more per 1.000 (from 64 fewer to 146 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Hospital	mortality											
1	randomised trials	not serious	not serious	serious ^b	not serious	none	151/502 (30.1%)	154/496 (31.0%)	RR 0.97 (0.80 to 1.17)	9 fewer per 1.000 (from 53 more to 62 fewer)	⊕⊕⊕⊖ MODERATE	CRITICAL
90-day r	mortality											

Certainty assessment								Nº of patients		fect		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7 g/dL)	more liberal RBC transfusion triggers (Hb <9 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
2	randomised trials	not serious	not serious	not serious	serious ^a	none	322/653 (49.3%)	311/645 (48.2%)	RR 1.06 (0.85 to 1.32)	29 more per 1.000 (from 72 fewer to 154 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
1-year m	nortality											
1	randomised trials	not serious	not serious	serious ^b	not serious	none	268/501 (53.5%)	271/496 (54.6%)	RR 0.98 (0.87 to 1.10)	11 fewer per 1.000 (from 55 more to 71 fewer)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Mortality	y at the time o	of longest f	follow-up									
1	randomised trials	not serious	not serious	serious ^b	not serious	none	284/501 (56.7%)	302/495 (61.0%)	RR 0.93 (0.84 to 1.03)	43 fewer per 1.000 (from 18 more to 98 fewer)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Patients	exposed to R	BC transfus	sion									

Certainty assessment								№ of patients		Effect		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7 g/dL)	more liberal RBC transfusion triggers (Hb <9 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
2	randomised trials	not serious	not serious	not serious	not serious	none	388/653 (59.4%)	581/645 (90.1%)	RR 0.66 (0.62 to 0.70)	306 fewer per 1.000 (from 270 fewer to 342 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Haemog	lobin concent	tration										
1	randomised trials	not serious	not serious	serious ^b	not serious	none	502	496	-	MD 1.7 lower (1.82 lower to 1.58 lower)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Myocarc	lial infarction	I	I	1	1	I	L	1	I	I		I
2	randomised trials	not serious	not serious	not serious	serious ^a	none	46/639 (7.2%)	30/638 (4.7%)	RR 1.49 (0.97 to 2.28)	23 more per 1.000 (from 1 fewer to 60 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Congest	ive heart failu	re		1					,	·		1
1	randomised trials	not serious	not serious	serious ^b	serious ^c	none	0/488 (0.0%)	0/489 (0.0%)	not estimable		⊕⊕⊖⊖ LOW	IMPORTANT

Certainty assessment								Nº of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7 g/dL)	more liberal RBC transfusion triggers (Hb <9 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
CVA-stro	oke											
2	randomised trials	not serious	not serious	not serious	serious ^a	none	7/639 (1.1%)	12/638 (1.9%)	RR 0.64 (0.19 to 2.20)	7 fewer per 1.000 (from 15 fewer to 23 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Rebleed	ing											
1	randomised trials	not serious	not serious	serious ^b	not serious	none	147/488 (30.1%)	148/489 (30.3%)	RR 1.00 (0.82 to 1.20)	0 fewer per 1.000 (from 54 fewer to 61 more)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Renal fai	ilure											
2	randomised trials	not serious	not serious	not serious	serious ^a	none	127/583 (21.8%)	101/578 (17.5%)	RR 1.25 (0.99 to 1.57)	44 more per 1.000 (from 2 fewer to 100 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Danish s	hort form hea	alth survey	questionnaire (S	F-36): physical	component su	mmary score						

Certainty assessment							Nº of patients		Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7 g/dL)	more liberal RBC transfusion triggers (Hb <9 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	randomised trials	not serious	not serious	serious ^b	serious ^a	none	311	318	-	MD 0.4 points higher (4.05 lower to 4.85 higher)	⊕⊕⊖⊖ LOW	IMPORTANT
Danish s	hort form hea	alth survey	questionnaire (S	F-36): mental c	omponent sun	nmary score						
1	randomised trials	not serious	not serious	serious ^b	serious ^a	none	311	318	-	MD 0.5 points higher (5.26 lower to 6.26 higher)	⊕⊕⊖⊖ LOW	IMPORTANT
60-day r	nortality											
1	randomised trials	not serious	not serious	serious ^d	serious ^a	none	99/151 (65.6%)	84/149 (56.4%)	RR 1.16 (0.97 to 1.40)	90 more per 1.000 (from 17 fewer to 226 more)	⊕⊕⊖⊖ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; a. Large variability in results; b. Lack of generalizibility: evidence from 1 study conducted in Denmark; c. Low number of events; d. Lack of generalizibility: evidence from 1 study conducted in Brazil
Detailed evidence summary (PICO 8)

Торіс	Patient Blood Management
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers
Intervention	Restrictive RBC transfusion triggers
Question (PICO)	In patients with septic shock (Population), is the use of a restrictive transfusion threshold (Intervention) effective to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusion threshold (Comparison)?
Search Strategy	 The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to: Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017) Identify observational studies in case no experimental studies were available.
	Databases The Cochrane Library (systematic reviews and controlled trials) using the following search strategy (from May 2016 until June 2017): #1 MeSH descriptor: [Blood Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST, Trends - TD] #2 MeSH descriptor: [Erythrocyte Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST] #3 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) near/5 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or strateg* or regimen* or criteri* or standard* or management or program*)) #4 ((h?emoglobin or h?ematocrit or HB or HCT) near/5 (polic* or practic* or protocol* or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or standard*)) #5 (blood near/3 (management or program*)) #6 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) and (critical* or intensive* or h?emorrhag* or bleed*)):ti #7 #1 or #2 or #3 or #4 or #5 or #6
	MEDLINE (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy (from 27th May 2016 until 30th June 2017): #1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI])) #2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR standard*[TI]) #3 (blood[TI] AND (management[TI] OR program*[TI]))

	#4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR
	haemorrhage*[TI] OR bleed*[TI]))
	#5 #1 OR #2 OR #3 OR #4
	Embase (via Embase.com interface) using the following search strategy (from
	27 th May 2016 until 30 th June 2017): #1 ((transfus*ti OR red cell*ti OR red blood cell*ti OR RBC*ti OR PRBC*) AND
	(trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR
	aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti
	OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR
	#2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR
	HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR
	standard*:ti)) #3 (blood:ti AND (management:ti OB program*:ti))
	#4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and
	(critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti))
	#5 #1 OR #2 OR #3 OR #4
	Transfusion evidence library (from 2016 until 2017)
	Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR
	liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit
	OR limits OR protocol OR policy OR policies OR practice OR indicator OR
	OR program OR programme) OR Red Cells AND title:(critical OR critically OR
	intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging
Counch data	OR haemorrhaging OR bleed OR bleeding)
Search date	2018)
	26/01/2018 (update after latest search date Carson review)
In/Exclusion criteria	Population: <u>Included</u> : patients with septic shock in different settings (e.g.
	intensive care unit).
	Intervention: the use of a restrictive transfusion threshold as a mean of
	guiding allogeneic or autologous RBC transfusion. A restrictive transfusion
	threshold most often refers to administration of blood transfusion when the
	haemoglobili level fails below 7 g/uL to 8 g/uL.
	Comparison: the use of a liberal transfusion threshold as a mean of guiding
	allogeneic or autologous RBC transfusion. A liberal transfusion threshold most
	falls below 9 g/dL to 10 g/dL.
	Outcomes: <u>Primary:</u> Mortality (e.g. 30-day mortality or in-hospital mortality,
	including outcomes related to RBC transfusion use (i.e. proportion of
	participants exposed to transfusion, participants exposed to allogeneic or
	autologous transfusion, units of blood transfused (in those receiving any
	transtusion)) and <u>Secondary:</u> morbidity-related outcomes that occurred during
	transfusion)) and <u>Secondary:</u> morbidity-related outcomes that occurred during hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction.

congestive heart failure, stroke, renal injury, pneumonia, septic shock, rebleeding, infection, and fatigue). **Study design:** Systematic reviews (+ meta-analyses) of experimental studies (RCT's). If not available, we will search for individual experimental studies (RCT's). To examine the evidence for the effect of transfusion threshold on the use of red blood cell (RBC) transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or haematocrit level (with or without a specified level of haemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic or autologous red blood cells, or both, at higher haemoglobin or haematocrit levels (transfusion threshold) than the intervention group, or transfused in accordance with current transfusion practices, which may not have included a well-defined transfusion threshold, but involved liberal rather than restrictive transfusion practices. We excluded trials that were not designed to include any clinical outcomes relevant to this review.

Author, year, Country	Study design	Population	Comparison	Study funding, financial COI and remarks
Bergamin, 2017, Brazil	Experimental: RCT	300 adult cancer patients with septic shock in the first 6 hours of ICU admission.	Restrictive group (intervention): RBC transfusion (1 unit) if Hb <7 g/dL	Dr. Park disclosed government work. The remaining authors have disclosed that they
		Restrictive group: n = 151, 84 males and 67 females, age=61.4±13.5 years	Liberal group: RBC transfusion (1 unit) if Hb <9 g/dL	do not have any potential conflicts of interest.
		Liberal group: n = 149, 70 males and 79 females, age=61.6±12.9 years	HB levels assessed after IC admission, twice a day during ICU stay and after evry transfusion.	Identified from the update.
			Transfusion: leukodepleted RBC units	
Holst, 2014, Denmark	Randomised controlled trial	998 participants in Denmark, Sweden, Norway and Finland with septic shock in the ICU and haemoglobin concentration less than 9 g/dL (clinical specialty subgroup (Carson, 2016): critical care)	Restrictive group (intervention): transfusion if Hb conc ≤7.0 g/dL Liberal group (control): transfusion if Hb ≤9.0 g/dL Haemoglobin	Research funded by hospitals, medical societies and foundations. Two authors received grant support from private industry. Identified from the
			concentrations were	systematic review

Characteristics of included studies

Restrictive group: n=502, 272 males and 230 females, median age (IQR)=67 (57-73) yrs Liberal group: n=496, 259 males and 237 females, median age (IQR)=67 (58-75) yrs	reassessed within 3 hours after termination of the transfusion or before the initiation of another transfusion. Transfusion: single units of cross- matched, prestorage leukoreduced red cells	of Carson et al., 2016. Two articles (one subgroup analysis and one follow-up) identified through the updated search: Rygård 2016 (follow-up) and Rygård 2017 (subgroup analysis). Relevant additional data from Rygård 2016 was extracted and
		additional data from Rygård 2016 was extracted and included in the synthesis of findings.

Synthesis of findings

Outcome	Comparison/Risk	Effect Size	#studies, #	Reference
Primany outcome			participants	
28-30 - day	s Restrictive vs liberal	Not statistically significant	2 653 vs 645	Bergamin
mortality	transfusion	252/653 vs 242/645	2,000 000	2017 Holst
inortanty	threshold	RR: 1 07 95%CI [0 83:1 39] ¥		2014
		(n=0.60)* (Figure 63)		2011
Hospital mortality	-	Not statistically significant:	1, 502 vs 496	Holst 2014
		151/502 vs 154/496	1, 302 13 130	
		RR: 0.97. 95%CI [0.80:1.17]		
		$(p=0.74)^*$ (Figure 64)		
60-dav mortality	-	Not statistically significant:	1, 151 vs 149	Bergamin
		99/151 vs 84/149	_,	2017
		RR: 1.16, 95%CI [0.97:1.40] ¥		
		$(p=0.10)^*$ (Figure 65)		
90-day mortality		Not statistically significant:	2, 653 vs 645	Bergamin
, , ,		322/653 vs 311/645	,	2017, Holst
		RR: 1.06, 95%CI [0.85;1.32] ¥		2014
		(p=0.59)* (Figure 66)		
1-year mortality		Not statistically significant:	1, 501 vs 496	Holst 2014
		268/501 vs 271/496	(data from Rygård	
		RR: 0.98, 95%CI [0.87;1.10]	2016 identified in	
		(p=0.72)* (Figure 67)	search update)	
Mortality at the		Not statistically significant:	1, 501 vs 495	
time of longest		284/501 vs 302/495	(data from Rygård	
follow-up		RR: 0.93, 95%CI [0.84;1.03]	2016 identified in	
		(p=0.17)* (Figure 68)	search update)	
Participants		Statistically significant:	1, 653 vs 645	Bergamin
exposed to blood		388/653 vs 581/645		2017, Holst
transfusions		RR: 0.66, 95%CI [0.62;0.70]		2014
		(p<0.00001)* (Figure 69)		

[
		In favour of restrictive		
		transfusion threshold		
Units of blood		Statistically significant:	1, 151 vs 149	Bergamin
transfused		Median (IQR): 0 (0-2) vs 1 (0-3)		2017
		Median difference: 1		
		(p<0.001)		
		In favour of restrictive		
		transfusion threshold		
		Statistically significant:	1, 502 vs 496	Holst 2014
		Median (IQR): 1 (0-3) vs 4 (2-7)		
		Median difference: 3		
		(p<0.001)		
		In favour of restrictive		
		transfusion threshold		
Secondary outcor	nes			
Haemoglobin	Restrictive vs liberal	Statistically significant:	1, 502 vs 496	Holst 2014
concentration	transfusion	7.6±1.0 vs 9.3±0.9		
	threshold	MD: -1.70, 95%CI [-1.82;-1.58]		
		(p<0.00001)* (Figure 70)		
Myocardial		Not statistically significant:	2, 639 vs 638	Bergamin
infarction		46/639 vs 30/638		2017, Holst
		RR: 1.49, 95%CI [0.97:2.28] ¥		2014
		$(p=0.07)^*$ (Figure 71)		
Congestive heart		0/488 vs 0/489 §	1 488 vs 489	Holst 2014
failure		RR: not estimable (Figure 72)	1, 100 13 105	110150 2011
Cerebrovascular		Not statistically significant:	2 639 vs 638	Bergamin
accident(CVA) -		7/639 vs 12/638	2,055 v3 050	2017 Holst
Stroke		RR: 0.64, 95%CI [0.19:2.20] ¥		2017, 110130
STORE		(n - 0.48)* (Figure 73)		2014
Poblooding	-	(p=0.48) (figure 75)	1 100 vc 100	Hold 2014
Replecting			1, 400 VS 409	10131 2014
		147/400 VS 140/409		
		RR. 1.00, 95%CI [0.82,1.20]		
	-	(p=0.96) [*] (Figure 74)	2 502 570	D .
Renal failure		Not statistically significant:	2, 583 vs 578	Bergamin
		12//583 vs 101/5/8		2017, Holst
		RR: 1.25, 95%CI [0.99;1.57] ¥		2014
		(p=0.06)* (Figure 75)		
Danish short form		Not statistically significant:	1, 311 vs 318	Holst 2014
health survey		7.6±27.8 vs 7.2±29.2	(data from Rygård	
questionnaire (SF-		MD: 0.40, 95%CI [-4.05;4.85] ¥	2016 identified in	
36): physical		(p=0.86)* (Figure 76)	search update)	
component				
summary score				
Danish short form		Not statistically significant:		
health survey		10±36 vs 9.5±37.7		
questionnaire (SF-		MD: 0.50, 95%CI [-5.26;6.26] ¥		
36): mental		(p=0.86)* (Figure 77)		
component				
summary score				

Mean ± SD (unless otherwise indicated)

CI: confidence interval, RR: relative risk, MD: mean difference

* Calculations (RR or MD, 95% CI and/or p-value) done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Forest plots

	Restrictive		Liberal			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Bergamin 2017	84	151	67	149	45.9%	1.24 [0.99, 1.55]	•	
Holst 2014	168	502	175	496	54.1%	0.95 [0.80, 1.13]	•	$\bullet \bullet ? \bullet \bullet \bullet \bullet$
Total (95% CI)		653		645	100.0 %	1.07 [0.83, 1.39]	•	
Total events	252		242					
Heterogeneity: Tau ² =	= 0.03; Chi	= 3.38	3, df = 1 (l	$P = 0.0^{\circ}$	7); I² = 70'	%		
Test for overall effect:	: Z = 0.52 (P = 0.6	0)				Favours restrictive Favours liberal	
Risk of bias legend								
(A) Random sequen	ce generat	tion (se	election b	ias)				
(B) Allocation concealment (selection bias)								

(C) Blinding of participants and personnel (performance bias)
 (D) Blinding of outcome assessment (detection bias)
 (E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 63: Forest plot of outcome: 28-30 - day mortality.



(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 64: Forest plot of outcome: Hospital mortality.

	Restrictive Liberal					Risk Ratio	Risk Ratio	Risk of Bias		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	ABCDEFG		
Bergamin 2017	99	151	84	149	100.0%	1.16 [0.97, 1.40]				
Total (95% CI)		151		149	100.0%	1.16 [0.97, 1.40]	•			
Total events	99		84							
Heterogeneity: Not ap	plicable							-		
Test for overall effect:	Z=1.62 (P = 0.1	0)				Favours restrictive Favours liberal	J		
Risk of bias legend										
(A) Random sequence generation (selection bias)										
(B) Allocation concealment (selection bias)										
(C) Blinding of partici	(C) Blinding of participants and personnel (performance bias)									

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 65: Forest plot of outcome: 60-day mortality.

	Restric	tive	Liber	al		Risk Ratio Risk Ratio Risk		Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Bergamin 2017	106	151	88	149	47.6%	1.19 [1.00, 1.41]	=	
Holst 2014	216	502	223	496	52.4%	0.96 [0.83, 1.10]	•	$\bullet \bullet ? \bullet \bullet \bullet \bullet$
Total (95% CI)		653		645	100.0%	1.06 [0.85, 1.32]	•	
Total events	322		311					
Heterogeneity: Tau ² = 0.02; Chi ² = 3.89, df = 1 (P = 0.05); l ² = 74%						%		1
Test for overall effect: Z = 0.54 (P = 0.59)							Favours restrictive Favours liberal	

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 66: Forest plot of outcome: 90-day mortality.



(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 67: Forest plot of outcome: 1-year mortality

	Restrictive Liberal				Risk Ratio	Risk Ratio	Risk of Bias	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Holst 2014	284	501	302	495	100.0%	0.93 [0.84, 1.03]		
Total (95% CI)		501		495	100.0%	0.93 [0.84, 1.03]	•	
Total events Heterogeneity: Not ap Test for overall effect:	284 oplicable : Z = 1.39 ((P = 0.1	302 7)				0.01 0.1 1 10 10	
<u>Risk of bias legend</u> (A) Random sequend (B) Allocation concea	ce genera Iment (se	tion (se lection	election b bias)	ias)				

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 68: Forest plot of outcome: Mortality at the time of longest follow-up

	Restric	tive	Liber	al		Risk Ratio	Ratio Risk Ratio		Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random,	95% CI	ABCDEFG
Bergamin 2017	62	151	91	149	7.4%	0.67 [0.53, 0.85]			
Holst 2014	326	502	490	496	92.6%	0.66 [0.62, 0.70]			••?•••
Total (95% CI)		653		645	100.0%	0.66 [0.62, 0.70]	1		
Total events	388		581						
Heterogeneity: Tau ² =	: 0.00; Chi	² = 0.04	l, df = 1 (l	P = 0.8	5); I ² = 0%				
Test for overall effect: Z = 13.09 (P < 0.00001)							Favours restrictive Fa	ivours liberal	
Risk of bias legend									

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 69: Forest plot of outcome: Participants exposed to blood transfusions.



(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 70: Forest plot of outcome: Haemoglobin concentration.



(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 71: Forest plot of outcome: Myocardial infarction.

	Restric	tive	Liber	al		Risk Ratio	Risk	Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Rand	om, 95% Cl	ABCDEFG
Holst 2014	0	488	0	489		Not estimable			••?•••
Total (95% CI)		488		489		Not estimable			
Total events	0		0						
Heterogeneity: Not ap	plicable								
Test for overall effect:	Not appli	cable					Favours restrictive	Favours liberal	
Risk of bias legend									

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 72: Forest plot of outcome: Congestive heart failure.



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 73: Forest plot of outcome: Cerebrovascular accident (CVA) - Stroke.



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 74: Forest plot of outcome: Rebleeding.

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Bergamin 2017	18	151	13	149	11.8%	1.37 [0.69, 2.69]	_ <u>_</u>	$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \bullet$
Holst 2014	109	432	88	429	88.2%	1.23 [0.96, 1.57]	••••••••••••••••••••••••••••••••••••••	
Total (95% CI)		583		578	100.0%	1.25 [0.99, 1.57]	•	
Total events	127		101					
Heterogeneity: Tau ² =	0.00; Chi	² = 0.08	3, df = 1 (l	P = 0.73	7); I² = 0%	•		
Test for overall effect:	Z=1.85 (P = 0.0	6)				Favours restrictive Favours liberal	

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 75: Forest plot of outcome: Renal failure.



(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 76: Forest plot of outcome: Danish short form health survey questionnaire (SF-36): physical component summary score



(F) Selective reporting (reporting bias)

(G) Other bias

Figure 77: Forest plot of outcome: Danish short form health survey questionnaire (SF-36): mental component summary score

Quality of e	vidence				
Author, Year	Lack of allocation concealment and random sequence generation (selection bias)	Lack of blinding (performance bias)	Incomplete accounting of outcome events (attrition bias)	Selective outcome reporting (reporting bias)	Other limitat ions
Bergamin, 2017	Randomization: no, an internet- based system was used Allocation concealment: no internet-based system concealed assignments	Personnel and participants: no, physicians and nurses of the ICU were aware, patients and investigators were blinded Outcome assessment: no, 2 blinded investigators assessed outcomes	No, no exclusions after randomization or loss to follow-up	No Pre-registration of study protocol @ ClinicalTrials.Gov (NCT01648946)	No
Holst, 2014	Randomization: No, a centralised computer generated the assignment sequence. Allocation concealment: No, use of a centralised computer ensured allocation concealment.	Participants and personnel: Unclear, clinicians were not blinded. Outcome assessors: No, the investigators assessing mortality (the DSMB) and the trial statistician were blinded.	main study (Holst 2014): No, near complete follow-up. follow-up study (Rygård 2016 identified in search update): Unclear, considerable loss to follow-up for health survey questionnaire. Responders are older and suffered more often had a pulmonary source of sepsis. Among responders, baseline characteristics were similar in the two intervention groups.	No Pre-registration of study protocol @ ClinicalTrials.Gov (NCT01485315)	No

Certainty of the body of evidence: see GRADE evidence tables

Conclusion	See Evidence-to-Decision template
	Articles
	Bergamin 2017
Reference(s)	Bergamin FS, Almeida JP, Landoni G, Galas FRBG, Fukushima JT, Fominskiy E, Park
	CHL, Osawa EA, Diz MPE, Oliveira GQ, Franco RA, Nakamura RE, Almeida EM,
	Abdala E, Freire MP, Filho RK, Auler JOC Jr, Hajjar LA. Liberal Versus Restrictive

	Transfusion Strategy in Critically Ill Oncologic Patients: The Transfusion
	Requirements in Critically Ill Oncologic Patients Randomized Controlled Trial. Crit
	Care Med. 2017, 45(5):766-773. Identified in search update.
	Holst 2014
	*Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S, et al.
	TRISS Trial Group. Scandinavian Critical Care Trials Group. Lower versus higher
	hemoglobin threshold for transfusion in septic shock. N Engl J Med 2014,
	371(15):1381-91.
	Rygård SL, Holst LB, Wetterslev J, Winkel P, Johansson PI, Wernerman J, et al. TRISS
	Trial Group. Scandinavian Critical Care Trials Group. Long-term outcomes in patients
	with septic shock transfused at a lower versus a higher haemoglobin threshold: the
	TRISS randomised, multicentre clinical trial. Intensive Care Med 2016, 42(11):1685-
	1694. Identified in search update.
	Rygård SL, Holst LB, Wetterslev J, Johansson PI, Perner A. TRISS trial group.
	Scandinavian Critical Care Trials Group. Higher vs. lower haemoglobin threshold for
	transfusion in septic shock: subgroup analyses of the TRISS trial. Acta Anaesthesiol
	Scand 2017, 61(2):166-175. Identified in search update.
	Systematic reviews
	Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC.
	Transfusion thresholds and other strategies for guiding allogeneic red blood cell
	transfusion. Cochrane Database Syst Rev. 2016, 10:CD002042.
	Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ,
	Goodman SG, Rao SV, Doree C, Hebert PC. Clinical trials evaluating red blood cell
	transfusion thresholds: an updated systematic review and with additional focus on
	patients with cardiovascular disease. In peer-review [February 2018].
	*Indicates the major publication for the study
Evidence used for	Consensus meeting PBM
Project	РВМ
Reviewer(s)	Anne-Catherine Vanhove

PICO 9: RBC transfusion triggers in adult cardiac surgery patients

Overview evidence table GRADE software (PICO 9)

	Certainty assessment				№ of patients		Effect					
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusio n triggers (Hb <7.5/8 g/dL)	more liberal RBC transfusion triggers (Hb <9-10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
30-day r	nortality											
3	randomised trials	not serious ª	not serious	not serious	serious ^b	none	44/1464 (3.0%)	38/1478 (2.6%)	RR 1.18 (0.77 to 1.81)	5 more per 1.000 (from 6 fewer to 21 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
30-day r	nortality (sub	group: pati	ents <60 years)	•	•	•	•	•	•		•	•
1	randomised trials	not serious	not serious	serious ^c	serious ^d	none	5/124 (4.0%)	5/118 (4.2%)	RR 0.95 (0.28 to 3.20)	2 fewer per 1.000 (from 31 fewer to 93 more)	⊕⊕⊖⊖ LOW	CRITICAL
30-day r	nortality (sub	group: pati	ents ≥60 years)						•			
1	randomised trials	not serious	not serious	serious ^c	serious ^d	none	10/125 (8.0%)	7/135 (5.2%)	RR 1.54 (0.61 to 3.93)	28 more per 1.000 (from 20 fewer to 152 more)	⊕⊕⊖⊖ LOW	CRITICAL
Hospital	mortality											

			Certainty as	sessment			Nº of p	patients	Ef	ffect		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusio n triggers (Hb <7.5/8 g/dL)	more liberal RBC transfusion triggers (Hb <9-10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
3	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	81/2667 (3.0%)	94/2676 (3.5%)	RR 0.88 (0.48 to 1.62)	4 fewer per 1.000 (from 18 fewer to 22 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
90-day r	nortality					·	·					
1	randomised trials	not serious	not serious	serious ^e	serious ^b	none	42/1000 (4.2%)	26/1003 (2.6%)	RR 1.62 (1.00 to 2.62)	16 more per 1.000 (from 0 fewer to 42 more)	⊕⊕⊖⊖ LOW	CRITICAL
Patients	exposed to R	BC transfu	sion	·				·				
7	randomised trials	not serious	not serious	not serious	not serious	none	2323/4299 (54.0%)	3324/4299 (77.3%)	RR 0.69 (0.66 to 0.73)	240 fewer per 1.000 (from 209 fewer to 263 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
RBC unit	s transfused	(mean)										
3	randomised trials	serious ^f	not serious ^g	not serious	not serious	none	272	274	-	MD 0.87 units lower (1.29 lower to 0.45 lower)	⊕⊕⊕⊖ MODERATE	IMPORTANT

	Certainty assessment				Nº of p	oatients	Effect					
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusio n triggers (Hb <7.5/8 g/dL)	more liberal RBC transfusion triggers (Hb <9-10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
RBC unit	s transfused ((median)										
1	randomised trials	not serious	not serious	serious ^h	not serious	none	2430	2430	-	median 1 unit lower (0 to 0)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Haemog	lobin concen	tration										
1	randomised trials	not serious	not serious	serious ^c	serious ^b	none	249	253	-	MD 1.4 lower (3.1 lower to 0.3 higher)	⊕⊕⊖⊖ LOW	IMPORTANT
Cardiac	events	•	•	•	•	•		•	•			
3	randomised trials	serious ^f	not serious	serious ⁱ	not serious	none	108/481 (22.5%)	109/487 (22.4%)	RR 0.99 (0.75 to 1.30)	2 fewer per 1.000 (from 56 fewer to 67 more)	⊕⊕⊖⊖ LOW	CRITICAL
Myocard	lial infarction											
6	randomised trials	not serious	not serious	serious ⁱ	not serious	none	150/3712 (4.0%)	149/3709 (4.0%)	RR 1.00 (0.81 to 1.25)	0 fewer per 1.000 (from 8 fewer to 10 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Congest	ive heart failu	ire										

			Certainty as	sessment			Nº of p	oatients	Ef	fect		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusio n triggers (Hb <7.5/8 g/dL)	more liberal RBC transfusion triggers (Hb <9-10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	randomised trials	serious ^f	not serious	serious ^j	serious ^d	none	0/20 (0.0%)	1/18 (5.6%)	RR 0.30 (0.01 to 6.97)	39 fewer per 1.000 (from 55 fewer to 332 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
CVA-stro	oke											
6	randomised trials	not serious	not serious	serious ⁱ	serious ^b	none	80/4074 (2.0%)	84/4064 (2.1%)	RR 0.94 (0.69 to 1.28)	1 fewer per 1.000 (from 6 fewer to 6 more)	⊕⊕⊖⊖ LOW	CRITICAL
Rebleed	ing											
3	randomised trials	not serious	not serious	serious ⁱ	serious ^b	none	25/1261 (2.0%)	29/1260 (2.3%)	RR 0.87 (0.51 to 1.48)	3 fewer per 1.000 (from 11 fewer to 11 more)	⊕⊕⊖⊖ LOW	IMPORTANT
Sepsis-b	acteraemia											
3	randomised trials	not serious	not serious	very serious ^k	not serious	none	217/1008 (21.5%)	210/1007 (20.9%)	RR 1.02 (0.87 to 1.21)	4 more per 1.000 (from 27 fewer to 44 more)	⊕⊕⊖⊖ LOW	IMPORTANT
Pneumo	nia											

	Certainty assessment			№ of patients		Effect						
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusio n triggers (Hb <7.5/8 g/dL)	more liberal RBC transfusion triggers (Hb <9-10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	randomised trials	not serious	not serious	serious ^h	serious ^d	none	4/25 (16.0%)	0/25 (0.0%)	RR 9.00 (0.51 to 158.85)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕⊕⊖⊖ LOW	IMPORTANT
Pneumo	nia or wound	infection										
4	randomised trials	not serious	not serious	serious ⁱ	not serious	none	394/3825 (10.3%)	369/3852 (9.6%)	RR 1.07 (0.94 to 1.22)	7 more per 1.000 (from 6 fewer to 21 more)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Thrombo	pembolism							·				
2	randomised trials	not serious	not serious	serious ^k	serious ^b	none	10/1010 (1.0%)	12/1006 (1.2%)	RR 0.82 (0.36 to 1.88)	2 fewer per 1.000 (from 8 fewer to 10 more)	⊕⊕⊖⊖ LOW	IMPORTANT
Renal fai	lure	l			1				l			
6	randomised trials	not serious	not serious	serious ⁱ	not serious	none	231/4266 (5.4%)	224/4266 (5.3%)	RR 1.04 (0.87 to 1.24)	2 more per 1.000 (from 7 fewer to 13 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Renal fai	lure (subgrou	ıp: patients	<60 years)									

			Certainty as	sessment			Nº of p	patients	Ef	fect		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusio n triggers (Hb <7.5/8 g/dL)	more liberal RBC transfusion triggers (Hb <9-10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	randomised trials	not serious	not serious	serious ⁱ	serious ^d	none	4/124 (3.2%)	3/118 (2.5%)	RR 1.27 (0.29 to 5.55)	7 more per 1.000 (from 18 fewer to 116 more)	⊕⊕⊖⊖ LOW	CRITICAL
Renal fa	ilure (subgrou	ip: patients	≥60 years)			·						
1	randomised trials	not serious	not serious	serious ⁱ	serious ^d	none	6/125 (4.8%)	10/135 (7.4%)	RR 0.65 (0.24 to 1.73)	26 fewer per 1.000 (from 54 more to 56 fewer)	⊕⊕⊖⊖ Low	CRITICAL
Health-r	elated quality	of life EQ-	5D at 6 weeks		·			·				
1	randomised trials	not serious	not serious	very serious ^e	not serious	none	1000	1003	-	MD 0.01 points higher (0.02 lower to 0.03 higher)	⊕⊕⊖⊖ LOW	IMPORTANT
Health-r	elated quality	of life EQ-	5D at 3 months		·			·				
1	randomised trials	not serious	not serious	very serious e	not serious	none	1000	1003	-	MD 0 points (0.03 lower to 0.02 higher)	⊕⊕⊖⊖ LOW	IMPORTANT

			Certainty as	sessment			Nº of p	oatients	Ef	fect		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusio n triggers (Hb <7.5/8 g/dL)	more liberal RBC transfusion triggers (Hb <9-10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Hospital	mortality or i	multisysten	n organ failure									
1	randomised trials	not serious	not serious	serious ¹	serious ^d	none	3/363 (0.8%)	6/354 (1.7%)	RR 0.49 (0.12 to 1.93)	9 fewer per 1.000 (from 15 fewer to 16 more)	⊕⊕⊖⊖ LOW	CRITICAL
Vascular	morbidity (ad	ortic or fem	noral artery disse	ction or acute	limb ischaemia)		•	•			
1	randomised trials	not serious	not serious	serious ¹	serious ^d	none	0/363 (0.0%)	3/354 (0.8%)	RR 0.14 (0.01 to 2.69)	7 fewer per 1.000 (from 8 fewer to 14 more)	⊕⊕⊖⊖ LOW	IMPORTANT
Pulmona	ary morbidity	(pneumoni	ia, pulmonary en	nbolus or prolo	onged postoper	rative ventilation >	24 hours)					
1	randomised trials	not serious	not serious	serious ¹	serious ^d	none	23/363 (6.3%)	19/354 (5.4%)	RR 1.18 (0.65 to 2.13)	10 more per 1.000 (from 19 fewer to 61 more)	⊕⊕⊖⊖ LOW	IMPORTANT
Gastroin	testinal morb	idity										
1	randomised trials	not serious	not serious	serious ¹	serious ^d	none	5/363 (1.4%)	2/354 (0.6%)	RR 2.44 (0.48 to 12.48)	8 more per 1.000 (from 3 fewer to 65 more)	⊕⊕⊖⊖ LOW	IMPORTANT

	Certainty assessment						Nº of patients		Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusio n triggers (Hb <7.5/8 g/dL)	more liberal RBC transfusion triggers (Hb <9-10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Reopera	tive morbidity	y (for bleed	ling/tamponade,	graft occlusior	n, valve dysfun	ction)						
1	randomised trials	not serious	not serious	serious ¹	serious ^d	none	9/363 (2.5%)	10/354 (2.8%)	RR 0.88 (0.36 to 2.13)	3 fewer per 1.000 (from 18 fewer to 32 more)	⊕⊕⊖⊖ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Decision not to downgrade by reviewer(s) although Bracey, 1999 has serious limitations. However, for these outcomes the results from Bracey do not have much influence on the point estimate and 95% CI as the study is assigned little weight; b. Large variability in results; c. Lack of generalizibility: evidence from 1 Brazilian study; d. Low number of events, limited sample size and large variability in results; e. Lack of generalizibility: evidence from 1 UK study; f. Selection bias and detection bias; g. Decision not to downgrade by reviewer(s) although point estimates vary, CIs show minimal or no overlap, tests for heterogeneity show a low p-value and I2>75%. This large inconsistency or variability is, however, not considered important as the direction of effect is the same for all studies which is most relevant for this outcome; h. Lack of generalizibility: evidence from 1 Canadian study; i. Lack of generalizibility: variation in outcome definitions; j. Lack of generalizibility: variation in outcome definitions and evidence from only 2 studies; l. Lack of generalizibility: evidence from 1 USA study.

Detailed evidence summary (PICO 9)

Торіс	Patient Blood Management							
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers							
Intervention	Restrictive RBC transfusion triggers							
Question	In patients undergoing cardiac surgery (Population), is the use of a restrictive							
(PICO)	transfusion threshold (Intervention) effective to reduce mortality and improve other							
	clinical outcomes (Outcomes) compared to a liberal transfusion threshold							
Carach	(Comparison)?							
Search	The Coonrane systematic review by Carson et al. (2016) and its updated/unpublished							
Strategy	to							
	- Identify relevant experimental studies (RCT's) published after the search by							
	Carson et al. (13 th November 2017)							
	- Identify observational studies in case no experimental studies were available.							
	Databases							
	The Cochrane Library (systematic reviews and controlled trials) using the following							
	search strategy (from May 2016 until June 2017):							
	1 MeSH descriptor: [Blood Transfusion] this term only and with qualifier(s): Methods - MT, Standards - ST, Trends - TD1							
	[Methods - MI, Standards - SI, Irends - ID] #2 MoSU descriptor: [Enthroute Transfusion] this term only and with qualifier(s).							
	#2 MeSH descriptor: [Erythrocyte Transfusion] this term only and with qualifier(s): [Methods - MT. Standards - ST]							
	#3 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) near/5 (trigger* or							
	thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or							
	prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or							
	strateg* or regimen* or criteri* or standard* or management or program*))							
	#4 ((h?emoglobin or h?ematocrit or HB or HCT) near/5 (polic* or practic* or protocol*							
	or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or							
	standard*))							
	#5 (blood near/3 (management or program [*]))							
	#6 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) and (critical* or							
	intensive* or h?emorrhag* or bleed*)):ti							
	MEDLINE (via PubMed interface) for systematic reviews and experimental and							
	observational studies using the following search strategy (from 27th May 2016 until							
	30th June 2017):							
	#1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND							
	(trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR							
	aggressive*[1] OR conservative*[1] OR prophylactic*[1] OR limit*[1] OR							
	protocol*[1] OR policy[1] OR policies[1] OR practic*[1] OR indicat*[1] OR							
	program*[TI]))							
	#2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR							
	HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR							
	threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR							
	standard*[TI]))							
	#3 (blood[TI] AND (management[TI] OR program*[TI]))							
	#4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI])							
	and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR							
	bleed*[TI]))							
	#5 #1 OR #2 OR #3 OR #4							

	Embase (via Embase.com interface) using the following search strategy (from 27 th May 2016 until 30 th June 2017): #1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti)) #3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4
	Transfusion evidence library (from 2016 until 2017) Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding)
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018)
In/Exclusion	Population: <u>Included:</u> adult patients undergoing cardiac surgery.
criteria	 Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL.
	Outcomes: <i>Primary:</i> Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and <i>Secondary</i> : Morbidity-related outcomes that occurred during hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction, congestive heart failure, stroke, renal injury, pneumonia, septic shock, rebleeding, infection, and fatigue).
	Study design: Systematic reviews (+ meta-analyses) of experimental studies (RCT's). If systematic reviews (published within 5 years of the search date) are not available, we will search for individual experimental studies (RCT's). To examine the evidence for the effect of transfusion threshold on the use of RBC transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also

known as a 'trigger'), defined as a haemoglobin or haematocrit level (without
hemodynamic instability) that had to be reached before a RBC transfusion was
administered. We required that control group participants had to have been either
transfused with allogeneic or autologous red blood cells, or both, at higher
haemoglobin or haematocrit levels (transfusion threshold) than the intervention
group, or transfused in accordance with current transfusion practices, which may not
have included a well-defined transfusion threshold, but involved liberal rather than
restrictive transfusion practices. We excluded trials that were not designed to include
any clinical outcomes.

Characteristics of included studies

Author, year, country	Study design	Population	Comparison	Study funding, financial COI and remarks
Bracey, 1999, USA	Experimental: Randomised controlled trial	428 consecutive participants undergoing elective primary coronary artery bypass graft surgery (clinical specialty subgroup (Carson, 2016): cardiac surgery) Restrictive group: n=216, 179 males and 37 females (M/F ratio = 83/17), age=62±11 years Liberal group: n=212, 174 males and 38 females (M/F ratio = 82/18), age=61±11 years	Restrictive group: transfusion in the postoperative period at a Hb level <8.0 g/dL Liberal group: on the instructions of the individual physician who considered clinical assessment of the patient and the institutional guidelines, which proposed a Hb level <9.0 g/dL as the postoperative threshold for RBC transfusion: PRC upits	No information provided on study funding or conflicts of interest. Identified from the systematic review of Carson et al., 2016.
Hajjar, 2010, Brazil	Experimental: Randomised controlled trial	502 adult participants who underwent cardiac surgery with cardiopulmonary bypass (clinical specialty subgroup (Carson, 2016): cardiac surgery) Restrictive group: n=249, 149 males and 100 females, age=58.6±12.5 years Liberal group:	Restrictive group: transfusion if haematocrit <24% (~Hb level <8 g/dL) Liberal group: transfusion if haematocrit <30% (~Hb level <10 g/dL) at any time from start of the surgery until discharge from ICU Transfusion:	Financial disclosures: none reported. Identified from the systematic review of Carson et al., 2016. The substudy Nakamura et al., 2015 (with subpopulations ≥60 years and >60 years) was

		n=253, 161 males and 92 females, age=60.7±12.5 years	allogeneic RBC transfusions	identified from the systematic review Lelubre in the search update.
Johnson, 1992, USA	Experimental: Randomised controlled trial	39 autologous blood donors undergoing elective myocardial revascularisation (clinical specialty subgroup (Carson, 2016): cardiac surgery) Restrictive group: n=20, 20 males, age=58.2±7.5 years Liberal group: n=18, 16 males and 2 females, age=60.5±6.9 years	Restrictive group: transfusion if post- operative haematocrit <25% (~Hb level <8.33 g/dL) Liberal group: transfusion to achieve post- operative haematocrit of 32% (~Hb level <10.67 g/dL) as long as autologous blood was available Transfusion: Autologous blood; sequestration of one or more units autologous blood in patients with haematocrit >35% after anaesthetic induction	One of the authors is supported in part by an NIH award. Identified from the systematic review of Carson et al., 2016.
Koch, 2017, USA	Experimental: Randomised controlled trial	717 adults undergoing CABG surgery or valve procedures (clinical specialty subgroup (Carson, 2016): cardiac surgery) Restrictive group: n=363, 63% males, age=59±15 years Liberal group: n=354, 66% males, age=60±13 years	Restrictive group: transfusion if haematocrit <24% (= +/- 8 g/dL) Liberal group: transfusion if haematocrit <28% (= +/- 9.3 g/dL) Transfusion: One unit of red blood cells was transfused if the hematocrit fell below the designated threshold.	This study was supported in part by the Gus P. Karos Registry Fund, the Kenneth Gee and Paula Shaw, PhD, Chair in Heart Research (EHB), and the Sheikh Hamdan bin Rashid Al Maktoum Distinguished Chair in Thoracic and Cardiovascular Surgery (JFS).
Laine, 2017, Finland	Experimental: Randomised controlled trial	80 patients scheduled for non-emergency coronary artery bypass grafting simple one valve (aortic or	Restrictive group: transfusion if Hb <8.0 g/dL until above this threshold	Trial was supported by a government and by the Finnish

		mitral) replacement or both, requiring cardiopulmonary bypass Restrictive group: n=40, 29 males and 11 females, age (95% confidence interval)=70.5 (67.8-73.2) years Liberal group: n= 40, 28 males and 12 females, age (95% confidence interval)=64.5 (60.6-68.3) years	Liberal group: transfusion if Hb <10.0 g/dL until above this threshold Transfusion: Packed RBC	Angiological Society. Two authors received travel reimbursements from companies, one of which is the supplier of tests used in the experiment. Identified through search update.
Mazer, 2017, Canada	Experimental: Randomised controlled trial	Participants (from 19 countries across the world) older than 18 years of age scheduled to undergo cardiac surgery with cardiopulmonary bypass and who had a preoperative additive EuroSCORE I of 6 or higher (predictive of in-hospital mortality >4%) Restrictive group: n=2430, 1553 males and 877 females, age=72±10 years Liberal group: n=2430, 1586 males and 844 females, age=72±10 years	Restrictive group: transfusion if Hb <7.5 g/dL intraoperatively or postoperatively Liberal group: transfusion if Hb <9.5 g/dL intraoperatively or postoperatively in ICU or if Hb <8.5 g/dL in non-ICU ward Transfusion: allogeneic red cells	Trial was supported by the Canadian Institutes of Health Research, the Canadian Blood Services–Health Canada, the National Health and Medical Research Council of Australia, and the Health Research Council of New Zealand TRICS II and TRIC III trial Identified through search update.
Murphy, 2015, UK	Experimental: Randomised controlled trial	Participants older than 16 years of age who were undergoing nonemergency cardiac surgery with haemoglobin level below 9 g/dL (clinical specialty subgroup (Carson, 2016): cardiac surgery) Restrictive group: n=1000, 693 males and 307 females, median age (interquartile range)=69.9 (63.1-76.0) years	Restrictive group: transfusion if post- surgery Hb level <7.5 g/dL Liberal group: transfusion if post- surgery Hb level <9.0 g/dL Transfusion: Red cells units	Research supported by government program (National Institute for Health Research NIHR)). One author and one research nurse team were supported in part by NIHR research unit. Three authors were supported by the

		Liberal group: n=1003, 680 males and		British Heart Foundation (a charitable
		323 females, median age		organisation). No
		(interquartile range)=70.8		conflicts of
		(64.1-76.7) years		interest reported.
				Identified from
				the systematic
				review of Carson
				et al., 2016.
				Two additional
				reports (Reeves,
				2016 (full report)
				and Stokes, 2016
				(CBA)) Identified
				undate
Shehata 2012	Experimental:	Adult participants	Restrictive aroun:	Study supported
Canada	Randomised	undergoing cardiac	RBC transfusions if	by Canadian
	controlled	surgery with a CARE score	Hb ≤7.0 g/dL during	Blood Service
	trial	(a score for cardiac surgery	cardiopulmonary	(charitable
		participants used to	bypass and ≤7.5	organization).
		predict morbidity and	g/dL postoperatively	Authors declared
		mortality) of 3 or 4, or		that they have no
		participants of advanced	Liberal group:	conflicts of
		age defined as greater	RBC transfusions if	interest.
		than or equal to 80 years	Hb \leq 9.5 g/dL during	
		(clinical specialty subgroup	cardiopulmonary	Identified from
		(Carson, 2016): cardiac	bypass and ≤10 g/dL	the systematic
		surgery)	postoperatively	review of Carson
		Restrictive aroup:	Transfusion	et al., 2010.
		n=25, 17 males and	RBC units	
		$8 \text{ females, age} = 67.2 \pm 11.2$		
		years		
		Liberal group:		
		n=25, 20 males and 5		
		females, age=68.8±9.2		
		years		

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Primary outcomes				
30-day mortality	Restrictive vs	Not statistically significant:	3, 1464 vs 1478	Bracey 1999,
	liberal	44/1464 vs 38/1478		Hajjar 2010,
	transfusion	RR: 1.18, 95%CI [0.77;1.81]¥		Murphy 2015
	threshold	(p=0.46) (Figure 78)		

		Subgroup analysis Hajjar 2010: Participants <60 years: Not statistically significant: 5/124 vs 5/118 § RR: 0.95, 95%CI [0.28;3.20]¥ (p=0.94)**	1, 124 vs 118	Hajjar 2010 (data from Nakamura 2016 identified in search update)
		Subgroup analysis Hajjar 2010: Participants ≥60 years: Not statistically significant: 10/125 vs 7/135 § RR: 1.54, 95%CI [0.61;3.93]¥ (p=0.36)**	1, 125 vs 135	Hajjar 2010 (data from Nakamura 2016 identified in search update)
Hospital mortality		Not statistically significant: 81/2667 vs 94/2676 RR: 0.88, 95%CI [0.48;1.62]¥ (p=0.69)** (Figure 79)	3, 2667 vs 2676	Bracey 1999, Mazer 2017, Shehata 2012
Hospital mortality or multisystem organ failure		Not statistically significant: 3/363 vs 6/354 § RR: 0.49, 95%CI [0.12;1.93]¥ (p=0.31)** (Figure 3)	1, 363 vs 354	Koch, 2017
90-day mortality		Not statistically significant: 42/1000 vs 26/1003 RR: 1.62, 95%CI [1.00;2.62]¥ (p=0.05)* (Figure 4)	1, 1000 vs 1003	Murphy 2015
Participants exposed to blood transfusion		<u>Statistically significant:</u> 2323/4299 vs 3324/4299 RR: 0.69, 95%CI [0.66;0.73] (p<0.00001)** (Figure 5) In favour of restrictive transfusion threshold	7, 4299 vs 4299	Bracey 1999, Hajjar 2010, Johnson 1992, Koch 2017, Mazer 2017, Murphy 2015, Shehata 2012
Units of blood transfused		Statistically significant: MD: -0.87, 95%CI [-1.29;-0.45] (p<0.0001)** (Figure 6) In favour of restrictive transfusion threshold	3, 272 vs 274	Bracey 1999, Johnson 1992, Laine 2017
		Statistically significant: Median (IQR): 2 (1-4) vs 3 (2-5) Rate Ratio: 0.85, 95%CI [0.82;0.88] (p<0.05)	1, 2430 vs 2430	Mazer 2017
Secondary outcomes				
Haemoglobin concentration	Restrictive vs liberal transfusion threshold	Not statistically significant: 9.4±10.5 vs 10.8±8.9 MD: -1.40, 95%CI [-3.10;0.30] (p=0.11)* (Figure 7)	1, 249 vs 253	Hajjar 2010
Cardiac events		Not statistically significant: 108/481 vs 109/487 RR: 0.99, 95%CI [0.75;1.30]¥ (p=0.93)* (Figure 8)	3, 481 vs 487	Bracey 1999, Hajjar 2010, Johnson 1992
Myocardial infarction		Not statistically significant: 150/3712 vs 149/3709 RR: 1.00, 95%CI [0.81;1.25]	6, 3712 vs 3709	Bracey 1999, Johnson 1992,

	(p=0.97)** (Figure 9)		Laine 2017, Mazer 2017, Murphy 2015,
Congestive heart failure	Not statistically significant: 0/20 vs 1/18 § RR: 0.30, 95%CI [0.01;6.97] ¥	1, 20 vs 18	Shehata 2012 Johnson 1992
	(p=0.45)* (Figure 10)		
Cerebrovascular accident (CVA) - stroke	Not statistically significant: 80/4074 vs 84/4064 RR: 0.94, 95%CI [0.69;1.28] ¥ (p=0.70)** (Figure 8011)	6, 4074 ∨s 4064	Hajjar 2010, Johnson 1992, Koch 2017 Mazer 2017, Murphy 2015, Shehata 2012
Rebleeding	Not statistically significant: 25/1261 vs 29/1260 RR: 0.87, 95%CI [0.51;1.48] ¥ (p=0.61)** (Figure 2)	3, 1261 vs 1260	Hajjar 2010, Murphy 2015 (data from Reeves 2016 identified in search update), Shehata 2012
Vascular morbidity	Not statistically significant:	1, 363 vs 354	Koch 2017
(aortic or femoral	0/363 vs 3/354		
artery dissection or	RR: 0.14, 95%CI [0.01;2.69] ¥		
acute limb ischaemia)	(p=0.19)* (Figure 3)		
Sepsis-bacteraemia	Not statistically significant: 218/1371 vs 211/1361 RR: 1.02, 95%CI [0.87;1.21] ¥ (p=0.78)* (Figure 4)	3, 1371 vs 1361	Koch 2017, Murphy 2015, Shehata 2012
Pneumonia	Not statistically significant: 4/25 vs 0/25 § RR: 9.00, 95%CI [0.51;158.85] ¥ (p=0.13)* (Figure 5)	1, 25 vs 25	Shehata 2012
Pneumonia or wound infection	Not statistically significant: 394/3825 vs 369/3852 RR: 1.07, 95%CI [0.94;1.22] (p=0.29)** (Figure 6)	4, 3825 vs 3852	Bracey 1999, Hajjar 2010, Mazer 2017, Murphy 2015
Pulmonary morbidity (pneumonia, pulmonary embolus or prolonged postoperative ventilation >24 hours)	Not statistically significant: 23/363 vs 19/354 § RR: 1.18, 95%CI [0.65;2.13] ¥ (p=0.58)** (Figure 17)	1, 363 vs 354	Koch, 2017
Thromboembolism	Not statistically significant: 10/1010 vs 12/1006 RR: 0.82, 95%CI [0.36;1.88] ¥ (p=0.64)** (Figure 8118)	2, 1010 vs 1006	Murphy 2015 (data from Reeves 2016 identified in search update), Shehata 2012
Renal failure	Not statistically significant: 231/4266 vs 224/4266 RR: 1.04, 95%CI [0.87;1.24] (p=0.66)** (Figure 8219)	6, 4266 vs 4266	Bracey 1999, Hajjar 2010, Koch 2017, Mazer 2017,

				Murphy 2015, Shehata 2012
	Su Pa Nc 4/1 RR (p:	bgroup analysis Hajjar 2010: articipants <60 years: ot statistically significant: 124 vs 3/118 § R: 1.27, 95%CI [0.29;5.55]¥ =0.75)**	1, 124 vs 118	Hajjar 2010 (data from Nakamura 2016 identified in search update)
	Su Pa Nc 6/2 RR (p:	bgroup analysis Hajjar 2010: articipants ≥60 years: ot statistically significant: 125 vs 10/135 § A: 0.65, 95%CI [0.24;1.73]¥ =0.39)**	1, 125 vs 135	Hajjar 2010 (data from Nakamura 2016 identified in search update)
Gastrointestinal morbidity	Nc 5/3 RR (p:	ot statistically significant: 363 vs 2/354 § R: 2.44, 95%CI [0.48;12.48] ¥ =0.28)* (Figure 20)	1, 363 vs 354	Koch, 2017
Reoperative morbidity (for bleeding/tamponade, graft occlusion, valve dysfunction)	Nc 9/3 RR (p=	ot statistically significant: 363 vs 10/354 § R: 0.88, 95%CI [0.36;2.13] ¥ =0.77)* (Figure 21)	1, 363 vs 354	Koch, 2017
Health-related quality of life EQ-5D at 6 weeks	Nс 0.6 МІ (р:	ot statistically significant: 692±0.253 vs 0.686±0.253 D: 0.01, 95%CI [-0.02;0.03] =0.60)** (Figure 22)	1, 1000 vs 1003	Murphy 2015 (data from Stokes 2016 identified in
Health-related quality of life EQ-5D at 3 months	Nc 0.7 МІ (р:	ot statistically significant: 748±0.285 vs 0.750±0.253 D: 0.00, 95%CI [-0.03;0.02] =0.87)** (Figure 23)		search update)

Mean ± SD (unless otherwise indicated)

CI: confidence interval, RR: relative risk, MD: mean difference, IQR: interquartile range

* Calculations (p-value) done by the reviewer(s) using Review Manager software

** Calculations (RR or MD, 95% CI and p-value) done by the reviewer(s) using Review Manager software ¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Forest Plots

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	lotal	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	ABCDEFG
Bracey 1999	3	215	6	222	9.9%	0.52 [0.13, 2.04]		
Hajjar 2010	15	249	13	253	35.7%	1.17 [0.57, 2.41]		
Murphy 2015	26	1000	19	1003	54.4%	1.37 [0.76, 2.46]		$\bullet \bullet ? \bullet \bullet \bullet \bullet$
Total (95% CI)		1464		1478	100.0%	1.18 [0.77, 1.81]	•	
Total events	44		38					
Heterogeneity: Tau ² =	0.00; Chi	i ^z = 1.65	5, df = 2 (P = 0.4-	4); I ² = 0%)		
Test for overall effect:	Z = 0.74 ((P = 0.4	6)				Favours restrictive Favours liberal	
Risk of bias legend								

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 78: Forest plot of outcome: 30-day mortality. Two subgroup analysis for Hajjar 2010 (participants <60 years and participants \geq 60 years respectively can be found in the synthesis of findings table).



(F) Selective reporting (reporting bias)

(G) Other bias

Figure 79: Forest plot of outcome: Hospital mortality.



(G) Other bias

Figure 3: Forest plot of outcome: Hospital mortality or multisystem organ failure.

	Restrictive Liberal			Risk Ratio	Risk Ratio	Risk of Bias		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Murphy 2015	42	1000	26	1003	100.0%	1.62 [1.00, 2.62]		•••
Total (95% CI)		1000		1003	100.0%	1.62 [1.00, 2.62]	◆	
Total events Heterogeneity: Not ap Test for overall effect:	42 plicable Z = 1.97 (P = 0.0	26 5)			F	0.01 0.1 1 10 avours [experimental] Favours [control	100]
Risk of bias legend	o doporo	tion (or	laction bi	iae)				

(A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias) (C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias) (E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias) (C) Otherwise

(G) Other bias

Figure 4: Forest plot of outcome: 90-day mortality.

	Restrictive Lib		Liber	Liberal		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Bracey 1999	74	212	104	216	4.2%	0.72 [0.58, 0.91]	+	•••••
Hajjar 2010	118	249	198	253	9.3%	0.61 [0.52, 0.70]	-	
Johnson 1992	15	20	18	18	3.2%	0.76 [0.58, 0.99]		??????
Koch 2017	195	363	265	354	13.7%	0.72 [0.64, 0.80]	-	
Mazer 2017	1271	2430	1765	2430	34.9%	0.72 [0.69, 0.75]	=	
Murphy 2015	637	1000	952	1003	33.2%	0.67 [0.64, 0.70]	-	
Shehata 2012	13	25	22	25	1.5%	0.59 [0.39, 0.88]		•••??•••
Total (95% CI)		4299		4299	100.0%	0.69 [0.66, 0.73]	1	
Total events	2323		3324					
Heterogeneity: Tau ² =	: 0.00; Chi		100					
Test for overall effect:	Z=14.67	'(P < 0.	00001)	Favours restrictive Favours liber	al			

<u>Risk of bias legend</u> (A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 5: Forest plot of outcome: Participants exposed to blood transfusion.

	Restrictive Liberal							Mean Difference	Mean Difference	Risk of Bias	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG	
Bracey 1999	0.9	1.5	212	1.4	1.8	216	34.5%	-0.50 [-0.81, -0.19]	-		
Johnson 1992	1	0.86	20	2.05	0.93	18	23.9%	-1.05 [-1.62, -0.48]		??????	
Laine 2017	0.9	0.22	40	1.98	0.23	40	41.7%	-1.08 [-1.18, -0.98]	•	?????+++	
Total (95% Cl) 272 274 100.0% -0.87 [-1.29, -0.45] Heterogeneity: Tau ² = 0.11; Chi ² = 11.96, df = 2 (P = 0.003); l ² = 83% -4 -2 0 2 4 Test for overall effect: Z = 4.07 (P < 0.0001)										-	
Test for overall effect: Z = 4.07 (P < 0.0001)											

(G) Other bias

Figure 6: Forest plot of outcome: Units of blood transfused.

	Restrictive Liberal							Mean Difference	Mean Difference	Risk of Bias	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	ABCDEFG	
Hajjar 2010	9.4	10.5	249	10.8	8.9	253	100.0%	-1.40 [-3.10, 0.30]			
Total (95% CI)			249			253	100.0%	-1.40 [-3.10, 0.30]			
Heterogeneity: Not applicable											
Test for overall effect:	Z = 1.61	(P = 0	0.11)						Favours restrictive Favours liberal		
Risk of bias legend											
(A) Random sequence generation (selection bias)											
(B) Allocation concealment (selection bias)											
(C) Blinding of participants and personnel (performance bias)											

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 7: Forest plot of outcome: Haemoglobin concentration.



(A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 8: Forest plot of outcome: Cardiac events.

	Restric	tive	Liber	al	Risk Ratio		Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Bracey 1999	1	212	0	216	0.5%	3.06 [0.13, 74.61]		
Johnson 1992	0	20	1	18	0.5%	0.30 [0.01, 6.97]		??????
Laine 2017	1	40	0	40	0.5%	3.00 [0.13, 71.51]		<mark>?????+++</mark>
Mazer 2017	144	2428	144	2429	95.9%	1.00 [0.80, 1.25]		
Murphy 2015	3	987	4	981	2.2%	0.75 [0.17, 3.32]		$\bullet \bullet ? \bullet \bullet \bullet \bullet$
Shehata 2012	1	25	0	25	0.5%	3.00 [0.13, 70.30]		••??•••
Total (95% CI)		3712		3709	100.0%	1.00 [0.81, 1.25]	•	
Total events	150		149					
Heterogeneity: Tau ² =	0.00; Chi	i ^z = 2.10), df = 5 (l	P = 0.83)		ł	
Test for overall effect:	Z=0.04 ((P = 0.9	7)				Favours restrictive Favours liberal	,

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias)

(G) Other bias

Figure 9: Forest plot of outcome: Myocardial infarction.



(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 10: Forest plot of outcome: Congestive heart failure.



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 801: Forest plot of outcome: Cerebrovascular accident (CVA) - stroke.

	Restrictive		Liberal			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Hajjar 2010	12	249	10	253	42.1%	1.22 [0.54, 2.77]		$\bullet \bullet ? \bullet \bullet \bullet \bullet$
Murphy 2015	12	987	17	982	52.7%	0.70 [0.34, 1.46]		
Shehata 2012	1	25	2	25	5.2%	0.50 [0.05, 5.17]		
Total (95% CI)		1261		1260	100.0%	0.87 [0.51, 1.48]	•	
Total events	25		29					
Heterogeneity: Tau ² =	= 0.00; Chi	² = 1.19	9, df = 2 (P = 0.5)		1	
Test for overall effect	: Z = 0.51 (P = 0.6	1)				Favours restrictive Favours liberal	

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias)

(F) Selective reporting (G) Other bias

Figure 12: Forest plot of outcome: Rebleeding.



(G) Other bias

Figure 13: Forest plot of outcome: Vascular morbidity (aortic or femoral artery dissection or acute limb ischaemia).



(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 14: Forest plot of outcome: Sepsis-bacteraemia.

	Restrictive		Liberal			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Shehata 2012	4	25	0	25	100.0%	9.00 [0.51, 158.85]		
Total (95% CI)		25		25	100.0%	9.00 [0.51, 158.85]		
Total events	4		0					
Heterogeneity: Not ap	oplicable							
Test for overall effect:	Z = 1.50 ((P = 0.1	3)				Favours restrictive Favours liberal	

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias





(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 16: Forest plot of outcome: Pneumonia or wound infection.



Figure 17: Forest plot of outcome: Pulmonary morbidity (pneumonia, pulmonary embolus, or prolonged postoperative ventilation >24 hours).



(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 818: Forest plot of outcome: Thromboembolism



(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 829: Forest plot of outcome: Renal failure. Two subgroup analysis for Hajjar 2010 (participants <60 years and participants \geq 60 years respectively) can be found in the synthesis of findings table.



Figure 20: Forest plot of outcome: Gastrointestinal morbidity.



Figure 21: Forest plot of outcome: Reoperative morbidity.
	Re	strictive	е	L	iberal			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	ABCDEFG
Murphy 2015	0.692	0.253	1000	0.686	0.253	1003	100.0%	0.01 [-0.02, 0.03]		
Total (95% CI)			1000			1003	100.0%	0.01 [-0.02, 0.03]		
Heterogeneity: Not ap	plicable	1								
Test for overall effect:	Z = 0.53) (P = 0.1	60)						Favours restrictive Favours liberal	
<u>Risk of bias legend</u>										
(A) Random sequend	e gener	ation (s	electio	n bias)						
(B) Allocation concea	lment (s	election	ı bias)							
(C) Blinding of partici	oants an	d perso	nnel (p	erforma	ance bia	is)				
(D) Blinding of outcome assessment (detection bias)										
(E) Incomplete outcome data (attrition bias)										
(F) Selective reporting (reporting bias)										
(G) Other bias										

Figure 22: : Forest plot of outcome: Health-related quality of life EQ-5D at 6 weeks.

Study - Sub-	Re	strictiv	e		iberal	T-4-1	184-1-1-4	Mean Difference	Mean Difference	Risk of Bias
Study of Subgroup	mean	50	lotal	mean	SD	lotal	vveight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
Murphy 2015	0.748	0.285	1000	0.75	0.253	1003	100.0%	-0.00 [-0.03, 0.02]		
Total (95% CI)			1000			1003	100.0%	-0.00 [-0.03, 0.02]		
Heterogeneity: Not ap	plicable								1	
Test for overall effect:	7 = 0.17	/P = 0	97)						-100 -50 0 50 100	
reation overall effect.	2-0.17	(i = 0.	01)						Favours restrictive Favours liberal	
Risk of higs leagend										
(A) Bandam soquan	o donor	ation /a	alactia	n hine)						
(A) Random sequence	e gener	auonis	electio	n pias)						
(B) Allocation concea	iment (s	election	i bias)							
(C) Blinding of partici	pants an	id perso	onnel (p	erform	ance bia	is)				
(D) Blinding of outcon	ne asse	ssment	(detec	tion bia	s)					
(E) Incomplete outcor	ne data	(attrition	n bias)							
(E) Selective reporting	(renorti	na hias	1							
(C) Other bios	(iopoin	ng blab	/							
(u) other blas										

Figure 23: : Forest plot of outcome: Health-related quality of life EQ-5D at 3 months.

Quality of evidence

Author, Year	Lack of allocation concealment and random sequence generation (selection bias)	Lack of blinding (performance bias)	Incomplete accounting of outcome events (attrition bias)	Selective outcome reporting (reporting bias)	Other limitations
Bracey, 1999	Randomization: Yes, participants were randomly assigned on the basis of the last digit of their medical record number. Allocation concealment: Yes, inadequate concealment (record number).	Participants and personnel: Unclear, no information provided. Outcome assessors: No, outcome of mortality allows a judgement of low risk of bias. Morbidity information was collected from the hospital database. The trial provided no information regarding the survey questionnaire	No, trial used intention-to- treat analysis and reported the exclusion of a small number of participants.	Yes No pre- registration of study protocol	No
Hajjar, 2010	Randomization: No, chief statistician prepared a random number table to use. Allocation concealment: No, opaque envelopes were opened sequentially.	Participants and personnel: Unclear, participants were blinded but clinicians were not. Outcome assessors: No, assessor was blinded.	No, intention-to- treat analysis was undertaken. Follow-up was complete.	No Pre- registration of study protocol @ ClinicalTrials. Gov (NCT0102163 1)	No
Johnson, 1992	Randomization: Unclear, a table of random numbers and an odd-even designation randomized participants. Allocation concealment: Unclear, no information provided.	Participants and personnel: Unclear, surgeons and anaesthesiologists were blinded as to the group of randomisation until the participant reached the intensive care unit (ICU). Outcome assessors: Unclear, no information provided.	Unclear, small number of exclusions were reported.	Yes No pre- registration of study protocol	No
Koch, 2017	Randomization: No, randomization was stratified by	Participants and personnel: No Outcome assessors: No	No, no lost to follow up or discontinued	No Pre- registration	No

	site, using within each site randomly sized blocks of 6, 8, 10, and 12 so that at any given time, approximately equal numbers of patients were randomized into each transfusion trigger group Allocation concealment: unclear, no information provided	Surgeons were blinded to the study arm, as were personnel assessing patient outcomes and the patients themselves.	intervention in both groups.	of study protocol @ ClinicalTrials. Gov (NCT0065157 3)	
Laine, 2017	Randomization: Unclear, randomization was done in blocks of 20 patients. Allocation concealment: Unclear, closed envelopes were used.	Participants and personnel: Unclear, blinding was not possible. Outcome assessors: Unclear, no information provided.	No, complete follow-up reported.	Unclear Pre- registration of study protocol @ Hospital District of Helsinki and Uusimaa (§94,9.05.201 4)	No
Mazer, 2017	Randomization: No, trial used a centralized, Web- based system which stratified according to center, with acomputer- generated random permuted blocks of varying sizes from two to six. Allocation concealment: No, a concealed centralized Web- based system was used.	Participants and personnel: Unclear, it was not possible to use formal blinding of the assigned transfusion strategy with regard to the participants and medical staff. However, participants were not actively informed about the treatment assignment. Outcome assessors: No, outcome adjudicators were unaware of the trial- group assignments.	No, low loss to follow-up.	No Pre- registration of study protocol @ ClinicalTrials. Gov (NCT0204289 8)	No
Murphy, 2015	Randomization: No, internet- based system	Participants and personnel:	No, Iow loss to follow-up.	No	No

	used with and cohort minimisation to balance assignments according to centre and type of surgery. Allocation concealment: No, trial used an internet-based system that concealed assignments.	Unclear, physicians and nurses were aware of the group assignments. Participants were meant to be unaware of assignment however at discharge 15.1% of patients believed they knew treatment and 75.6% was correct. Outcome assessors: No, outcomes were adjudicated.		Pre- registration of study protocol (Current Controlled Trials number, ISRCTN70923 932)	
Shehata, 2012	Randomization: No, randomization sequence was created using permuted blocks of four stratified by age and the Cardiac Anesthesia Risk Score (CARE). Allocation concealment: No, opaque sequential sealed envelopes were opened at the start of surgery.	Participants and personnel: Unclear, clinicians and participants were not blinded. Outcome assessors: Unclear, no information provided.	No, outcome data were complete.	No Pre- registration of study protocol @ ClinicalTrials. Gov (NCT0047044 4)	No

Certainty of the body of evidence: see GRADE evidence tables

Conclusion	See Evidence-to-Decision template
	Articles
	Bracey 1999
	Bracey AW, Radovancevic R, Riggs SA, Houston S, Cozart H, Vaughn WK, et al.
	Lowering the hemoglobin threshold for transfusion in coronary artery bypass
	procedures: effect on patient outcome. Transfusion 1999, 39(10):1070–1077.
	Hajjar 2010
Reference(s)	*Hajjar LA, Vincent JL, Galas FR, Nakamura RE, Silva CM, Santos MH, et al.
	Transfusion requirements after cardiac surgery: the TRACS randomized controlled
	trial. JAMA 2010, 304(14):1559–1567.
	Nakamura RE, Vincent JL, Fukushima JT, de Almeida JP, Franco RA, Lee Park C, et al.
	A liberal strategy of red blood cell transfusion reduces cardiogenic shock in elderly
	patients undergoing cardiac surgery. J Thorac Cardiovasc Surg 2015, 150(5):1314-
	1320. Identified from systematic review (Lelubre 2016) in search update.

	Johnson 1992
	Johnson RG, Thurer RL, Kruskall MS, Sirois C, Gervino EV, Critchlow J, et al.
	Comparison of two transfusion strategies after elective operations for myocardial
	revascularization 1 Thorac Cardiovasc Surg 1992·104(2)·307–314
	Koch 2017
	Koch CG. Sosslar DI. Mascha El. Sabik IE. Li I. Duncan AI. Zimmarman NM
	Noch CG, Sessier Di, Mascha EJ, Sabik JF, EFE, Duncan AI, Zimmerman Nivi,
	Blackstone EH. A randomized clinical trial of rea blood cell transfusion triggers in
	cardiac surgery. Ann Thorac Surg 2017;104:1243-1250.
	Laine 2017
	Laine A, Niemi T, Schramko A. <i>Transfusion threshold of hemoglobin 80 g/L is</i>
	comparable to 100 g/L in terms of bleeding in cardiac surgery: a prospective
	randomized study. J Cardiothorac Vasc Anesth 2017, pii: S1053-0770(17)30721-8.
	[Epub ahead of print]
	Mazer 2017
	Mazer CD Whitlock RP Fergusson DA Hall J Belley-Cote F Connolly K et al
	Restrictive or Liberal Red-Cell Transfusion for Cardiac Surgery, N Engl Med 2017
	D//(22).2100-2144.
	Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD, et al. <i>Liberal</i>
	or restrictive transfusion after cardiac surgery. N Engl J Med 2015, 372: 997–1008.
	*Reeves BC, Pike K, Rogers CA, Brierley RC, Stokes EA, Wordsworth S, et al. A
	multicentre randomised controlled trial of Transfusion Indication Threshold
	Reduction on transfusion rates, morbidity and health-care resource use following
	cardiac surgery (TITRe2). Health Technol Assess 2016, 20(60):1-260. Identified in
	search update.
	Stokes EA. Wordsworth S. Bargo D. Pike K. Rogers CA. Brierley RC. et al. Are lower
	levels of red blood cell transfusion more cost-effective than liberal levels after cardiac
	surgery? Findings from the TITRe? randomised controlled trial BMI Open 2016
	Shahata 2012
	Shehata 2012 Shehata N. Burns I.A. Nathan I.I. Hahart D. Hara C.M. Fargusson D. at al. A
	Shehala N, Burlis LA, Nathan H, Hebert P, Hare Givi, Fergusson D, et al. A
	ranaomized controlled pilot study of danerence to transfusion strategies in cardiac
	surgery. Transfusion 2012, 52(1):91–99.
	<u>Systematic reviews</u>
	Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC.
	Transfusion thresholds and other strategies for guiding allogeneic red blood cell
	transfusion. Cochrane Database Syst Rev. 2016, 10:CD002042.
	Lelubre C, Vincent JL, Taccone FS. Red blood cell transfusion strategies in critically ill
	patients: lessons from recent randomized clinical studies. Minerva Anestesiol 2016,
	82(9):1010-6.
	Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ,
	Goodman SG. Rao SV. Doree C. Hebert PC. Clinical trials evaluating red blood cell
	transfusion thresholds: an undated systematic review and with additional focus on
	nations with cardiovascular disease In near-review (February 2018)
	patients with curatovascular discuse. In peer review [rebruary 2010].
	*Indicates the major publication for the study
Evidence used for	Consensus meeting PBM
Project	PBM
Reviewer(s)	Anne-Catherine Vanhove

PICO 10: RBC transfusion triggers in adult haematological patients

Overview evidence table GRADE software (PICO 10)

Certainty assessment							Nº of p	oatients	E	ffect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7/8 g/dL)	more liberal RBC transfusion triggers (Hb <8/12 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
RBC tran	nsfusion (units	5)										
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	59	30	-	MD 3.1 RBC units lower (5.31 lower to 0.89 lower)	⊕⊕⊖⊖ LOW	IMPORTANT
30-day r	nortality	•		•	•	•	•	•	•	•		•
2	randomised trials	not serious	not serious	not serious	very serious	none	2/88 (2.3%)	4/61 (6.6%)	RR 0.37 (0.07 to 1.95)	41 fewer per 1.000 (from 61 fewer to 62 more)	⊕⊕⊖⊖ LOW	CRITICAL
Patients	received RBC	transfusio	n									
2	randomised trials	not serious	not serious	not serious	very serious	none	85/88 (96.6%)	59/61 (96.7%)	RR 1.00 (0.95 to 1.05)	0 fewer per 1.000 (from 48 fewer to 48 more)	⊕⊕⊖⊖ LOW	CRITICAL
Bleeding	g events (by g	rade: 0-1 v	s 2-4)									

	Certainty assessment							oatients	Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7/8 g/dL)	more liberal RBC transfusion triggers (Hb <8/12 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	50/59 (84.7%)	25/30 (83.3%)	RR 1.02 (0.84 to 1.23)	17 more per 1.000 (from 133 fewer to 192 more)	⊕⊕⊖⊖ Low	IMPORTANT
Length o	of inpatient st	ay (days)										
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	59	30	-	median 0.5 days lower (0 to 0)	⊕⊕⊖⊖ LOW	IMPORTANT
Fatigue	scale score		•	•	•							
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	59	30	-	median 0.3 points higher (0 to 0)	⊕⊕⊖⊖ LOW	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

a. Lack of generalizibility: evidence from 1 USA study; b. Limited sample size or low number of events; c. Large variability of results

Detailed evidence summary (PICO 10)

Topic Patient Blood Management Evidence-based transfusion strategies: RBC transfusion triggers Subtopic Restrictive RBC transfusion triggers Intervention In adult haematological patients (Population), is the use of a restrictive **Question (PICO)** transfusion threshold (Intervention) effective to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusion threshold (Comparison)? The Cochrane systematic review by Carson et al. (2016) and its Search Strategy updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to: Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017) Identify observational studies in case no experimental studies were available. Databases The Cochrane Library (systematic reviews and controlled trials) using the following search strategy: **Systematic reviews** #1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti)) #3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4 Results #hits (on Wednesday 6 July: 25 Cochrane reviews) **Individual experimental studies** #1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti)) #2 thrombocytopeni*:ti OR thrombocytopaeni*:ti OR leukemi*:ti OR leukaemi*:ti OR lymphom*:ti OR "aplastic anemia":ti OR "aplastic anaemia":ti OR myelodysplas*:ti OR myeloproliferat*:ti OR myeloma:ti OR lymphogranulomato*:ti OR histiocy*:ti OR granulom*:ti OR thrombocythemi*:ti OR thrombocythaemi*:ti OR polycythemi*:ti OR polycythaemi*:ti OR myelofibros*:ti OR AML:ti OR CLL:ti OR CML:ti OR Hodgkin*:ti OR burkitt*:ti OR lymphosarcom*:ti OR brill-symmer*:ti OR sezary:ti OR ((haematolog*:ti OR hematolog*:ti OR blood:ti OR red cell*:ti OR white cell*:ti OR marrow:ti OR platelet*:ti) AND (malignan*:ti OR oncolog*:ti OR cancer*:ti OR neoplasm*:ti OR carcinoma*:ti)) OR chemotherap*:ti OR radiotherap*:ti OR chemoradiotherap*:ti

EVIDENCE SUMMARY

OR "stem cell":ti OR "stem cells" OR "progenitor cell":ti OR "progenitor cells":ti OR bone marrow transplant*:ti OR bone marrow graft*:ti OR "bone marrow rescue":ti OR rituximab:ti OR antineoplast*:ti OR anti-neoplast*:ti OR ASCT:ti OR ABMT:ti OR PBPC:ti OR PBSCT:ti OR PSCT:ti OR BMT:ti OR SCT:ti OR HSCT:ti OR "haematology patients":ti OR "hematology patients":ti OR "haematological patients":ti OR "hematological patients":ti OR "hemato-oncology patients":ti OR "haemato-oncology patients":ti OR remission:ti OR ((consolidat*:ti OR induct*:ti OR maintenance:ti OR conditioning*:ti) AND (therap*:ti OR treat*:ti OR regimen*:ti OR patient*:ti)) OR ((cytosta*:ti OR cytotox*:ti) AND (therap*:ti OR treat*:ti OR regimen*:ti)) OR ((multimodal*:ti OR multi-modal*:ti) AND (treat*:ti OR therap*:ti)) OR (combi*:ti AND modalit*:ti) OR (allograft*:ti OR allo-graft*:ti OR allotransplant*:ti OR allo-transplant*:ti OR ((allogen*:ti OR allo-gen*:ti) AND (transplant*:ti OR trasplant*:ti OR graft*:ti OR rescue*)) OR homograft*:ti OR homo-graft*:ti OR homolog*:ti OR homotransplant*:ti OR homo-transplant*:ti OR homotrasplant*:ti OR homo trasplant*:ti) OR (autograft*:ti OR autograft*:ti OR autotransplant*:ti OR auto-transplant*:ti OR mini-transplant*:ti) OR (autolog*:ti AND (transplant*:ti OR graft*:ti OR trasplant*:ti OR rescu*:ti)) #3 #1 AND #2 (results #hits on 13 July 2017: 531 trials)

MEDLINE (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy:

Systematic reviews

#1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI]))

#2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI]))

#3 (blood[TI] AND (management[TI] OR program*[TI])) #4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI]))

#5 #1 OR #2 OR #3 OR #4

#6 (((((((((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR (((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh])))

#7 #5 AND #6 (Results #hits (on 6 July 2017): 224)

Individual experimental/observational studies

#1 (((erythrocyte*[TI] OR blood[TI]) AND (unit*[TI] AND trigger*[TI] OR level*[TI] OR threshold*[TI] OR rule*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR requir*[TI] OR reduc*[TI] OR limit*[TI])) OR (hemotransfus*[TI] OR

haemotransfus*[TI] OR hemotherap*[TI] OR haemotherap*[TI] OR "red cell*"[TI]OR "red blood cell*"[TI] OR RBC*[TI] OR transfus*[TI])) #2 (thrombocytopeni*[TI] OR thrombocytopaeni*[TI] OR leukemi*[TI] OR leukaemi*[TI] OR lymphom*[TI] OR "aplastic anemia"[TI] OR "aplastic anaemia"[TI] OR myelodysplas*[TI] OR myeloproliferat*[TI] OR myeloma[TI] OR lymphogranulomato*[TI] OR histiocy*[TI] OR granulom*[TI] OR thrombocythemi*[TI] OR thrombocythaemi*[TI] OR polycythemi*[TI] OR polycythaemi*[TI] OR myelofibros*[TI] OR AML[TI] OR CLL[TI] OR CML[TI] OR Hodgkin*[TI] OR burkitt*[TI] OR lymphosarcom*[TI] OR brill-symmer*[TI] OR sezary[TI] OR ((haematolog*[TI] OR hematolog*[TI] OR blood[TI] OR red cell*[TI] OR white cell*[TI] OR marrow[TI] OR platelet*[TI]) AND (malignan*[TI] OR oncolog*[TI] OR cancer*[TI] OR neoplasm*[TI] OR carcinoma*[TI])) OR chemotherap*[TI] OR radiotherap*[TI] OR chemoradiotherap*[TI] OR "stem cell"[TI] OR "stem cells" OR "progenitor cell"[TI] OR "progenitor cells"[TI] OR bone marrow transplant*[TI] OR bone marrow graft*[TI] OR "bone marrow rescue"[TI] OR rituximab[TI] OR antineoplast*[TI] OR anti-neoplast*[TI] OR ASCT[TI] OR ABMT[TI] OR PBPC[TI] OR PBSCT[TI] OR PSCT[TI] OR BMT[TI] OR SCT[TI] OR HSCT[TI] OR "haematology patients"[TI] OR "hematology patients"[TI] OR "haematological patients"[TI] OR "hematological patients"[TI] OR "hemato-oncology patients" [TI] OR "haemato-oncology patients" [TI] OR remission[TI] OR ((consolidat*[TI] OR induct*[TI] OR maintenance[TI] OR conditioning*[TI]) AND (therap*[TI] OR treat*[TI] OR regimen*[TI] OR patient*[TI])) OR ((cytosta*[TI] OR cytotox*[TI]) AND (therap*[TI] OR treat*[TI] OR regimen*[TI])) OR ((multimodal*[TI] OR multi-modal*[TI]) AND (treat*[TI] OR therap*[TI])) OR (combi*[TI] AND modalit*[TI]) OR (allograft*[TI] OR allograft*[TI] OR allotransplant*[TI] OR allo-transplant*[TI] OR ((allogen*[TI] OR allo-gen*[TI]) AND (transplant*[TI] OR trasplant*[TI] OR graft*[TI] OR rescue*)) OR homograft*[TI] OR homo-graft*[TI] OR homolog*[TI] OR homotransplant*[TI] OR homo-transplant*[TI] OR homotransplant*[TI] OR homo trasplant*[TI]) OR (autograft*[TI] OR autograft*[TI] OR autotransplant*[TI] OR auto-transplant*[TI] OR mini-transplant*[TI]) OR (autolog*[TI] AND (transplant*[TI] OR graft*[TI] OR trasplant*[TI] OR rescu*[TI])) #3 ("Epidemiologic Studies"[Mesh] OR "case control"[TIAB] OR "casecontrol"[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR controls[TIAB]) OR "cohort study"[TIAB] OR "cohort analysis"[TIAB] OR "follow up study"[TIAB] OR "follow-up study"[TIAB] OR "observational study"[TIAB] OR "longitudinal"[TIAB] OR "retrospective"[TIAB] OR "cross sectional"[TIAB] OR "cross-sectional"[TIAB] OR questionnaire[TIAB] OR questionnaires[TIAB] OR survey[TIAB]) #4 (random* OR blind* OR "control group" OR placebo* OR controlled OR groups OR trial* OR "systematic review" OR "metaanalysis" OR metaanalysis OR "literature search" OR medline OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb]) #5 #3 OR #4 #6 #1 AND #2 AND #5 (Results #hits (on 12 July 2017): 1325) **Embase** (via Embase.com interface) using the following search strategy: Systematic reviews #1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR

standard*:ti))

#3 (blood:ti AND (management:ti OR program*:ti))

#4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #2 OR #4
#5 #1 OR #2 OR #5 OR #4
#6 (systematic reviews) meta analysis (topic) /exp OR meta analysis /exp OR
meta analysis :ab,ti OR meta-analysis :ab,ti OR systematic review (topic) /exp
OR systematic review /exp OR cochrane :ab,ti OR embase :ab,ti OR
pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti
OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR
'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR
'data extraction':ab,ti
#7 #5 AND #6 (systematic reviews) (Results #hits on 6 July 2017: 227)
Individual experimental/observational studies
#1 (((erythrocyte^:ti OR blood:ti) AND (unit^:ti AND trigger^:ti OR level^:ti OR
CP roduc*ti OP limit*ti) OP (homotropefus*ti OP homotropefus*ti OP
hemotheran*ti OR haemotheran*ti OR "red cell*"ti OR "red blood cell*"ti OR
RBC*:ti OR transfus*:ti))
#2 thrombocytopeni*:ti OR thrombocytopaeni*:ti OR leukemi*:ti OR
leukaemi*:ti OR lymphom*:ti OR "aplastic anemia":ti OR "aplastic anaemia":ti
OR myelodysplas*:ti OR myeloproliferat*:ti OR myeloma:ti OR
lymphogranulomato*:ti OR histiocy*:ti OR granulom*:ti OR thrombocythemi*:ti
OR thrombocythaemi*:ti OR polycythemi*:ti OR polycythaemi*:ti OR
myelofibros*:ti OR AML:ti OR CLL:ti OR CML:ti OR Hodgkin*:ti OR burkitt*:ti OR
lymphosarcom*:ti OR brill-symmer*:ti OR sezary:ti OR ((haematolog*:ti OR
hematolog*:ti OR blood:ti OR red cell*:ti OR white cell*:ti OR marrow:ti OR
platelet*:ti) AND (malignan*:ti OR oncolog*:ti OR cancer*:ti OR neoplasm*:ti OR
carcinoma*:ti)) OR chemotherap*:ti OR radiotherap*:ti OR chemoradiotherap*:ti
OR "stem cell":ti OR "stem cells" OR "progenitor cell":ti OR "progenitor cells":ti
OR bone marrow transplant*:ti OR bone marrow graft*:ti OR "bone marrow
rescue":ti OR rituximab:ti OR antineoplast*:ti OR anti-neoplast*:ti OR ASCT:ti OR
ABMT:ti OR PBPC:ti OR PBSCT:ti OR PSCT:ti OR BMT:ti OR SCT:ti OR HSCT:ti OR
"haematology patients":ti OR "hematology patients":ti OR "haematological
patients":ti OR "hematological patients":ti OR "hemato-oncology patients":ti OR
"haemato-oncology patients":ti OR remission:ti OR ((consolidat*:ti OR induct*:ti
OR maintenance:ti OR conditioning*:ti) AND (therap*:ti OR treat*:ti OR
regimen*:ti OR patient*:ti)) OR ((cytosta*:ti OR cytotox*:ti) AND (therap*:ti OR
treat*:ti OR regimen*:ti)) OR ((multimodal*:ti OR multi-modal*:ti) AND (treat*:ti
OR therap*:ti)) OR (combi*:ti AND modalit*:ti) OR (allograft*:ti OR allo-graft*:ti
OR allotransplant*:ti OR allo-transplant*:ti OR ((allogen*:ti OR allo-gen*:ti) AND
(transplant*:ti OR trasplant*:ti OR graft*:ti OR rescue*)) OR homograft*:ti OR
homo-graft*:ti OR homolog*:ti OR homotransplant*:ti OR homo-transplant*:ti
OR homotrasplant*:ti OR homo trasplant*:ti) OR (autograft*:ti OR autograft*:ti
OR autotransplant*:ti OR auto-transplant*:ti OR mini-transplant*:ti) OR
(autolog*:ti AND (transplant*:ti OR graft*:ti OR trasplant*:ti OR rescu*:ti))
#3 ('clinical study'/exp OR 'cohort analysis'/exp OR 'case control':ab,ti OR
'case-control':ab,ti OR ((case:ab,ti OR cases:ab,ti) AND (control:ab,ti OR
controls:ab,ti)) OR 'cohort study':ab,ti OR 'cohort analysis':ab,ti OR 'follow up
study':ab,ti OR 'follow-up study':ab,ti OR 'observational study':ab,ti OR
'longitudinal':ab,ti OR 'retrospective':ab,ti OR 'cross sectional':ab,ti OR 'cross-
sectional':ab,ti OR questionnaire:ab,ti OR questionnaires:ab,ti OR survey:ab,ti
OR 'epidemiological study':ab,ti)
#4 ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative
study'/exp OR random*:ab,ti OR control*:ab,ti OR 'intervention study':ab,ti OR

	'experimental study':ab,ti OR 'comparative study':ab,ti OR trial:ab,ti OR evaluat*:ab,ti OR 'before and after':ab,ti OR 'interrupted time series':ab,ti) NOT ('animal'/oxp NOT 'buman'/oxp)
	(animal/exp NOT human/exp) #5 #3 OR #4
	#6 #1 AND #2 AND #5 (Results #hits (on 13 July 2017): 735)
	Transfusion evidence library
	Systematic reviews
	 #1 Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding) #2 systematic review filter #3 #1 AND #2 (results #hits on 6 July 2017: 427 SRs)
	Individual experimental studies
	#1 Clinical specialty: Haematology and oncology
	#2 restrict* OR liberal OR trigger* OR threshold* OR hemoglobin OR
	#3 #1 AND #2 (results #hits on 11 July 2017: 361 RCTs)
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson
	2018)
	26/01/2018 (update)
In/Exclusion criteria	Population: <u>Included:</u> adult haematological patients, a.) acute malignant haematological diseases like acute lymphatic leukemia (ALL), etc. under
	different therapeutic regimen: aa.) chemotherapy, ab.) hematopoietic stem cell
	transplantation; b.) chronic malignant haematological diseases (extremely rare
	in children) c.) hereditary haematological diseases (typically "benign")
	associated with anemia like sickle cell disease, thalassemia, etc an increasing
	problem in Europe! Based on the amount of evidence that will be identified,
	conducted Excluded: children infants or neonates
	Intervention: the use of a restrictive transfusion threshold as a mean of
	guiding allogeneic or autologous RBC transfusion. A restrictive transfusion
	threshold most often refers to administration of blood transfusion when the
	haemoglobin level fails below 7 g/dL to 8 g/dL.
	Comparison: the use of a liberal transfusion threshold as a mean of guiding
	allogeneic or autologous RBC transfusion. A liberal transfusion threshold most
	often refers to administration of blood transfusion when the haemoglobin level
	Tails below 9 g/dL to 10 g/dL.
	Outcomes: Primary: Mortality (30-day mortality or in-hospital mortality, during
	hospital admission, at 90 days or long term) or other clinical outcomes
	including outcomes related to RBC transfusion use (i.e. proportion of
	participants exposed to transfusion, participants exposed to allogeneic or
	autologous transtusion, units of blood transfused (in those receiving any transfusion)) and Secondary. Morbidity-related outcomes that occurred during
	hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction,

congestive heart failure, stroke, renal injury, pneumonia, septic shock, rebleeding, infection, and fatigue).
Study design: <u>Included:</u> The following study designs were included: 1) (cluster) randomized controlled trials included in the Cochrane review by Carson et al (May 2016) or other systematic reviews identified in the update and 2) individual (cluster) randomized controlled trials not included in a systematic review or 3) observational studies if no experimental studies were identified. To examine the evidence for the effect of transfusion threshold on the use of RBC transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or haematocrit level (without hemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic or autologous red blood cells, or both, at higher haemoglobin or haematocrit levels (transfusion threshold) than the intervention group, or transfused in accordance with current transfusion practices, which may not have included a well-defined transfusion threshold, but involved liberal rather than restrictive transfusion practices. We excluded trials that were not designed to include any clinical outcomes.

Author, year, Country	Study design	Population	Comparison	Study funding, financial COI and remarks
DeZern, 2016, USA	Experimental: RCT	89 acute leukaemia participants (acute myeloid leukaemia, acute lymphoblastic leukaemia/ lymphoma, acute promyelocytic leukaemia, treatment-related myeloid neoplasm, highgrade myelodysplastic syndrome) more than 18 years of age admitted to the inpatient leukaemia services with plans for inpatient myelosuppressive chemotherapy	Restrictive group: single-unit RBC transfusion if Hb <7 g/dL Liberal group: single- unit RBC transfusion if Hb <8 g/dL	The authors have disclosed no COI. This work was supported by a grant from the Society for the Advancement of Blood Management (SABM) sponsored by Haemonetics Corp. (Braintree, MA; to AED).
		 Restrictive group (n=59): mean age (interquartile range) = 56 (45.5 to 67) years Liberal group (n=30): mean age (interquartile range) = 62.5 (55.2 to 67.8) years 		

Characteristics of included studies

Webert, 2008, Canada	Experimental: RCT	60 adult participants with acute leukaemia were randomly allocated to 1 of 2 groups:	Restrictive group: 2- unit RBC transfusion if Hb <8 g/dL, with a target range of 8.5 to	This study was funded by a grant from Canadian Blood Services
			9.5 g/dL	and a CIHR
		 Restrictive group: n=29; 		Canada Research
		M/F=18/11; mean (SD) age		Chair. KEW was
		= 50.8 (15.3) years	Liberal group: 2-unit	supported
			RBC transfusion if Hb	by a Canadian
		 Liberal group: n=31; M/F 	<12 g/dL	Blood
		= 14/17; mean (SD) age =		Services/Novo
		45.3 (16.8) years		Nordisk Research
				Fellowship in
				Hemostasis. RJC
				is a Canada
				Research Chair.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
PRIMARY OUTCON	<mark>//ES</mark>			
RBC transfusions (units)	Restrictive vs liberal	<u>Statistically significant:</u> 8.2±4.2 vs 42.4±5.0 MD: -3.10, 95%CI [-5.31;-0.89] (p=0.006)* (Figure 1) In favour of restrictive group	1, 59 vs 30 §	DeZern, 2016
30-day mortality	Restrictive vs liberal	Not statistically significant: 2/88 vs 4/61 § RR: 0.37, 95%CI [0.07;1.95] ¥ (p=0.24)* (Figure 2)	2, 88 vs 61	DeZern, 2016, Webert 2008
Participants exposed to blood transfusion	Restrictive vs liberal	Not statistically significant: 85/88 vs 59/61 § RR: 1.0, 95%CI [0.95;1.05] (p=1.00)* (Figure 3)	2, 88 vs 61	DeZern, 2016, Webert 2008
SECONDARY OUT				
Bleeding events (by grade: 0-1 vs 2-4)	Restrictive vs liberal	Not statistically significant: 50/59 vs 25/30 § RR: 1.02, 95%CI [0.84;1.23] (p=0.86)* (Figure 4)	1, 59 vs 30	DeZern, 2016
Length of inpatient stay (days)	Restrictive vs liberal	Not statistically significant: 35.5 (31.2-43.8) vs 36.0 (29.2- 44.0) (median (interquartile range)) (p=0.53)	1, 59 vs 30 §	DeZern, 2016
Fatigue scale score	Restrictive vs liberal	Not statistically significant: 4.8 (4.0-5.2) vs 4.5 (3.6-5.0) (median (interquartile range)) (p=0.32)	1, 59 vs 30 §	DeZern, 2016

Episodes of	Restrictive vs liberal	Not statistically significant:	1, 59 vs 30	DeZern,
neutropenic fever		38/59 vs 22/30 §		2016
(0-1 vs 2-5)		RR: 0.88, 95%CI [0.66;1.17] ¥		
		(p=0.38)* (Figure 5)		

Mean ± SD (unless otherwise indicated)

CI: confidence interval, RR: relative risk, MD: mean difference

* Calculations (RR or MD, 95% CI and/or p-value) done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Forest plots

-	Rest	trictiv	/e	Lil	beral			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	ABCDEFG
DeZern 2016	8.2	4.2	59	42.4	5	30	100.0%	-34.20 [-36.29, -32.11]		
Total (95% CI)			59			30	100.0%	-34.20 [-36.29, -32.11]	•	
Heterogeneity: Not applicable Test for overall effect: Z = 32.14 (P < 0.00001)									-50 -25 0 25 Favours restrictive Favours liberal	50
<u>Risk of bias legend</u> (A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias)										

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 83: Forest plot of outcome: RBC transfusions (units).



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 2: Forest plot of outcome: 30-day mortality

	Restric	estrictive Liberal			Risk Ratio		Risk Ratio	Risk of Bias	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG	
DeZern 2016	59	59	30	30	90.3%	1.00 [0.95, 1.05]			
Webert 2008	26	29	29	31	9.7%	0.96 [0.82, 1.12]	+		
Total (95% CI)		88		61	100.0%	1.00 [0.95, 1.05]			
Total events	85		59						
Heterogeneity: Tau ² =	: 0.00; Chi	ř = 0.55	5, df = 1 (l	P = 0.48	5); I ² = 0%			ł	
Test for overall effect:	Z=0.17 (P = 0.8	7)				Favours restrictive Favours liberal		
Risk of bias legend									
(A) Random sequence generation (selection bias)									
(B) Allocation concealment (selection bias)									
(C) Directions of eachietic									

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 3: Forest plot of outcome: Participants exposed to blood transfusion



(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 4: Forest plot of outcome: Bleeding events (by grade: 0-1 vs 2-4)

	Restrictive Liberal			Risk Ratio	Risk Ratio	Risk of Bias					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG			
DeZern 2016	38	59	22	30	100.0%	0.88 [0.66, 1.17]					
Total (95% CI)		59		30	100.0%	0.88 [0.66, 1.17]	•				
Total events	38		22								
Heterogeneity: Not ap	Heterogeneity: Not applicable										
Test for overall effect:	Z = 0.89 (P = 0.3	8)				Favours restrictive Favours liberal				
<u>Risk of bias legend</u>											
(A) Random sequend	e generat	tion (se	election b	ias)							
(B) Allocation concea	lment (sel	lection	bias)								
(C) Blinding of partici	pants and	persor	nnel (perf	orman	ce bias)						
(D) Blinding of outcon	ne assess	sment	(detectior	ı bias)							
(E) Incomplete outcor	ne data (a	attrition	bias)								

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 5: Forest plot of outcome: Episodes of neutropenic fever (0-1 vs 2-5)

Quality of evidence

Author, Year	Lack of allocation concealment and random sequence generation (selection bias)	Lack of blinding (performance bias)	Incomplete accounting of outcome events (attrition bias)	Selective outcome reporting (reporting bias)	Other limitations
DeZern, 2016	Randomization:	Participants and personnel: yes	No	No	No
	software	(participants and		Pre-	
	generated the	personnel were not		registration	
	random number	blinded)		of study	
	sequence)			protocol @	
				ClinicalTrials.	
	Allocation	Outcome assessors: no		Gov	
	concealment: no	(risk varied by outcome:		(NC10208677	
	(sealed opaque	of mortality: other		3)	
	numbered	secondary outcomes			
	envelopes were	had a high risk)			
	used)	,			
Webert,	Randomization:	Participants and	No (no	Yes	No
2008	no (sequence	personnel: unclear	missing data)		
	generation was	(participants and		No pre-	
	computer-	personnel were not		registration	
	generated)	blinded)		of study	
	Allocation			ριστοςοι	
	concealment: no	Outcome assessors: no			
	(allocation was	(outcomes were			
	internet-based	assessed blinded)			
	and central)	, , , , , , , , , , , , , , , , , , ,			

Certainty of the body of evidence: see GRADE Evidence tables

Conclusion	See Evidence-to-Decision template						
Reference(s)	Articles DeZern 2016 DeZern AE, Williams K, Zahurak M, Hand W, Stephens RS, King KE, Frank SM, Ness PM. Red blood cell transfusion triggers in acute leukemia: a randomized pilot study. Transfusion 2016, 56(7): 1750-1757. Webert 2008 Webert KE, Cook RJ, Couban S, Carruthers J, Lee KA, Blajchman MA, Lipton JH, Brandwein JM, Heddle NM. A multicenter pilot-randomized controlled trial of the feasibility of an augmented red blood cell transfusion strategy for patients treated with induction chemotherapy for acute leukemia or stem cell transplantation. Transfusion 2008, 48(1):81–91. Systematic reviews Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell						
	Systematic reviews Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC. <i>Transfusion thresholds and other strategies for guiding allogeneic red blood cell</i> <i>transfusion</i> . Cochrane Database Syst Rev. 2016, 10:CD002042.						

	Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, Goodman SG, Rao SV, Doree C, Hebert PC. <i>Clinical trials evaluating red blood cell</i> <i>transfusion thresholds: an updated systematic review and with additional focus on</i> <i>patients with cardiovascular disease.</i> In peer-review [February 2018].
Evidence used for	Consensus meeting PBM
Project	PBM
Reviewer(s)	Hans Van Remoortel

PICO 11: RBC transfusion triggers in adult patients with solid tumours

Overview evidence table GRADE software (PICO 11)

			Certainty as	sessment			Nº of p	oatients	Ef	ffect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7/9.7/10 g/dL)	more liberal RBC transfusion triggers (Hb <9/11.5/12 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Patients	exposed to R	BC transfu	sions									
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	33/101 (32.7%)	47/97 (48.5%)	RR 0.67 (0.48 to 0.95)	160 fewer per 1.000 (from 24 fewer to 252 fewer)	⊕⊕⊖⊖ LOW	IMPORTANT
30-day r	nortality			·		·						
1	randomised trials	not serious	not serious	serious ^a	very serious	none	23/101 (22.8%)	8/97 (8.2%)	RR 2.76 (1.30 to 5.87)	145 more per 1.000 (from 25 more to 402 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Renal fa	ilure			·		·						
1	randomised trials	not serious	not serious	serious ^a	very serious c	none	44/101 (43.6%)	45/97 (46.4%)	RR 0.94 (0.69 to 1.28)	28 fewer per 1.000 (from 130 more to 144 fewer)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Myocard	dial infarction											

			Certainty as	sessment			Nº of p	patients	Ef	ffect		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7/9.7/10 g/dL)	more liberal RBC transfusion triggers (Hb <9/11.5/12 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	randomised trials	not serious	not serious	serious ^a	very serious c	none	1/101 (1.0%)	0/97 (0.0%)	RR 1.17 (0.33 to 4.10)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Congest	Congestive heart failure											
1	randomised trials	not serious	not serious	serious ^a	very serious c	none	5/101 (5.0%)	2/97 (2.1%)	RR 2.40 (0.48 to 12.08)	29 more per 1.000 (from 11 fewer to 228 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
Cardiac	events							·				
1	randomised trials	not serious	not serious	serious ^a	serious ^c	none	14/101 (13.9%)	5/97 (5.2%)	RR 2.69 (1.01 to 7.18)	87 more per 1.000 (from 1 more to 319 more)	⊕⊕⊖⊖ LOW	CRITICAL
CVA-stro	oke		·			·		·				
1	randomised trials	not serious	not serious	serious ^a	very serious c	none	3/101 (3.0%)	0/97 (0.0%)	RR 6.73 (0.35 to 128.52)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕⊖⊖⊖ VERY LOW	CRITICAL

Certainty assessment				Nº of patients		Effect						
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7/9.7/10 g/dL)	more liberal RBC transfusion triggers (Hb <9/11.5/12 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Sepsis-b	acteraemia											
1	randomised trials	not serious	not serious	serious ^a	very serious c	none	22/101 (21.8%)	7/97 (7.2%)	RR 1.10 (0.41 to 2.91)	7 more per 1.000 (from 43 fewer to 138 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
Pneumo	nia											
1	randomised trials	not serious	not serious	serious ^a	very serious c	none	8/101 (7.9%)	13/97 (13.4%)	RR 1.63 (0.87 to 3.04)	84 more per 1.000 (from 17 fewer to 273 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
Pneumo	nia or wound	infection										
1	randomised trials	not serious	not serious	serious ^a	very serious c	none	31/101 (30.7%)	21/97 (21.6%)	RR 1.42 (0.88 to 2.29)	91 more per 1.000 (from 26 fewer to 279 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
Thrombo	pembolism											

Certainty assessment				Nº of patients		Effect						
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7/9.7/10 g/dL)	more liberal RBC transfusion triggers (Hb <9/11.5/12 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	randomised trials	not serious	not serious	serious ^a	very serious c	none	1/101 (1.0%)	1/97 (1.0%)	RR 0.96 (0.06 to 15.47)	0 fewer per 1.000 (from 10 fewer to 149 more)	⊕○○○ VERY LOW	CRITICAL
Transfus	ion-related he	emolysis (a	cute or delayed)		·			·				
1	randomised trials	not serious	not serious	serious ^d	very serious ^c	none	0/44 (0.0%)	0/43 (0.0%)	not estimable		⊕⊖⊖⊖ VERY LOW	IMPORTANT
Transfus	ion-related fe	ever		•	•	•		•				
1	randomised trials	not serious	not serious	serious ^d	very serious c	none	8/44 (18.2%)	10/43 (23.3%)	RR 0.78 (0.34 to 1.79)	51 fewer per 1.000 (from 153 fewer to 184 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
Transfus	ion-related p	ulmonary e	edema									
1	randomised trials	not serious	not serious	serious ^d	very serious c	none	0/44 (0.0%)	2/43 (4.7%)	RR 0.20 (0.01 to 3.96)	37 fewer per 1.000 (from 46 fewer to 138 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
Transfus	ion-related ne	ew alloanti	bodies									

Certainty assessment				Nº of patients Effect		fect						
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7/9.7/10 g/dL)	more liberal RBC transfusion triggers (Hb <9/11.5/12 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	randomised trials	not serious	not serious	serious ^d	very serious c	none	2/44 (4.5%)	1/43 (2.3%)	RR 1.95 (0.18 to 20.77)	22 more per 1.000 (from 19 fewer to 460 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
Complications from RBC transfusions												
1	randomised trials	not serious	not serious	serious ^e	very serious c	none	0/65 (0.0%)	0/68 (0.0%)	not estimable		⊕○○○ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Lack of generalizibility: evidence from 1 Brazilian (feasibility) study; b. Limited sample size/low number of events; c. Limited sample size, low number of events and/or large variability of results; d. Lack of generalizibility: evidence from 1 South Korean study; e. Lack of generalizibility: evidence from 1 Danish study

Detailed evidence summary (PICO 11)

Торіс	Patient Blood Management
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers
Intervention	Restrictive RBC transfusion triggers
Question (PICO)	In adult patients with solid tumours (Population), is the use of a restrictive transfusion threshold (Intervention) effective to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusion threshold (Comparison)?
Search Strategy	 The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to: Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017) Identify observational studies in case no experimental studies were available.
	Databases The Cochrane Library (systematic reviews and controlled trials) using the following search strategy: <u>Systematic reviews</u> #1 (true fortation panel culture of culture of culture of the panel block of the pan
	#1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR
	#3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4 Results #hits (on Wednesday 6 July: 25 Cochrane reviews)
	Individual experimental studies #1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti)) #2 neoplas*:ti OR tumor*:ti OR tumour*:ti OR Krebsti OR cancer*ti OR malignan*ti OR carcino*ti OR karzino*ti OR sarcom*ti OR leukaem*ti OR leukam*ti OR leuc*ti OR lymphom*ti OR melano*ti OR metastas*ti OR glioblastom*ti OR osteo*sarcom*ti OR blastom*ti OR neuroblastom*ti OR adenocarcinoma*ti OR choriocarcinoma*ti OR teratoma*ti #3 #1 AND #2 (results #hits on 13 July 2017: 36 trials)
	MEDLINE (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy:

Systematic reviews
#1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*)
AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI]
OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR
protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR
strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR
management[TI] OR program*[TI]))
#2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI]
OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR
trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI]
OR criteri*[TI] OR standard*[TI]))
#3 (blood[11] AND (management[11] OR program*[11]))
#4 ((transfus*[1]] OR red cell*[1]] OR red blood cell*[1] OR RBC*[1] OR
PRBC^[II]) and (critical^[II] OR intensive^[II] OR hemorrhag^[II] OR
#5 #1 OR #2 OR #3 OR #4
#6 ((((((((((((((((((((((((((((((((((((
((metaanaly*[IIABJ))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic
review^[IIAB] OR systematic overview^[IIAB]))) OR ((Review Literature as
IOPIC[Mesn])))) OR ((cocnrane[IIAB] OR embase[IIAB] OR psychilt[IIAB] OR
psyciit[IIAB] OR psychinto[IIAB] OR psychito[IIAB] OR cinani[IIAB] OR
CINNAI[IIAB] OR Science citation index[IIAB] OR blos[IIAB] OR cancerlit[IIAB])))
OR ((reference list"[TIAB] OR bibliograph"[TIAB] OR hand-search"[TIAB] OR
OP data extraction[TIAB]) AND ((Perview[PT])))) NOT (((Selection Chiena[TIAB])
Lotter[PT] OP Editorial[PT] OP animal[Moch] NOT ([Comment[PT] OK
#7 #5 AND #6 (Results #hits (on 6 July 2017): 224)
Individual experimental/observational studies
#1 (((erythrocyte*[TI] OR blood[TI]) AND (unit*[TI] AND trigger*[TI] OR level*[TI]
OR threshold*[TI] OR rule*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR
requir*[TI] OR reduc*[TI] OR limit*[TI])) OR (hemotransfus*[TI] OR
haemotransfus*[TI] OR hemotheran*[TI] OR haemotheran*[TI] OR "red
coll*"[TI]OP "rod blood coll*"[TI] OP PBC*[TI] OP transfus*[TI]))
#2 "Neoplacms by bistologic type"[Mach] OP "Neoplacms by site"[Mach] OP
#2 Neoplastis by histologic type [Mesh] OR Neoplastis by site [Mesh] OR
maiignan^[1]] UK carcino^[1]] UK karzino*[1]] UK sarcom*[1]] UK leukaem*[1]
OR leukam*[TI] OR leuc*[TI] OR lymphom*[TI] OR melano*[TI] OR metastas*[TI]
OR mesothelio*[TI] OR mesotelio*[TI] OR carcinomatous*[TI] OR gliom*[TI] OR
glioblastom*[TI] OR osteo*sarcom*[TI] OR blastom*[TI] OR neuroblastom*[TI]
OR adenocarcinoma*[TI] OR choriocarcinoma*[TI] OR teratoma*[TI]
#3 ("Epidemiologic Studies"[Mesh] OR "case control"[TIAB] OR "case-
control"[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR
controls[TIAB)) OR "cohort study"[TIAB] OR "cohort analysis"[TIAB] OR "follow
up study"[TIAB] OR "follow-up study"[TIAB] OR "observational study"[TIAB] OR
"longitudinal"[TIAB] OR "retrospective"[TIAB] OR "cross sectional"[TIAB] OR
"cross-sectional"[TIAB] OR questionnaire[TIAB] OR questionnaires[TIAB] OR
#1 (random* OR blind* OR "control group" OP placebo* OP controlled OP
around OR trials OR "evetematic review" OR "metaenelyric" OR metaenelyric" OR
gioups on that on systematic review on metadhalysis on metadhalysis on
interature search OK medine OK cochrane OK embase) AND (publisher[sb]
UK Inprocess[sb] UK pubmeanotmedline[sb])
#5 #3 AND #4
#6 #1 AND #2 AND #5 (Results #hits (on 13 July 2017): 1315)

Embase (via Embase.com interface) using the following search strategy:
<u>Systematic reviews</u> #1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR BBC*:ti OR PBBC*) AND
(trigger*ti OR threshold*ti OR target*ti OR restrict*ti OR liberal*ti OR
aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti
OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR
regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti))
#2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR
HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR
threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR
standard*:ti))
#3 (blood:ti AND (management:ti OR program*:ti))
#4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and
(critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti))
#5 #1 OR #2 OR #3 OR #4 #6 (systematic reviews) (meta analysis (tenic)) (even OP (meta analysis' (even OP
#0 (systematic reviews) meta analysis (topic) / exp OK meta analysis / exp OK
ΩR 'systematic review'/exp ΩR 'cochrane' at ti ΩR 'embase' at ti ΩR
'nubmed'ab ti OR 'medline'ab ti OR 'reference list'ab ti OR 'reference lists'ab ti
OR 'bibliography':ab.ti OR 'bibliographies':ab.ti OR 'hand-search':ab.ti OR
'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR
'data extraction':ab,ti
#7 #5 AND #6 (systematic reviews) (Results #hits on 6 July 2017: 227)
Individual experimental/observational studies
#1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR
threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti
OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR
hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR
RBC*:ti OR transfus*:ti))
#2 neoplas*:ti OR tumor*:ti OR tumour*:ti OR Krebsti OR cancer*ti OR
malignan*ti OR carcino*ti OR karzino*ti OR sarcom*ti OR leukaem*ti OR
leukam*ti OR leuc*ti OR lymphom*ti OR melano*ti OR metastas*ti OR
mesothelio*ti OR mesotelio*ti OR carcinomatous*ti OR gliom*ti OR
glioblastom*ti OR osteo*sarcom*ti OR blastom*ti OR heuroblastom*ti OR
#2. ('clinical study'/ovn OP 'cohort analysis'/ovn OP 'cose control':ab ti OP
"s (clinical study /exp OK conditionallysis /exp OK case control ab, if OK
controls ab ti)) OR (cobort study) ab ti OR (cobort analysis' ab ti OR (follow up
study':ab.ti OR 'follow-up study':ab.ti OR 'observational study':ab.ti OR
'longitudinal':ab.ti OR 'retrospective':ab.ti OR 'cross sectional':ab.ti OR 'cross-
sectional':ab,ti OR guestionnaire:ab,ti OR guestionnaires:ab,ti OR survey:ab,ti
OR 'epidemiological study':ab,ti)
#4 ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative
study'/exp OR random*:ab,ti OR control*:ab,ti OR 'intervention study':ab,ti OR
'experimental study':ab,ti OR 'comparative study':ab,ti OR trial:ab,ti OR
evaluat*:ab,ti OR 'before and after':ab,ti OR 'interrupted time series':ab,ti) NOT
('animal'/exp NOT 'human'/exp)
#5 #3 OR #4
#6 #1 AND #2 AND #5 (Results #hits (on 13 July 2017): 735)
Transfusion evidence library
······································

	Systematic reviews #1 Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding) #2 systematic review filter #3 #1 AND #2 (results #hits on 6 July 2017: 427 SRs)
	#1 Clinical specialty: Haematology and oncology #2 restrict* OR liberal OR trigger* OR threshold* OR hemoglobin OR haemoglobin OR hematocrit* OR haematocrit* OR hb OR ht
	#3 #1 AND #2 (results #hits on 11 July 2017: 361 RCTs)
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018)
	26/01/2018 (update after latest search date Carson review)
In/Exclusion criteria	Population: <u>Included:</u> aa: chemotherapy ab: surgery ac: radiotherapy; ad: combinations of aa to ac
	Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL.
	Comparison: the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL.
	Outcomes: <i>Primary:</i> Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and <i>Secondary</i> : Morbidity-related outcomes that occurred during hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction, congestive heart failure, stroke, renal injury, pneumonia, septic shock, rebleeding, infection, and fatigue). Exclude: QoL
	Study design: <u>Included:</u> The following study designs were included: 1) (cluster) randomized controlled trials included in the Cochrane review by Carson et al (May 2016) or other systematic reviews identified in the update and 2) individual (cluster) randomized controlled trials not included in a systematic review or 3) observational studies if no experimental studies were identified. To examine the evidence for the effect of transfusion threshold on the use of RBC transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or haematocrit level (without hemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic

or autologous red blood cells, or both, at higher haemoglobin or haematocrit
levels (transfusion threshold) than the intervention group, or transfused in
accordance with current transfusion practices, which may not have included a
well-defined transfusion threshold, but involved liberal rather than restrictive
transfusion practices. We excluded trials that were not designed to include any
clinical outcomes.

Author, year, Country	Study design	Population	Comparison	Study funding, financial COI and remarks
De Almeida, 2015, Brazil	Experimental: RCT	 198 adult participants who underwent a major surgical procedure for abdominal cancer and required postoperative care in the ICU Liberal: n = 97; mean age (SD) = 64 (14) years Restrictive: n = 101; mean age (SD) = 64 (12) years 	Restrictive group: RBC transfusion if Hb <7 g/dL Liberal group: RBC transfusion if Hb <9 g/dL	The authors have disclosed no COI. Support was provided solely from institutional and/or departmental sources.
Park, 2008, South Korea	Experimental: RCT	 87 adult patients with a confirmed diagnosis of measurable advanced gastric cancer and scheduled to receive 5-fluorouracil-based first-line chemotherapy for metastatic/recurrent disease Liberal: n = 43; median age (interquartile range) = 61 (32-75) years Restrictive: n = 44; median age (interquartile range) = 55 (28-74) years 	Restrictive group: RBC transfusion if Hb <10 g/dL Liberal group: RBC transfusion if Hb <12 g/dL	This study was financially supported by an unrestricted research grant from Gachon University Gil Medical Center, Incheon, South Korea.
Yakymenko, 2017, Denmark	Experimental: RCT	 133 patients, 18 years of age or older, with a confirmed diagnosis of malignant solid tumour and planned treatment with chemotherapy Liberal: n = 68; mean age (SD) = 65 (9.7) years Restrictive: n = 65; mean age (SD) = 65 (9.9) years 	Restrictive group: RBC transfusion if Hb <9.7 g/dL Liberal group: RBC transfusion if Hb <11.5 g/dL (females) or <13.1 g/dL (males)	The authors have disclosed no COI.

Characteristics of included studies

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, #	Reference
			participants	
PRIMARY OUTCON	1ES			
Patients exposed to RBC transfusions	Restrictive vs liberal	<u>Statistically significant:</u> 33/101 vs 47/97 RR: 0.67, 95%CI [0.48;0.95] (p<0.03)*	1, 101 vs 97 §	de Almeida, 2015
		In favour of restrictive group	1 (5 (0))	
Median number of RBC transfused	Restrictive vs liberal	Not statistically significant: 2 (median), [1-2, range] vs 2 (median), [1-5, range] (p=0.26)	1, 65 vs 68 §	Yakymenko, 2017
Mortality at 30 days	Restrictive vs liberal	Not statistically significant 23/101 vs 8/97 RR: 2.76, 95%CI [1.30;5.87] (p=0.008)*	1, 101 vs 97 §	de Almeida 2015
SECONDARY OUTC	OMES		I	I.
Renal failure	Restrictive vs liberal	Not statistically significant 44/101 vs 45/97 RR: 0.94, 95%CI [0.69;1.28] ¥ (p>0.05)	1, 101 vs 97 §	de Almeida 2015
Myocardial infarction	Restrictive vs liberal	Not statistically significant 1/101vs 0/97 RR: 2.88, 95%CI [0.12;69.91] ¥ (p=0.52)*	1, 101 vs 97 §	de Almeida 2015
Congestive heart failure	Restrictive vs liberal	Not statistically significant 5/101 vs 2/97 RR: 2.40, 95%CI [0.48;12.08] ¥ (p>0.05)	1, 101 vs 97 §	de Almeida 2015
Cardiac events	Restrictive vs liberal	Not statistically significant 14/101 vs 5/97 RR: 2.69, 95%CI [1.01;7.18] ¥ (p>0.05)	1, 101 vs 97 §	de Almeida 2015
CVA-stroke	Restrictive vs liberal	Not statistically significant 3/101 vs 0/97 RR: 6.73, 95%CI [0.35;128.52] ¥ (p>0.05)	1, 101 vs 97 §	de Almeida 2015
Sepsis - bacteraemia	Restrictive vs liberal	Not statistically significant 22/101 vs 7/97 RR: 1.10, 95%CI [0.41;2.91] ¥ (p>0.05)	1, 101 vs 97 §	de Almeida 2015
Pneumonia	Restrictive vs liberal	Not statistically significant 8/101 vs 13/97 RR: 1.63, 95%CI [0.87;3.04] ¥ (p>0.05)	1, 101 vs 97 §	de Almeida 2015
Pneumonia or wound infection	Restrictive vs liberal	Not statistically significant 31/101 vs 21/97 RR: 1.42, 95%CI [0.88;2.29] ¥ (p>0.05)	1, 101 vs 97 §	de Almeida 2015
Thromboembolism	Restrictive vs liberal	Not statistically significant 1/101 vs 1/97	1, 101 vs 97 §	de Almeida 2015

		RR: 0.96, 95%CI [0.06;15.47] ¥ (p>0.05)		
Transfusion- related hemolysis (acute or delayed)	Restrictive vs liberal	Not statistically significant 0/44 vs 0/43 RR: not estimable (p>0.05)*	1, 44 vs 43 §	Park 2008
Transfusion- related fever	Restrictive vs liberal	Not statistically significant 8/44 vs 10/43 RR: 0.78, 95%CI [0.34;1.79] ¥ (p=0.56)*	1, 44 vs 43 §	Park 2008
Transfusion- related allergy with urticaria	Restrictive vs liberal	Not statistically significant 8/44 vs 9/43 RR: 0.87, 95%CI [0.37;2.04] ¥ (p=0.75)*	1, 44 vs 43 §	Park 2008
Transfusion- related pulmonary edema (acute)	Restrictive vs liberal	Not statistically significant 0/44 vs 2/43 RR: 0.20, 95%CI [0.01;3.96] ¥ (p=0.28)*	1, 44 vs 43 §	Park 2008
Transfusion- related viral infection	Restrictive vs liberal	Not statistically significant 0/44 vs 0/43 RR: not estimable (p>0.05)*	1, 44 vs 43 §	Park 2008
Transfusion- related new alloantibodies	Restrictive vs liberal	Not statistically significant 2/44 vs 1/43 RR: 1.95, 95%CI [0.18;20.77] ¥ (p=0.58)*	1, 44 vs 43 §	Park 2008
Number of chemotherapy cycles	Restrictive vs liberal	Not statistically significant 4 (median) [0-9, range] vs 5 (median) [1-12, range] (p=0.537)*	1, 44 vs 43 §	Park 2008
Duration of chemotherapy (months)	Restrictive vs liberal	Not statistically significant 3.8 (median) [IQR not reported] vs 4.1 (median) [IQR not reported] (p=0.773)*	1, 44 vs 43 §	Park 2008
Chemotherapy- related neutropenia	Restrictive vs liberal	Not statistically significant 28/44 vs 23/43 RR: 1.19, 95%CI [0.83;1.70] ¥ (p=0.34)*	1, 44 vs 43 §	Park 2008
Chemotherapy- related neutropenic infection	Restrictive vs liberal	Not statistically significant 7/44 vs 8/43 RR: 0.86, 95%CI [0.34;2.15] ¥ (p=0.74)*	1, 44 vs 43 §	Park 2008
Chemotherapy- related thrombocytopenia	Restrictive vs liberal	Not statistically significant 10/44 vs 11/43 RR: 0.89, 95%CI [0.42;1.87] ¥ (p=0.76)*	1, 44 vs 43 §	Park 2008
Chemotherapy- related fatigue	Restrictive vs liberal	Not statistically significant 11/44 vs 9/43 RR: 1.19, 95%CI [0.55;2.59] ¥ (p=0.65)*	1, 44 vs 43 §	Park 2008

Chemotherapy- related nausea and vomiting	Restrictive vs liberal	Not statistically significant 25/44 vs 23/43 RR: 1.06, 95%CI [0.73;1.55] ¥ (p=0.75)*	1, 44 vs 43 §	Park 2008
Chemotherapy- related oral mucositis	Restrictive vs liberal	Not statistically significant 12/44 vs 16/43 RR: 0.73, 95%CI [0.39;1.36] ¥ (p=0.32)*	1, 44 vs 43 §	Park 2008
Chemotherapy- related diarrhea	Restrictive vs liberal	Not statistically significant 13/44 vs 14/43 RR: 0.91, 95%CI [0.48;1.70] ¥ (p=0.76)*	1, 44 vs 43 §	Park 2008
Chemotherapy- related constipation	Restrictive vs liberal	Not statistically significant 11/44 vs 9/43 RR: 1.19, 95%CI [0.55;2.59] ¥ (p=0.65)*	1, 44 vs 43 §	Park 2008
Complications from RBC transfusions	Restrictive vs liberal	Not statistically significant 0/65 vs 0/68 RR: not estimable	1, 65 vs 68 §	Yakymenko, 2017

Mean ± SD (unless otherwise indicated)

CI: confidence interval, RR: relative risk, MD: mean difference

* Calculations (RR or MD, 95% CI and/or p-value) done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Forest plots

	Restric	tive	e Liberal			Risk Ratio	Risk Ratio	Risk of Bias		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI	ABCDEFG		
de Almeida 2015	33	101	47	97	100.0%	0.67 [0.48, 0.95]				
							•			
Total (95% CI)		101		97	100.0%	0.67 [0.48, 0.95]	•			
Total events	33		47							
Heterogeneity: Not ap	plicable							<u>_</u>		
Test for overall effect:	Z = 2.22 (P = 0.0	3)				Eavours restrictive group Eavours liberal group	UU		
							r avours restrictive group in avours riberar group			
Risk of bias legend										
(A) Random sequenc	e genera	tion (se	election b	ias)						
(B) Allocation conceal	(B) Allocation concealment (selection bias)									
(C) Blinding of participants and personnel (performance bias)										
(D) Blinding of outcome assessment (detection bias)										
(E) Incomplete outcon	ne data (a	attrition	bias)							
(F) Selective reporting	(reportin	g bias)								
(C) Other bias										

(G) Other bias

Figure 84: Forest plot of outcome: patients exposed to RBC transfusions



Figure 2: Forest plot of outcome: 30-day mortality



Figure 3: Forest plot of outcome: Renal failure

	Restric	tive	Liberal			Risk Ratio	Risk Ratio	Risk of Bias		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI	ABCDEFG		
de Almeida 2015	1	101	0	97	100.0%	2.88 [0.12, 69.91]				
Total (95% CI)		101		97	100.0%	2.88 [0.12, 69.91]				
Total events	1		0							
Heterogeneity: Not ap	plicable							ł		
Test for overall effect:	Z=0.65(P = 0.5	2)				Favours restrictive group Favours liberal group			
Risk of bias legend										
(A) Random sequenc	e generat	tion (se	lection b	ias)						
(B) Allocation conceal	ment (sel	ection	bias)							
(C) Blinding of participants and personnel (performance bias)										
(D) Blinding of outcome assessment (detection bias)										
(E) Incomplete outcon	ne data (a	attrition	bias)							
(F) Selective reporting (reporting bias)										

(G) Other bias

Figure 4: Forest plot of outcome: Myocardial infarction



Figure 5: Forest plot of outcome: Congestive heart failure



Risk of bias legend

(A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 6: Forest plot of outcome: Cardiac events

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio	Risk of Bias			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG			
de Almeida 2015	3	101	0	97	100.0%	6.73 [0.35, 128.52]					
Total (95% CI)		101		97	100.0%	6.73 [0.35, 128.52]					
Total events	3		0								
Heterogeneity: Not ap	plicable										
Test for overall effect: Z = 1.27 (P = 0.21) 0.01 0.1 1 10 100 Favours restrictive group Favours liberal group											
Risk of bias legend											
(A) Random sequenc	e generat	tion (se	lection b	ias)							
(B) Allocation concealment (selection bias)											
(C) Blinding of participants and personnel (performance bias)											
(D) Blinding of outcome assessment (detection bias)											

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 7: Forest plot of outcome: CVA-stroke



(G) Other bias

Figure 8: Forest plot of outcome: Sepsis-bacteraemia



(G) Other bias

Figure 9: Forest plot of outcome: Pneumonia

	Restric	tive	Liberal			Risk Ratio	Risk Ratio	Risk of Bias		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI	ABCDEFG		
de Almeida 2015	31	101	21	97	100.0%	1.42 [0.88, 2.29]				
Total (95% CI)		101		97	100.0%	1.42 [0.88, 2.29]	◆			
Total events	31		21							
Heterogeneity: Not ap	plicable							ł		
Test for overall effect: .	Z=1.43 (P = 0.1	5)				Favours restrictive group Favours liberal group	1		
Risk of bias legend										
(A) Random sequenc	e genera	tion (se	lection b	ias)						
(B) Allocation conceal	ment (se	lection	bias)							
(C) Blinding of participants and personnel (performance bias)										
(D) Blinding of outcome assessment (detection bias)										
(E) Incomplete outcon	ne data (a	attrition	bias)							
(F) Selective reporting (reporting bias)										

(G) Other bias

Figure 850: Forest plot of outcome: Pneumonia or wound infection



Figure 861: Forest plot of outcome: Thromboembolism



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 872: Forest plot of outcome: Transfusion-related hemolysis (acute or delayed)

	Experimental		Control		Risk Ratio		Risk Ratio	Risk of Bias		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	ABCDEFG		
Park 2008	8	44	10	43	100.0%	0.78 [0.34, 1.79]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \bullet$		
Total (95% CI)		44		43	100.0%	0.78 [0.34, 1.79]	-			
Total events	8		10							
Heterogeneity: Not ap	plicable							<u></u>		
Test for overall effect:	Z = 0.58 (P	= 0.56)			F	U.UI U.I I IU IU avours [experimental] Eavours [control]	10		
							avours [experimental] 1 avours [control]			
Risk of bias legend										
(A) Random sequend	ce generatio	on (sele	ection bia	s)						
(B) Allocation concea	lment (sele	ction bi	ias)							
(C) Blinding of participants and personnel (performance bias)										
(D) Blinding of outcome assessment (detection bias)										
(E) Incomplete outcor	me data (att	rition b	ias)							
(F) Selective reporting	(reporting	bias)								

(G) Other bias

Figure 883: Forest plot of outcome: Transfusion-related fever



Figure 894: Forest plot of outcome: Transfusion-related edema

	Experimental		Control			Risk Ratio	Risk Ratio	Risk of Bias				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	ABCDEFG				
Park 2008	2	44	1	43	100.0%	1.95 [0.18, 20.77]						
Total (95% CI)		44		43	100.0%	1.95 [0.18, 20.77]						
Total events	2		1									
Heterogeneity: Not ap	plicable							4				
Test for overall effect:	Z = 0.56 (F	= 0.58)			F	avours [experimental] Eavours [control])				
							avours [experimental] + avours [control]					
Risk of bias legend												
(A) Random sequence	e generati	on (sele	ection bia	s)								
(B) Allocation conceal	lment (sele	ction bi	ias)									
(C) Blinding of particip	(C) Blinding of participants and personnel (performance bias)											
(D) Blinding of outcome assessment (detection bias)												
(E) Incomplete outcom	(E) Incomplete outcome data (attrition bias)											
(F) Selective reporting	(reporting	bias)										
(G) Other bias												

Figure 905: Forest plot of outcome: Transfusion-related new alloantibodies
Quality of evidence

Author, Year	Lack of allocation concealment and random sequence generation (selection bias)	Lack of blinding (performance bias)	Incomplete accounting of outcome events (attrition bias)	Selective outcome reporting (reporting bias)	Other limitations
de Almeida, 2015	Randomization: no (the chief statistician ensured random sequence generation) Allocation concealment: no (the trial used opaque envelopes that were opened sequentially)	Personnel and participants: unclear (clinicians or participants were not blinded) Outcome assessment: no (the participants and the study investigators who classified outcomes and those who conducted the follow-up telephone assessments were blinded to the study-group assignments and had no access to transfusion data	No	No Pre- registration of study protocol @ ClinicalTrial s.gov (NCT01502 215)	No
Park, 2008	Randomization: no Allocation concealment: no (The random allocation sequence was generated by a table made from the permuted block method. A permuted block size of four was used but there was no stratification.)	Personnel and participants: unclear Outcome assessment: no (an independent investigator was blinded to the study results)	No	Yes No pre- registration of study protocol	No
Yakymenko, 2017	Randomization: no (computer	Personnel and participants:	No (all analyses were performed	No	No

program was used)	Outcome	according to the intention- to-treat	Pre- registration of study
Allocation		principles)	protocol @ ClinicalTrial
concealment: unclear			s.gov (NCT01116 479)

Certainty of the body of evidence: see GRADE Evidence tables

Conclusion	See Evidence-to-Decision template						
	Articles						
	de Almeida 2015						
	de Almeida JP, Vincent JL, Galas FR, de Almeida EP, Fukushima JT, Osawa EA,						
	Bergamin F, Park CL, Nakamura RE, Fonseca SM, Cutait G, Alves JI, Bazan M, Vieira						
	S, Sandrini AC, Palomba H, Ribeiro U Jr, Crippa A, Dalloglio M, Diz Mdel P, Kalil						
	Filho R, Auler JO Jr, Rhodes A, Hajjar LA. <i>Transfusion requirements in surgical</i>						
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Project	РВМ						
Reviewer(s)	Hans Van Remoortel						

PICO 12: RBC transfusion triggers in adult patients with acute central nervous system injury

Overview evidence table GRADE software (PICO 12)

			Certainty as	sessment			Nº of p	oatients	E	ffect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7 g/dL)	more liberal RBC transfusion triggers (Hb <10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Hospital	mortality											
1	observational studies	not serious	not serious	serious ^a	serious ^b	none	49/586 (8.4%)	101/979 (10.3%)	RR 0.81 (0.59 to 1.12)	20 fewer per 1.000 (from 12 more to 42 fewer)	⊕○○○ VERY LOW	CRITICAL
Hospital	mortality (pati	ents with G	GCS ≤8)	•	•	•	•	•	•		•	
1	observational studies	not serious	not serious	serious ^a	serious ^b	none	24/110 (21.8%)	56/177 (31.6%)	RR 0.69 (0.46 to 1.04)	98 fewer per 1.000 (from 13 more to 171 fewer)	⊕○○○ VERY LOW	CRITICAL
Patients	with GCS score	e ≤8 that re	eceived RBC trans	sfusion								
1	observational studies	not serious	not serious	serious ^a	not serious	none	47/112 (42.0%)	112/203 (55.2%)	RR 0.76 (0.59 to 0.98)	132 fewer per 1.000 (from 11 fewer to 226 fewer)	⊕○○○ VERY LOW	IMPORTANT
ICU leng	th of stay											

			Certainty as	sessment			Nº of p	oatients	E	ffect		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7 g/dL)	more liberal RBC transfusion triggers (Hb <10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	observational studies	not serious	not serious	serious ^a	not serious	none	586	979	_	MD 1.2 days more (2.13 more to 4.53 more)	⊕○○○ VERY LOW	IMPORTANT
ICU leng	ICU length of stay in patients with GCS score ≤8											
1	observational studies	not serious	not serious	serious ^a	not serious	none	112	203	-	MD 0.7 days more (2.07 more to 3.47 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
Days rec	uiring mechan	ical ventila	tion									
1	observational studies	not serious	not serious	serious ^a	not serious	none	586	979	-	MD 0.8 days fewer (3.19 fewer to 1.59 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
Days rec	Days requiring mechanical ventilation in patients with GCS score ≤8											
1	observational studies	not serious	not serious	serious ^a	not serious	none	112	203	-	MD 1 days fewer (3.2 fewer to 1.2 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
Days wit	h fever											

			Certainty as	sessment			Nº of p	oatients	Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7 g/dL)	more liberal RBC transfusion triggers (Hb <10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	observational studies	not serious	not serious	serious ^a	serious ^b	none	Statistically s transfusion to	ignificant in fa rigger (p=0.01	vour of res)	strictive	⊕○○○ VERY LOW	NOT IMPORTANT
Days wit	Days with fever in patients with GCS ≤8											
1	observational studies	not serious	not serious	serious ^a	serious ^b	none	112	203	-	MD 0.2 days fewer (0.75 fewer to 0.35 more)	⊕○○○ VERY LOW	NOT IMPORTANT
ARDS/A	LI											
1	observational studies	not serious	not serious	serious ^a	serious ^b	none	7/561 (1.2%)	22/848 (2.6%)	RR 0.48 (0.21 to 1.12)	13 fewer per 1.000 (from 3 more to 20 fewer)	⊕○○○ VERY LOW	CRITICAL
ARDS/A	LI in patients w	ith GCS ≤8		•	•	•	•	•	•	•		
1	observational studies	not serious	not serious	serious ^a	serious ^b	none	5/110 (4.5%)	15/177 (8.5%)	RR 0.54 (0.20 to 1.43)	39 fewer per 1.000 (from 36 more to 68 fewer)	⊕○○○ VERY LOW	CRITICAL
DVT/PE												

			Certainty as	sessment			Nº of µ	patients	Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7 g/dL)	more liberal RBC transfusion triggers (Hb <10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	observational studies	not serious	not serious	serious ^a	serious ^b	none	38/561 (6.8%)	46/848 (5.4%)	RR 1.25 (0.82 to 1.89)	14 more per 1.000 (from 10 fewer to 48 more)	⊕○○○ VERY LOW	CRITICAL
DVT/PE	in patients with	n GCS ≤8										
1	observational studies	not serious	not serious	serious ^a	serious ^b	none	13/110 (11.8%)	18/177 (10.2%)	RR 1.16 (0.59 to 2.28)	16 more per 1.000 (from 42 fewer to 130 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL
30-day/	60-day/hospita	l mortality										
1	randomised trials	not serious	not serious	serious ^c	very serious	none	5/29 (17.2%)	5/38 (13.2%)	RR 1.31 (0.42 to 4.10)	41 more per 1.000 (from 76 fewer to 408 more)	⊕○○○ VERY LOW	CRITICAL
Number	of RBC transfu	sions (unit	s per patient)				·	·				
1	randomised trials	serious ^d	not serious	serious ^c	serious ^b	none	29	38	-	MD 3.2 units per patient lower (4.33 lower to 2.07 lower)	⊕⊖⊖⊖ VERY LOW	IMPORTANT

	Certainty assessment						Nº of patients		Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb <7 g/dL)	more liberal RBC transfusion triggers (Hb <10 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Proporti	Proportion transfused											
1	randomised trials	serious ^d	not serious	serious ^c	serious ^b	none	17/29 (58.6%)	38/38 (100.0%)	RR 0.59 (0.44 to 0.80)	410 fewer per 1.000 (from 200 fewer to 560 fewer)	⊕○○○ VERY LOW	IMPORTANT
Multiple	organ dysfund	tion										
1	randomised trials	not serious	not serious	serious ^c	very serious	none	29	38	-	MD 0.7 higher (1.07 lower to 2.47 higher)	⊕○○○ VERY LOW	IMPORTANT
Proporti	on who develo	ped infecti	on	•	•	•	•	•	•		•	
1	randomised trials	not serious	not serious	serious ^c	very serious	none	2/29 (6.9%)	2/38 (5.3%)	RR 1.31 (0.20 to 8.76)	16 more per 1.000 (from 42 fewer to 408 more)	⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. Lack of generalizibility: evidence from 1 USA study; b. Large variability in results and/or low number of events or lack of data; c. Lack of generalizibility: evidence from 1 Canadian study; d. Detection bias

Detailed evidence summary (PICO 12)

Торіс	Patient Blood Management
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers
Intervention	Restrictive RBC transfusion triggers
Question (PICO)	In patients with acute central nervous system (CNS) injury (Population), is the use of a restrictive transfusion threshold (Intervention) not inferior to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusion threshold (Comparison)?
Search Strategy	 The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to: Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017) Identify observational studies in case no experimental studies were available.
	Databases The Cochrane Library (systematic reviews and controlled trials) using the following search strategy: <u>Systematic reviews</u> #1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR BBC*:ti OR PBBC*) AND
	1 ((transitus :ti OK red cen :ti OK red blood cen :ti OK RBC :ti OK PKBC) AND (trigger:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR strateg*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti))
	#3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4 Results #hits (on Wednesday 6 July: 25 Cochrane reviews)
	Individual experimental studies #1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti)) #2 [mh "Central Nervous System Diseases"] #3 (Disease*:ti,ab OR disorder*:ti,ab OR injury:ti,ab OR injuries:ti,ab) AND (brain:ti,ab OR "spinal cord":ti,ab OR "central nervous system":ti,ab OR CNS:ti,ab) #4 #2 OR #3 #5 #1 AND #4 (results #hits on 13 July 2017: 205 trials
	MEDLINE (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy: <u>Systematic reviews</u>

#1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI])) #2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI])) #3 (blood[TI] AND (management[TI] OR program*[TI])) #4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI]) OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI])) #5 #1 OR #2 OR #3 OR #4 #6 ((((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB] OR prior (ITAB] OR psychit[TIAB] OR psyclit[TIAB] OR sychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR sychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR had-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR ((selection criteria]TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR ((selection criteria]TIAB] OR data extraction[TIAB] OR manual search*[TIAB] OR (((selection criteria]TIAB] OR data extraction[TIAB] OR manual search*[TIAB]) NOT (((comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) #7 #5 AND #6 (Results #hits (on 6 July 2017): 224)
Individual experimental/observational studies
#1 (((erythrocyte*[TI] OR blood[TI]) AND (unit*[TI] AND trigger*[TI] OR level*[TI] OR threshold*[TI] OR rule*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR requir*[TI] OR reduc*[TI] OR limit*[TI])) OR (hemotransfus*[TI] OR haemotransfus*[TI] OR hemotherap*[TI] OR haemotherap*[TI] OR "red cell*"[TI]OR "red blood cell*"[TI] OR RBC*[TI] OR transfus*[TI])) #2 "Central Nervous System Diseases"[Mesh] #3 (Disease*[TIAB] OR disorder*[TIAB] OR injury[TIAB] OR injuries[TIAB]) AND (brain[TIAB] OR "spinal cord"[TIAB] OR "central nervous system"[TIAB] OR CNS[TIAB]) #4 #2 OR #3
#5 ("Epidemiologic Studies"[Mesh] OR "case control"[TIAB] OR "case- control"[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR controls[TIAB)) OR "cohort study"[TIAB] OR "cohort analysis"[TIAB] OR "follow up study"[TIAB] OR "follow-up study"[TIAB] OR "observational study"[TIAB] OR "longitudinal"[TIAB] OR "retrospective"[TIAB] OR "cross sectional"[TIAB] OR "cross-sectional"[TIAB] OR questionnaire[TIAB] OR questionnaires[TIAB] OR survey[TIAB])
#6 (random* OR blind* OR "control group" OR placebo* OR controlled OR groups OR trial* OR "systematic review" OR "metaanalysis" OR metaanalysis OR "literature search" OR medline OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb]) #7 #5 AND #6 #8 #1 AND #4 AND #7 (Results #hits (on 13 July 2017): 743)
Embase (via Embase.com interface) using the following search strategy: Systematic reviews

#1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti))

#3 (blood:ti AND (management:ti OR program*:ti))

#4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4

#6 (systematic reviews) 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti

#7 #5 AND #6 (systematic reviews) (Results #hits on 6 July 2017: 227)

Individual experimental/observational studies

#1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR haemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti))

#2 (Disease*:ab,ti OR disorder*:ab,ti OR injury:ab,ti OR injuries:ab,ti) AND (brain:ab,ti OR "spinal cord":ab,ti OR "central nervous system":ab,ti OR CNS) #3 ('clinical study'/exp OR 'cohort analysis'/exp OR 'case control':ab,ti OR (case:ab,ti OR cases:ab,ti) AND (control:ab,ti OR controls:ab,ti)) OR 'cohort study':ab,ti OR 'cohort analysis':ab,ti OR 'follow up study':ab,ti OR 'follow-up study':ab,ti OR 'observational study':ab,ti OR 'longitudinal':ab,ti OR 'retrospective':ab,ti OR 'cross sectional':ab,ti OR 'cross-sectional':ab,ti OR questionnaire:ab,ti OR questionnaires:ab,ti OR survey:ab,ti OR 'epidemiological study':ab,ti)

#4 ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR random*:ab,ti OR control*:ab,ti OR 'intervention study':ab,ti OR 'experimental study':ab,ti OR 'comparative study':ab,ti OR trial:ab,ti OR evaluat*:ab,ti OR 'before and after':ab,ti OR 'interrupted time series':ab,ti) NOT ('animal'/exp NOT 'human'/exp)

#5 #3 OR #4

#6 #1 AND #2 AND #5 (Results #hits (on 13 July 2017): 781)

Transfusion evidence library Systematic reviews

#1 Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR

	intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging
	OR haemorrhaging OR bleed OR bleeding) #2 systematic review filter
	#3 #1 AND #2 (results #hits on 6 July 2017: 427 SRs)
	Individual experimental studies
	#1 Clinical specialty: Medicine – Neurological disorders
	#2 restrict* OR liberal OR trigger* OR threshold* OR hemoglobin OR
	haemoglobin OR hematocrit* OR haematocrit* OR hb OR ht
	#3 #1 AND #2 (results #hits on 13 July 2017: 11 RCTs)
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson
In (Fuchusian aritaria	26/01/2018 (update after latest search date Carson review)
In/Exclusion criteria	spinal cord; ac. Increase in intracranial pressure
	Intervention: the use of a restrictive transfusion threshold as a mean of
	guiding allogeneic or autologous RBC transfusion. A restrictive transfusion
	threshold most often refers to administration of blood transfusion when the
	haemoglobin level falls below 7 g/dL to 8 g/dL.
	Comparison: the use of a liberal transfusion threshold as a mean of guiding
	allogeneic or autologous RBC transfusion. A liberal transfusion threshold most
	often refers to administration of blood transfusion when the haemoglobin level
	falls below 9 g/dL to 10 g/dL.
	Outcomes: <i>Primary:</i> Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and <i>Secondary</i> : Morbidity-related outcomes that occurred during hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction, congestive heart failure, stroke, renal injury, pneumonia, septic shock, rebleeding, infection, and fatigue).
	Study design: <u>Included:</u> The following study designs were included: 1) (cluster) randomized controlled trials included in the Cochrane review by Carson et al (May 2016) or other systematic reviews identified in the update and 2) individual (cluster) randomized controlled trials not included in a systematic review or 3) observational studies if no experimental studies were identified. To examine the evidence for the effect of transfusion threshold on the use of RBC transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or haematocrit level (without hemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic or autologous red blood cells, or both, at higher haemoglobin or haematocrit level (by the provided that in the provided that
	accordance with current transfusion practices, which may not have included a
	well-defined transfusion threshold, but involved liberal rather than restrictive

transfusion practices. We excluded trials that were not designed to include any
clinical outcomes.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Study funding, financial COI
McIntyre, 2006, Canada	Experimental: randomized controlled trial	 67 multiple trauma patients with a closed head injury Restrictive group (n=29): age = 41.7±20.4 years Liberal group (n=38): age = 39.8±18.1 years 	Restrictive group: single-unit RBC transfusion if Hb <7 g/dL Liberal group: single-unit RBC transfusion if Hb <10 g/dL	Subgroup analysis of the TRICC trial (Hebert 2001 and Wu 2001)
Ngwenya, 2017, USA	Observational: cohort study (retrospective)	1565 consecutive patients with a diagnosis of TBI who were admitted to the intensive care unit (ICU) at San Francisco General Hospital (SFGH) between January 2011 and September 2015. Patients <16 years of age and those who died within 24 hours of admission were excluded: restrictive group (n=586): mean age: 55.0±21.5 years liberal group (n=979): mean age: 52.4±21.8 years	Restrictive RBC transfusion trigger: Hb <7 g/dL Liberal RBC transfusion trigger: Hb <10 g/dL	The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, #	Reference
			participants	
PRIMARY OUTCO	MES			<u>.</u>
30-day mortality	Restrictive vs liberal	Not statistically significant: 5/29 vs 5/38 § RR: 1.31 [95%CI: 0.42;4.10] ¥ (p=0.64)* (Figure 1)	1, 29 vs 38	McIntyre, 2006
60-day mortality	Restrictive vs liberal	Not statistically significant: 5/29 vs 5/38 § RR: 1.31 [95%CI: 0.42;4.10] ¥ (p=0.64)* (Figure 2)	1, 29 vs 38	McIntyre, 2006

Hospital mortality	Restrictive vs liberal	Not statistically significant: 5/29 vs 5/38 § RR: 1.31 [95%CI: 0.42;4.10] ¥ (p=0.64)* (Figure 3)	1, 29 vs 38	McIntyre, 2006
Hospital mortality (all patients)	Restrictive vs liberal	Not statistically significant: 49/586 vs 101/979 RR: 0.81 [95%CI: 0.59;1.12] ¥ (p=0.21)* (Figure 4)	1, 586 vs 979	Ngwenya, 2017
Hospital mortality (Patients with GCS score ≤8)	Restrictive vs liberal	Not statistically significant: 24/110 vs 56/177 § RR: 0.69 [95%CI: 0.46;1.04] ¥ (p=0.08)* (Figure 5)	1, 110 vs 177	Ngwenya, 2017
Number of RBC transfusions (units per patient)	Restrictive vs liberal	<u>Statistically significant:</u> 1.4±2.2 vs 4.6±2.5 MD: -3.20 (95%CI: -4.33;-2.07] (p<0.00001)* (Figure 6) In favour of a restrictive transfusion trigger	1, 29 vs 38 §	McIntyre, 2006
Proportion transfused	Restrictive vs liberal	<u>Statistically significant:</u> 17/29 vs 38/38 § RR: 0.59 [95%CI: 0.44;0.80] ¥ (p=0.0007)* (Figure 7)	1, 29 vs 38	McIntyre, 2006
Patients with GCS score ≤8 that received RBC transfusion	Restrictive vs liberal	<u>Statistically significant:</u> 47/112 vs 112/203 RR: 0.76 [95%CI: 0.59;0.98] (p=0.03)* (Figure 8) In favour of a restrictive transfusion trigger	1, 112 vs 203	Ngwenya, 2017
SECONDARY OUTC	COMES		1	1
ICU (days) median and IQ range	Restrictive vs liberal	Not statistically significant: 10 (5-21) vs 8 (5-11) Median difference 2 (p=0.26)*	1, 29 vs 38	McIntyre, 2006
ICU Length of stay (days) (all patients)	Restrictive vs liberal	Not statistically significant: 7.7±26.6 vs 6.5±40.6 λ Adjusted MD: 1.20 (95%CI: - 2.13;4.53] (p=0.48)* (Figure 9)	1, 586 vs 979	Ngwenya, 2017
ICU Length of stay (days) (Patients with GCS score ≤8)	Restrictive vs liberal	Not statistically significant: 10.6±10.6 vs 9.9±14.2 Adjusted MD: 0.70 (95%CI: - 2.07;3.47] (p=0.62)* (Figure 10)	1, 112 vs 203	Ngwenya, 2017
Multiple organ dysfunction	Restrictive vs liberal	Not statistically significant: 9.3±3.7 vs 8.6±3.6 MD: 0.70 [95%CI: -1.07;2.47] ¥ (p=0.44)* (Figure 11)	1, 29 vs 38 §	McIntyre, 2006
Proportion who developed infection	Restrictive vs liberal	Not statistically significant: 2/29 vs 2/38 § RR: 1.31 [95%CI: 0.20;8.76] ¥ (p=0.78)* (Figure 12)	1, 29 vs 38	McIntyre, 2006
Days requiring mechanical ventilation (all patients)	Restrictive vs liberal	Not statistically significant: 4.1±24.2 vs 4.9±21.9 λ Adjusted MD: -0.80 (95%CI: - 3.19;1.59] (p=0.51)* (Figure 13)	1, 586 vs 979	Ngwenya, 2017

Days requiring mechanical ventilation (Patients with GCS score ≤8)	Restrictive vs liberal	Not statistically significant: 6.8±8.4 vs 7.8±11.3 Adjusted MD: -1.00 (95%CI: - 3.20;1.20] (p=0.37)* (Figure 14)	1, 112 vs 203	Ngwenya, 2017
Days with fever (all patients)	Restrictive vs liberal	Statistically significant: Raw data not available † (p=0.01) In favour of restrictive transfusion trigger	1, 586 vs 979	Ngwenya, 2017
Days with fever (Patients with GCS score ≤8)	Restrictive vs liberal	Not statistically significant: 0.3±2.1 vs 0.5±2.8 Adjusted MD: -0.20 (95%CI: - 0.75;0.35] ¥ (p=0.47)* (Figure 15)	1, 112 vs 203	Ngwenya, 2017
ARDS/ALI (all patients)	Restrictive vs liberal	Not statistically significant: 7/561 vs 22/848 RR: 0.48 [95%CI: 0.21;1.12] ¥ (p=0.09)* (Figure 16)	1, 561 vs 848	Ngwenya, 2017
ARDS/ALI (Patients with GCS score ≤8)	Restrictive vs liberal	Not statistically significant: 5/110 vs 15/177 § RR: 0.54 [95%CI: 0.20;1.43] ¥ (p=0.21)* (Figure 17)	1, 110 vs 177	Ngwenya, 2017
DVT/PE (all patients)	Restrictive vs liberal	Not statistically significant: 38/561 vs 46/848 RR: 1.25 [95%CI: 0.82;1.89] ¥ (p=0.30)* (Figure 18)	1, 561 vs 848	Ngwenya, 2017
DVT/PE (Patients with GCS score ≤8)	Restrictive vs liberal	Not statistically significant: 13/110 vs 18/177 § RR: 1.16 [95%CI: 0.59;2.28] ¥ (p=0.66)* (Figure 19)	1, 110 vs 177	Ngwenya, 2017

Mean ± SD (unless otherwise indicated), MD: mean difference, RR: risk ratio, OR: odds ratio, SD: standard deviation

* Calculations done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Forest plots

	Restrictive tric	gger	Liberal tr	igger		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI	ABCDEFG
McIntyre 2006	5	29	5	38	100.0%	1.31 [0.42, 4.10]		••?••
Total (05% CI)		20		30	100.0%	1 31 [0 / 2 / 10]		
Total events	5	25	5	50	100.0%	1.51 [0.42, 4.10]		
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.46 (P = 0.6	64)					Favours restrictive group Favours liberal group	
Risk of bias legend (A) Random sequenc (B) Allocation concea (C) Blinding of particip (D) Blinding of outcon (E) Incomplete outcor (F) Selective reporting (G) Other bias	ce generation (se Iment (selection pants and perso ne assessment me data (attrition g (reporting bias)	election bias) nnel (p (detecti bias))	i bias) erformanc ion bias)	e bias)				

Figure 91: Forest plot of primary outcome: 30-day mortality (experimental study).



Figure 2: Forest plot of primary outcome: 60-day mortality (experimental study).



Figure 3: Forest plot of primary outcome: Hospital mortality (experimental study).

	Restrictive trigger Liberal trigger					Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDE
Ngwenya 2017	49	586	101	979	100.0%	0.81 [0.59, 1.12]		
Total (95% CI)		586		979	100.0%	0.81 [0.59, 1.12]	•	
Total events	49		101					
Heterogeneity: Not ap	plicable							Ä
Test for overall effect:	Z = 1.27 (P = 0	.21)					Favours restrictive group Favours liberal group	U
Risk of bias legend								
(A) Inappropriate eligi	bility criteria							
(B) Inappropriate met	, hods for expos	ure and	outcome	ariables				
(C) Not controlled for	confounding							
(D) Incomplete or inac	dequate follow-	up						
(E) Other limitations								

Figure 4: Forest plot of primary outcome: Hospital mortality (all patients) (observational study).

	Restrictive tr	igger	Liberal tr	igger		Risk Ratio	Risk Ratio	Risk of Bias		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDE		
Ngwenya 2017	24	110	56	177	100.0%	0.69 [0.46, 1.04]				
Total (95% CI)		110		177	100.0%	0.69 [0.46, 1.04]	•			
Total events Heterogeneity: Not ap Test for overall effect:	24 plicable Z = 1.76 (P = 0	.08)	56				0.01 0.1 1 10 10 Favours restrictive group Favours liberal group	T _o		
Risk of bias legend (A) Inappropriate eligibility criteria (B) Inappropriate methods for exposure and outcome variables (C) Not controlled for confounding (D) Incomplete or inadequate follow-up (E) Other limitations										

Figure 5: Forest plot of primary outcome: Hospital mortality (Patients with GCS score \leq 8) (observational study).



Figure 6: Forest plot of primary outcome: Number of RBC transfusions (units per patient) (experimental study study).

	Restrictive tr	rigger	Liberal tr	igger		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI	ABCDEFG
McIntyre 2006	17	29	38	38	100.0%	0.59 [0.44, 0.80]		•••?•••
Total (95% CI)		29		38	100.0%	0.59 [0.44, 0.80]	•	
Total events	17		38					
Heterogeneity: Not ap	plicable							ł
Test for overall effect:	Z = 3.39 (P = 0	.0007)					Favours restrictive group Favours liberal group)
Risk of bias legend								
(A) Random sequence	e generation (selection	n bias)					
(B) Allocation conceal	Iment (selectio	n bias)						
(C) Blinding of particip	pants and pers	onnel (p	erformanc	e bias)				
(D) Blinding of outcon	ne assessmen	nt (detect	ion bias)					
(E) Incomplete outcor	ne data (attritio	n bias)						
(F) Selective reporting	(reporting bia:	s)						
(G) Other bias								

Figure 7: Forest plot of primary outcome: Proportion transfused (experimental study).

	Restrictive trigger Liberal trigger					Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDE
Ngwenya 2017	47	112	112	203	100.0%	0.76 [0.59, 0.98]	•	
Total (95% CI)		112		203	100.0%	0.76 [0.59, 0.98]	•	
Total events Heterogeneity: Not ap Test for overall effect: <u>Risk of bias legend</u> (A) Inappropriate eligi (B) Inappropriate met (C) Not controlled for (D) Incomplete or inac (E) Other limitations	47 plicable Z = 2.14 (P = 0 bility criteria hods for exposi confounding dequate follow-	03) ure and up	112 outcome v	rariables			0.01 0.1 1 10 100 Favours restrictive group Favours liberal group	1

Figure 8: Forest plot of primary outcome: Patients with GCS score ≤ 8 that received RBC transfusion (observational study)



Figure 9: Forest plot of secondary outcome: ICU Length of stay (days) (all patients).

	Restric	tive trig	ger	Liber	al trigg	jer		Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	ABCDE
Ngwenya 2017	10.6	10.6	112	9.9	14.2	203	100.0%	0.70 [-2.07, 3.47]		
Total (95% CI)			112			203	100.0%	0.70 [-2.07, 3.47]	•	
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 0.50 (P = 0.62	2)						-100 -50 0 50 1	00
	,	•	<i>.</i>						Favours restrictive group Favours liberal group	
Risk of bias legend										
(A) Inappropriate eligi	bility crite	ria								
(B) Inappropriate met	hods for e	exposure	e and o	utcome	variabl	es				
(C) Not controlled for a	confoundi	ing								
(D) Incomplete or inac	lequate fo	ollow-up)							
(E) Other limitations										

Figure 10: Forest plot of secondary outcome: ICU Length of stay (days) (Patients with GCS score ≤ 8) (observational study design).

	Restrictive trigger Liberal trigger							Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
McIntyre 2006	9.3	3.7	29	8.6	3.6	38	100.0%	0.70 [-1.07, 2.47]	•	••?••
Total (95% CI)			29			38	100.0%	0.70 [-1.07, 2.47]		
Heterogeneity: Not ap	plicable									
Test for overall effect. Z = 0.78 (P = 0.44) -100 -50 -50 -100 Favours restrictive group Favours liberal group										
Risk of bias legend (A) Random sequenc (B) Allocation conceal (C) Blinding of particip (D) Blinding of outcom (E) Incomplete outcom (F) Selective reporting (G) Other bias	e generati ment (sele pants and j ne assess ne data (at (reporting	on (sel ection b person ment (o ttrition b i bias)	ection b bias) nel (per detectio bias)	bias) formanc n bias)	e bias	5)				

Figure 11: Forest plot of secondary outcome: Multiple organ dysfunction (experimental study design).



Figure 12: Forest plot of secondary outcome: Proportion who developed infection (experimental study design).

e trigger	Liberal t	trigger		Mean Difference	Mean Difference	Risk of Bias
SD Total	Mean	SD Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	ABCDE
4.2 586	4.9 21	1.9 979	100.0%	-0.80 [-3.19, 1.59]	—	
586		979	100.0%	-0.80 [-3.19, 1.59]	•	
						<u>,</u>
= 0.51)					Favours restrictive group Favours liberal group	10
osure and o	utcome var	riables				
w-up						
	e trigger <u>SD Total</u> 14.2 586 586 : 0.51) osure and o w-up	e trigger Liberal 1 <u>SD Total Mean</u> 4.2 586 4.9 2 586 0.51) osure and outcome var w-up	e trigger Liberal trigger <u>SD</u> Total Mean <u>SD</u> Total 4.2 586 4.9 21.9 979 586 979 0.51) osure and outcome variables w-up	e trigger Liberal trigger <u>SD</u> Total Mean <u>SD</u> Total Weight 4.2 586 4.9 21.9 979 100.0% 586 979 100.0 % : 0.51) osure and outcome variables w-up	e trigger Liberal trigger Mean Difference SD Total Mean SD Total Weight IV, Random, 95% CI 44.2 586 4.9 21.9 979 100.0% -0.80 [-3.19, 1.59] 586 979 100.0% -0.80 [-3.19, 1.59] : 0.51)	e trigger Liberal trigger Mean Difference Mean Difference <u>SD</u> Total Mean SD Total Weight V, Random, 95% Cl V, Random, 95% Cl 4.2 586 4.9 21.9 979 100.0% -0.80 [-3.19, 1.59] 586 979 100.0% -0.80 [-3.19, 1.59] -100 -50 0 50 10 Favours restrictive group Favours liberal group osure and outcome variables w-up

(E) Other limitations

Figure 13: Forest plot of secondary outcome: Days requiring mechanical ventilation (all patients) (observation study design)

	Restrict	ive trig	jger	Liber	al trigg	jer		Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	ABCDE
Ngwenya 2017	6.8	8.4	112	7.8	11.3	203	100.0%	-1.00 [-3.20, 1.20]		
Total (95% CI)			112			203	100.0 %	-1.00 [-3.20, 1.20]		
Heterogeneity: Not ap	plicable								-100 -50 0 50 100	1
Test for overall effect: .	Z = 0.89 (P	' = 0.37	0						Favours restrictive group Favours liberal group	
Risk of bias legend										
(A) Inappropriate eligi	bility criteri	а								
(B) Inappropriate meth	nods for ex	posure	e and o	utcome	variabl	es				
(C) Not controlled for a	onfoundin	g								
(D) Incomplete or inadequate follow-up										
(E) Other limitations										

Figure 14: Forest plot of secondary outcome: Days requiring mechanical ventilation (Patients with GCS score ≤ 8) (observational study design)



Figure 15: Forest plot of secondary outcome: Days with fever (Patients with GCS score ≤ 8) (observational study design).

Restrictive trigger Liberal trigger				Risk Ratio	Risk Ratio	Risk of Bias		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDE
Ngwenya 2017	7	561	22	848	100.0%	0.48 [0.21, 1.12]		
Total (95% CI)		561		848	100.0%	0.48 [0.21, 1.12]	-	
Total events 7 22 Heterogeneity: Not applicable 0.01 0.1 Test for overall effect: Z = 1.70 (P = 0.09) Favours restrict							0.01 0.1 1 10 10 Favours restrictive group Favours liberal group	To
<u>Risk of bias legend</u> (A) Inappropriate eligibility criteria (B) Inappropriate methods for exposure and outcome variables (C) Not controlled for confounding								

(D) Incomplete or inadequate follow-up

(E) Other limitations

Figure 16: Forest plot of secondary outcome: Acute Respiratory Distress Syndrome (ARDS)/Acute Lung Injury (ALI) (all patients) (observational study design).



Figure 17: Forest plot of secondary outcome: Acute Respiratory Distress Syndrome (ARDS)/Acute Lung Injury (ALI) (Patients with GCS score ≤ 8) (observational study design)



Figure 18: Forest plot of secondary outcome: Deep Vein Thrombosis (DVT)/Pulmonary Embolism (PE) (all patients) (observational study design)

	Restrictive trigger Liberal trigger Risk Ratio		Risk Ratio	Risk of Bias				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	I M-H, Random, 95% Cl	ABCDE
Ngwenya 2017	13	110	18	177	100.0%	1.16 [0.59, 2.28] –	
Total (95% CI)		110		177	100.0%	1.16 [0.59, 2.28]	1 +	
Total events	13		18					
Heterogeneity: Not a	pplicable							d d
Test for overall effect	Z = 0.44 (P = 1	0.66)					Favours [experimental] Favours [control]	U
<u>Risk of bias legend</u>								
(A) Inappropriate elig	ibility criteria							

(A) Inappropriate eligibility criteria
 (B) Inappropriate methods for exposure and outcome variables
 (C) Not controlled for confounding
 (D) Incomplete or inadequate follow-up
 (E) Other limitations

Figure 19: Forest plot of secondary outcome: Deep Vein Thrombosis (DVT)/Pulmonary Embolism (PE) (Patients with GCS score ≤ 8) (observational study design)

Quality of evidence Experimental studies

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
McIntyre, 2006	Randomization: No, computer generated randomization. Allocation concealment: No, sealed opaque envelopes prepared by data co- ordinating centre, opened sequentially in ICU to determine participants assignment	Participants and personnel: Unclear, unfeasible to blind personnel. Patients were in ICU. Outcome assessors: No, mortality was primary outcome and most outcomes were laboratory measures.	No	No	No

Observational studies

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Ngwenya, 2017	No (table 2: matching for age and gender borderline)	No Because of our standardized hospital guidelines for the management of patients with TBI, all patients received identical care throughout their hospital stay, including avoidance of hypoxia and	No Controlled for age, Injury Severity Score (ISS), Massive Transfusion Protocol (MTP) activation, number of operating room visits, and total hospital days.	No If an admission or outcomes variable was missing due to incomplete data in the Trauma Registry or medical record, pairwise deletion was used for group means and	Retrospective study
		hyperglycemia, which have been shown to be risk		listwise deletion was used for	

	factors for poor	regression	
	outcome	analysis.	

Certainty of the body of evidence: see GRADE evidence tables

Conclusion	
	Articles <u>McIntyre LA</u> , Fergusson DA, Hutchison JS, Pagliarello G, Marshall JC, Yetisir E, Hare GMT, Hébert PC. Effect of a liberal versus restrictive transfusion strategy on mortality in patients with moderate to severe head injury. Neurocritical Care 2006, 5:4-9. <u>Ngwenya LB</u> , Suen CG, Tarapore PE, Manley GT, Huang MC. Safety and cost efficiency of a restrictive transfusion protocol in patients with traumatic brain injury. L
Reference(s)	Neurosurg. 2017 Jun 23:1-8. Systematic reviews Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev. 2016, 10:CD002042.
	Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, Goodman SG, Rao SV, Doree C, Hebert PC. <i>Clinical trials evaluating red blood cell</i> <i>transfusion thresholds: an updated systematic review and with additional focus on</i> <i>patients with cardiovascular disease</i> . In peer-review [February 2018].
Evidence used for	Consensus meeting PBM
Project	PBM
Reviewer(s)	Hans Van Remoortel

PICO 13: RBC transfusion triggers in adult patients with cerebral perfusion disorder

Overview evidence table GRADE software (PICO 13)

	Certainty assessment						Nº of patients Effect					
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb<10 g/dL)	more liberal RBC transfusion triggers (Hb <11.5 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Any pac	ked RBC trans	fusion give	en									
1	randomised trials	not serious	not serious	serious ^a	very serious	none	19/23 (82.6%)	20/21 (95.2%)	RR 0.87 (0.70 to 1.07)	124 fewer per 1.000 (from 67 more to 286 fewer)	⊕○○○ VERY LOW	IMPORTANT
Number	Number of seperate packed RBC transfusions per patient											
1	randomised trials	not serious	not serious	serious ^a	very serious	none	23	21	-	median 0 transfusion (0 to 0)	⊕○○○ VERY LOW	IMPORTANT
Packed F	RBC units per	transfusio	n	•		•	•		•		•	
1	randomised trials	not serious	not serious	serious ^a	very serious	none	23	21	-	median 0 units (0 to 0)	⊕○○○ VERY LOW	IMPORTANT
Total pa	cked RBC unit	s given pe	r patient					·				
1	randomised trials	not serious	not serious	serious ^a	very serious	none	23	21	-	median 1 units per patient fewer (0 to 0)	⊕○○○ VERY LOW	IMPORTANT
Any adv	erse event rela	ated to tra	nsfusion									

	Certainty assessment						Nº of patients Effect					
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (Hb<10 g/dL)	more liberal RBC transfusion triggers (Hb <11.5 g/dL)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	randomised trials	not serious	not serious	serious ^a	very serious	none	8/23 (34.8%)	6/21 (28.6%)	RR 1.22 (0.51 to 2.93)	63 more per 1.000 (from 140 fewer to 551 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Pulmona	Pulmonary edema or respiratory distress											
1	randomised trials	not serious	not serious	serious ^a	very serious	none	8/23 (34.8%)	3/21 (14.3%)	RR 2.43 (0.74 to 7.99)	204 more per 1.000 (from 37 fewer to 999 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Any cere	bral infarction	n on MRI			,	ļ	F	,	ł		l	
1	randomised trials	not serious	not serious	serious ^a	very serious	none	9/22 (40.9%)	6/20 (30.0%)	RR 1.36 (0.59 to 3.15)	108 more per 1.000 (from 123 fewer to 645 more)	⊕○○○ VERY LOW	IMPORTANT
Delayed	cerebral infar	ction										
1	randomised trials	not serious	not serious	serious ^a	very serious	none	11/23 (47.8%)	9/21 (42.9%)	RR 1.12 (0.58 to 2.14)	51 more per 1.000 (from 180 fewer to 489 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Lack of generalizibility: evidence from 1 USA study; b. Limited sample size and/or large variability in results

Detailed evidence summary (PICO 13)

Topic	Patient Blood Management
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers
Intervention	Restrictive RBC transfusion triggers
Question (PICO)	In patients with cerebral perfusion disorders (Population), is the use of a
	restrictive transfusion threshold (Intervention) not inferior to reduce mortality
	and improve other clinical outcomes (Outcomes) compared to a liberal
	transfusion threshold (Comparison)?
Search Strategy	The Cochrane systematic review by Carson et al. (2016) and its
	databases was conducted to:
	- Identify relevant experimental studies (RCT's) published after the
	search by Carson et al. (13 th November 2017)
	- Identify observational studies in case no experimental studies were
	available.
	Databases
	The Cochrane Library (systematic reviews and controlled trials) using the
	following search strategy:
	Systematic reviews
	#1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND
	(trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR
	OR policy ti OR policies ti OR practic* ti OR indicat* ti OR strateg* ti OR
	regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti))
	#2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR
	HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR
	threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR
	standard*:ti))
	#3 (blood:ti AND (management:ti OR program*:ti))
	#4 ((transtus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and
	(critical: ti OR Intensive: ti OR nemorrhag: ti OR naemorrhage: ti OR bleed: ti))
	reviews)
	Individual experimental studies
	#1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR
	threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti
	OR reduc^:ti OR IImit^:ti)) OR (nemotranstus^:ti OR naemotranstus^:ti OR
	RBC*ti OR transfus*ti))
	#2 [mh stroke] OR [mh "cerebral hemorrhage"]
	#3 (cerebral:ti,ab OR intracerebral:ti,ab) AND hemorrhage*:ti,ab
	#4 CVA:ti,ab OR stroke:ti,ab OR "cerebrovascular accident":ti,ab OR
	"cerebrovascular accidents":ti,ab
	#5 #2 OR #3 OR #4
	#6 #1 AND #5 (results #hits on 14 July 2017: 316 trials)
	MEDLINE (via PubMed interface) for systematic reviews and experimental and
	observational studies using the following search strategy:
	Systematic reviews

#1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI]))
#2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI]))
#3 (blood[TI] AND (management[TI] OR program*[TI])) #4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI]))
#5 #1 OR #2 OR #3 OR #4 #6 ((((((((((((((((((((((((((((((((((((
psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh])))
#7 #5 AND #6 (Results #hits (on 6 July 2017): 224)
Individual experimental/observational studies #1 (((erythrocyte*[TI] OR blood[TI]) AND (unit*[TI] AND trigger*[TI] OR level*[TI] OR threshold*[TI] OR rule*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR requir*[TI] OR reduc*[TI] OR limit*[TI])) OR (hemotransfus*[TI] OR haemotransfus*[TI] OR hemotherap*[TI] OR haemotherap*[TI] OR "red cell*"[TI]OR "red blood cell*"[TI] OR RBC*[TI] OR transfus*[TI])) #2 stroke[Mesh] OR "cerebral hemorrhage"[Mesh] #3 (cerebral[TIAB] OR intracerebral[TIAB]) AND hemorrhage*[TIAB] #4 CVA[TIAB] OR stroke[TIAB] OR "cerebrovascular accident"[TIAB] OR "cerebrovascular accidents"[TIAB] #5 #2 OR #3 OR #4
#6 ("Epidemiologic Studies"[Mesh] OR "case control"[TIAB] OR "case- control"[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR controls[TIAB)) OR "cohort study"[TIAB] OR "cohort analysis"[TIAB] OR "follow up study"[TIAB] OR "follow-up study"[TIAB] OR "observational study"[TIAB] OR "longitudinal"[TIAB] OR "retrospective"[TIAB] OR "cross sectional"[TIAB] OR "cross-sectional"[TIAB] OR questionnaire[TIAB] OR questionnaires[TIAB] OR survev[TIAB])
 #7 (random* OR blind* OR "control group" OR placebo* OR controlled OR groups OR trial* OR "systematic review" OR "metaanalysis" OR metaanalysis OR "literature search" OR medline OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb]) #8 #6 OR #7
#9 #1 AND #5 AND #8 (Results #hits (on 13 July 2017): 488)
Embase (via Embase.com interface) using the following search strategy: Systematic reviews

#1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR strateg*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR standard*:ti))
#3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti))
 #5 #1 OR #2 OR #3 OR #4 #6 (systematic reviews) 'meta analysis (topic)'/exp OR 'meta analysis':ab,ti OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'menual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti #7 #5 AND #6 (systematic reviews) (Results #hits on 6 July 2017: 227)
Individual experimental/observational studies #1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti)) #2 'cerebrovascular accident'/exp OR 'brain hemorrhage'/exp #3 (cerebral:ab,ti OR intracerebral:ab,ti) AND hemorrhage*:ab,ti
'cerebrovascular accidents':ab,ti
#5 #2 OR #3 OR #4 #6 ('clinical study'/exp OR 'cohort analysis'/exp OR 'case control':ab,ti OR (case- control':ab,ti OR ((case:ab,ti OR cases:ab,ti) AND (control:ab,ti OR controls:ab,ti)) OR 'cohort study':ab,ti OR 'cohort analysis':ab,ti OR 'follow up study':ab,ti OR 'follow-up study':ab,ti OR 'observational study':ab,ti OR 'longitudinal':ab,ti OR 'retrospective':ab,ti OR 'cross sectional':ab,ti OR 'cross-sectional':ab,ti OR questionnaire:ab,ti OR questionnaires:ab,ti OR survey:ab,ti OR 'epidemiological ctudy':ab ti)
#7 ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR random*:ab,ti OR control*:ab,ti OR 'intervention study':ab,ti OR 'experimental study':ab,ti OR 'comparative study':ab,ti OR trial:ab,ti OR evaluat*:ab,ti OR 'before and after':ab,ti OR 'interrupted time series':ab,ti) NOT ('animal'/exp NOT 'human'/exp) #8 #6 OR #7
#9 #1 AND #5 AND #8 (Results #hits (on 14 July 2017):1988)
Transfusion evidence library Systematic reviews
μ #1 Red (alls (NIL) (triager ()R threshold ()R target ()R restrict ()R restrictive ()R

#1 Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit

	OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding) #2 systematic review filter #3 #1 AND #2 (results #hits on 6 July 2017: 427 SRs) Individual experimental studies #1 Clinical specialty: Medicine – Neurological disorders #2 restrict* OR liberal OR trigger* OR threshold* OR hemoglobin OR haemoglobin OR hematocrit* OR haematocrit* OR hb OR ht #3 #1 AND #2 (results #hits on 13 July 2017: 11 RCTs)
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review)
In/Exclusion criteria	 Population: Included: a.) acute ischemic stroke; b.) acute intracerebral bleeding: ba: old patients (> 50yrs); bb: young pts. (< 50 yrs) Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. Comparison: the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL. Outcomes: Primary: Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and Secondary: Morbidity-related outcomes that occurred during hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction, congestive heart failure, stroke, renal injury, pneumonia, septic shock, rebleeding, infection, and fatigue).
	Study design: Included: The following study designs were included: 1) (cluster) randomized controlled trials included in the Cochrane review by Carson et al (May 2016) or other systematic reviews identified in the update and 2) individual (cluster) randomized controlled trials not included in a systematic review or 3) observational studies if no experimental studies were identified. To examine the evidence for the effect of transfusion threshold on the use of RBC transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or haematocrit level (without hemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic or autologous red blood cells, or both, at higher haemoglobin or haematocrit levels (transfusion threshold) than the intervention group, or transfused in accordance with current transfusion practices, which may not have included a

well-defined transfusion threshold, but involved liberal rather than restrictive
transfusion practices. We excluded trials that were not designed to include any
clinical outcomes.

Characteristics of included studies

Author, year,	Study	Population	Comparison	Study funding,
Country	design			financial COI and
				remarks
Naidech, 2010,	Experimental:	44 patients with	Restrictive RBC	This study was
USA	RCT	subarachnoid hemorrhage	transfusion trigger:	funded by grants
		and high risk for	Hb <10 g/dL	to AMN from the
		vasospasm		Neurocritical Care
				Society, supported
		• Restrictive group (n=23):	Liberal RBC	by Novo-
		mean age (±SD) =	transfusion trigger:	Nordisk (for partial
		59.2±11.9 years	Hb <11.5 g/dL	salary support) and
				from the
		• Liberal group (n=21):		Northwestern
		mean age $(\pm SD) =$		Memorial
		54.1±14.9 years		Foundation for MIRI
				scans and additional
				PRBC transfusions
				above usual care.
				vero cont to the
				Neuro critical
				care society, but
				no rolo in the design
				of the
				protocol selection of
				patients collection of
				data statistical
				analysis.
				or decision to submit
				for publication. AMN
				is listed as a Co-
				Investigator
				for the proposed
				study Transfusion in
				Subarachnoid
				Hemorrhage (PI:
				Peter D LeRoux), and
				some of these data
				have been
				used to plan it. The
				grant has not yet
				been submitted, and
				there has
				been no
				compensation
				(financial or

		otherwise) for that
		study.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
PRIMARY OUTCOM	1ES			
Any packed RBC transfusion given	Restrictive vs liberal	Not statistically significant: 19/23 vs 20/21 RR 0.87 [95%CI: 0.70; 1.07] ¥ (p=0.19)* (Figure 1)	1, 23 vs 21 §	Naidech, 2010
Number of separate packed RBC transfusions per patient	Restrictive vs liberal	Not statistically significant: 2 (1-3) (median, Q1-Q3) vs 2 (1- 4), median difference 0 (IQR could not be calculated) (p>0.05)	1, 23 vs 21 §	Naidech, 2010
Packed RBC units per transfusion	Restrictive vs liberal	Statistically significant: 1 (1-1) (median, Q1-Q3) vs 1 (1- 2) (p<0.05) In favour of restrictive transfusion trigger	1, 23 vs 21 §	Naidech, 2010
Total packed RBC units given per patient	Restrictive vs liberal	Not statistically significant: 2 (1-3) (median, Q1-Q3) vs 3 (2- 4), median difference -1 (IQR could not be calculated) (p=0.05)	1, 23 vs 21 §	Naidech, 2010
SECONDARY OUTC				
Days to first transfusion	Restrictive vs liberal	Not statistically significant: 3.8±5.2 vs 2.3±1.9 MD 1.50 (95%CI: -0.78; 3.78] ¥ (p=0.20)* (Figure 2)	1, 23 vs 21 §	Naidech, 2010
Days to last transfusion	Restrictive vs liberal	Not statistically significant: 8.5±4.8 vs 6.7±5.1 MD 1.80 (95%CI: -1.13;4.73] ¥ (p=0.23)* (Figure 3)	1, 23 vs 21 §	Naidech, 2010
Any adverse event related to transfusion	Restrictive vs liberal	Not statistically significant: 8/23 vs 6/21 RR 1.22 [95%CI: 0.51;2.93] ¥ (p=0.66)* (Figure 4)	1, 23 vs 21 §	Naidech, 2010
Days with fever ≥ 100.4F core	Restrictive vs liberal	Not statistically significant: 7 (2-11) (median, Q1-Q3) vs 5 (1-8.5), median difference 2 (IQR could not be calculated) (p>0.05)	1, 23 vs 21 §	Naidech, 2010
Pulmonary edema or respiratory distress	Restrictive vs liberal	Not statistically significant: 8/23 vs 3/21 RR 2.43 [95%CI: 0.74;7.99] ¥ (p=0.14)* (Figure 5)	1, 23 vs 21 §	Naidech, 2010
Rash	Restrictive vs liberal	Not statistically significant: 0/23 vs 1/21	1, 23 vs 21 §	Naidech, 2010

		RR 0.31 [95%CI: 0.01;7.12] ¥ (p=0.46)* (Figure 6)		
Hypotension	Restrictive vs liberal	Not statistically significant: 1/23 vs 1/21 RR 0.91 [95%CI: 0.06;13.69] ¥ (p=0.95)* (Figure 7)	1, 23 vs 21 §	Naidech, 2010
Ventilator-free day (max 14)	Restrictive vs liberal	Not statistically significant: 14 (5-14) (median, Q1-Q3) vs 12 (6.5-14), median difference 2 (IQR could not be calculated) (p>0.05)	1, 23 vs 21 §	Naidech, 2010
Symptomatic vasospasm	Restrictive vs liberal	Not statistically significant: 5/23 vs 5/21 RR 0.91 [95%CI: 0.31;2.71] ¥ (p=0.87)* (Figure 8)	1, 23 vs 21 §	Naidech, 2010
Any cerebral infarction on MRI	Restrictive vs liberal	Not statistically significant: 9/22 vs 6/20 RR 1.36 [95%CI: 0.59;3.15] ¥ (p=0.47)* (Figure 9)	1, 22 vs 20 §	Naidech, 2010
Delayed cerebral infarction	Restrictive vs liberal	Not statistically significant: 11/23 vs 9/21 RR 1.12 [95%CI:0.58;2.14] ¥ (p=0.74)* (Figure 10)	1, 23 vs 21 §	Naidech, 2010

Mean ± SD (unless otherwise indicated), MD: mean difference, RR: risk ratio, OR: odds ratio, SD: standard deviation

* Calculations (specifieer welke waarden precies) done by the reviewer(s) using Review Manager software (plaats symbool: na hetgene je berekend hebt; in geval van meerdere zaken zelf berekend: ster helemaal onderaan (na p-waarde))

* Calculations (weighted mean and pooled SD, based on the means and SDs of the individual studies) done by the reviewer using Excel (dit is het geval voor Cochrane SRs waar enkel de pooled MD en CI gegeven zijn)

£ No raw data/SD's available (or specify), effect size and CI cannot be calculated (Use ££ or £££ if necessary) (plaats symbool: waar data ontbreken)

¥ Imprecision (large variability of results) (plaats symbool: na CI)

+ Imprecision (lack of data) (na £)

§ Imprecision (limited sample size or low number of events) (plaats symbool: na # participants in geval van limited sample size; na breuken in geval van low number of events of na #participants als number of events niet gegeven is maar sample size <300)

 $\boldsymbol{\lambda}$ data extracted from graph

Forest plots

	Restrictive group Liberal group		roup Bisk Batio		Risk Ratio	Risk Ratio	Risk of Bias	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl A B C D E	
Naidech 2010	19	23	20	21	100.0%	0.87 [0.70, 1.07]		? • • • • • •
Total (95% CI)		23		21	100.0%	0.87 [0.70, 1.07]	•	
Total events	19		20					
Heterogeneity: Not ap	plicable							1
Test for overall effect:	Z = 1.32 (P = 0	.19)					Eavours restrictive group. Eavours liberal group	
							rateare restricting group in around instrangioup	
Risk of bias legend								
(A) Random sequend	e generation (s	selectio	on bias)					
(B) Allocation concea	Iment (selectio	n bias)						
(C) Blinding of particip	pants and pers	onnel (performar	nce bias)			
(D) Blinding of outcome assessment (detection bias)								
(E) Incomplete outcome data (attrition bias)								
(F) Selective reporting	(reporting bias	s)						
(G) Other bias								

Figure 92: Forest plot of outcome: Any packed RBC transfusion given.



Figure 2: Forest plot of outcome: Days to first transfusion.





Figure 4: Forest plot of outcome: Any adverse event related to transfusion.

	Experim	ental	Contr	Control Risk Ratio Risk Ratio		Risk Ratio	Risk of Bias	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Naidech 2010	8	23	3	21	100.0%	2.43 [0.74, 7.99]		? • • • • • •
Total (95% CI)		23		21	100.0%	2.43 [0.74, 7.99]		
Total events	8		3					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.47 (P = 0.14) Favours [experimental] Favours [control]								
Risk of bias legend	Risk of bias leaend							
(A) Random sequend	(A) Random sequence generation (selection bias)							
(B) Allocation concealment (selection bias)								
(C) Blinding of participants and personnel (performance bias)								
(D) Blinding of outcome assessment (detection bias)								
(E) Incomplete outcor	me data (at	ttrition b	ias)					

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 5: Forest plot of outcome: Pulmonary edema or respiratory distress.





(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 7: Forest plot of outcome: Hypotension.

	Restrictive group Liberal group		Risk Ratio		Risk Ratio	Risk of Bias		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI A B C D E F	
Naidech 2010	5	23	5	21	100.0%	0.91 [0.31, 2.71]		? • • • • • •
Total (95% CI)		23		21	100.0%	0.91 [0.31, 2.71]	-	
Total events	5		5					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.16 (P = 0.87) 0.01 0.1 1 10 100 Favours restrictive group Favours liberal group								
Risk of bias legend								
(A) Random sequenc	e generation (selectio	on bias)					
(B) Allocation conceal	lment (selectio	n bias)						
(C) Blinding of particip	pants and pers	onnel (performar	nce bias)			
(D) Blinding of outcome assessment (detection bias)								
(E) Incomplete outcome data (attrition bias)								
(F) Selective reporting	(reporting bia	s)						
(G) Other bias								

Figure 8: Forest plot of outcome: Symptomatic vasospasm.



Figure 9: Forest plot of outcome: Any cerebral infarction on MRI.



Figure 10: Forest plot of outcome: Delayed cerebral infarction.

Quality of evidence

Author, Year	Lack of allocation concealment and random sequence generation (selection bias)	Lack of blinding (performance bias)	Incomplete accounting of outcome events (attrition bias)	Selective outcome reporting (reporting bias)	Other limitations
Naidech,	Randomization:	Participants and	No	No	No
2010	unclear	personnel: yes			
	Allocation	personnel were not			
	concealment: no	blinded)			
	(sealed opaque sequentially				
	numbered	Outcome assessors: no			
	envelopes were	(All the MRI scans were			
	used)	performed by a single			
		certified neuro-			
		radiologist who was			
		blinded vascular			
		neurologist ascertained			
		the NIH Stroke Scale)			

Certainty of the body of evidence: see GRADE evidence tables

Conclusion	See Evidence-to-Decision template
Reference(s)	 Articles Naidech 2010 Naidech AM, Shaibani A, Garg RK, Duran IM, Liebling SM, Bassin SL, Bendok BR, Bernstein RA, Batjer HH, Alberts MJ. Prospective, randomized trial of higher goal hemoglobin after subarachnoid hemorrhage. Neurocrit Care. 2010; 13(3):313-320. Systematic reviews Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev. 2016, 10:CD002042. Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, Goodman SG, Rao SV, Doree C, Hebert PC. Clinical trials evaluating red blood cell transfusion thresholds: an updated systematic review and with additional focus on patients with cardiovascular disease. In peer-review [February 2018]
Evidence used for	Consensus meeting PBM
Project	PBM
Reviewer(s)	Hans Van Remoortel
PICO 14: RBC transfusion triggers in adult patients with acute bleeding

Overview evidence table GRADE software (PICO 14)

			Certainty as	ssessment		Nº of patients		Effect				
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	more restrictive RBC transfusion triggers (70-80% of RBC volume)	more liberal RBC transfusion triggers (100% of RBC volume)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Blood us	sage (units)											
1	randomised trials	serious ^a	not serious	serious ^b	not serious	none	12	10	_	MD 6.5 units lower (12.21 lower to 0.79 lower)	⊕⊕⊖⊖ LOW	IMPORTANT
Number	of participan	ts transfuse	ed									
1	randomised trials	serious ^a	not serious	serious ^b	serious ^c	none	8/12 (66.7%)	10/10 (100.0%)	RR 0.68 (0.45 to 1.04)	320 fewer per 1.000 (from 40 more to 550 fewer)	⊕⊖⊖⊖ VERY LOW	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

a. Selection, detection and performance bias unclear

b. Study of 1956 (not generalizible to 2018)

c. Limited sample size and large variability in results

Detailed evidence summary (PICO 14)

Торіс	Patient Blood Management
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers
Intervention	Restrictive RBC transfusion triggers
Question (PICO)	In patients with acute bleeding (Population), is the use of a restrictive transfusion threshold (Intervention) effective to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusion threshold (Comparison)?
Search Strategy	 The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to: Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017) Identify observational studies in case no experimental studies were available.
	Databases The Cochrane Library (systematic reviews and controlled trials) using the following search strategy: Systematic reviews #1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR trigger*:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti)) #3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4 Results #hits (on Wednesday 6 July: 25 Cochrane reviews)
	Individual experimental studies #1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti)) #2 (acute:ti,ab OR massive:ti,ab) AND (bleeding:ti,ab OR hemorrhage*:ti,ab OR "blood loss":ti,ab) #3 #1 AND #2 (results #hits on 14 July 2017: 170 trials) MEDLINE (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy: Systematic reviews #1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR prophylactic*[TI] OR liberal*[TI] OR aggressive*[TI] OR policie/[TI] OR practic*[TI] OR liberal*[TI]

strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR
management[TI] OR program*[TI]))
#2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI]
OR HB[1] OR HC1[1]) AND (polic^[1] OR practic^[1] OR protocol^[1] OR
trigger^[1] OR threshold*[1] OR maintain*[1] OR indicator*[1] OR strateg*[1]
UK (nien"[1] UK standard"[1]))
#3 ($10001[1]$ AND ($110100[1]$ OR product [1] OR program [1]))
PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR
haemorrhage*[TI] OR bleed*[TI]))
#5 #1 OR #2 OR #3 OR #4
#6 ((((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR
((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic
review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as
Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR
psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR
cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB])))
OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR
relevant journals[IIAB] OR manual search^[IIAB]))) OR ((((selection criteria[IIAB]
OR data extraction[IIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR
Letter[F1] OK Eutonal[F1] OK animal[Mesh] NOT (animal[Mesh] AND
#7 #5 AND #6 (Results #hits (on 6 July 2017): 224)
Individual experimental/observational studies
#1 (((erythrocyte*[TI] OR blood[TI]) AND (unit*[TI] AND trigger*[TI] OR level*[TI]
OR threshold*[TI] OR rule*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR
requir*[TI] OR reduc*[TI] OR limit*[TI])) OR (hemotransfus*[TI] OR
haemotransfus*[TI] OR hemotherap*[TI] OR haemotherap*[TI] OR "red
cell*"[TI]OR "red blood cell*"[TI] OR RBC*[TI] OR transfus*[TI]))
#2 (acute[TIAB] OR massive [TIAB]) AND (bleeding[TIAB] OR hemorrhage*[TIAB]
OR "blood loss"[TIAB])
#3 ("Epidemiologic Studies"[Mesh] OR "case control"[TIAB] OR "case-
control"[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR
controls[TIAB)) OR "cohort study"[TIAB] OR "cohort analysis"[TIAB] OR "follow
up study"[TIAB] OR "follow-up study"[TIAB] OR "observational study"[TIAB] OR
"longitudinal"[TIAB] OR "retrospective"[TIAB] OR "cross sectional"[TIAB] OR
"cross-sectional"[TIAB] OR questionnaire[TIAB] OR questionnaires[TIAB] OR
survey[TIAB])
#4 (random* OR blind* OR "control group" OR placebo* OR controlled OR
groups OR trial* OR "systematic review" OR "metaanalysis" OR metaanalysis OR
"literature search" OR medline OR cochrane OR embase) AND (publisher[sb]
OR inprocess[sb] OR pubmednotmedline[sb])
#5 #3 OR #4
#6 #1 AND #2 AND #5 (Results #hits (on 13 July 2017): 450)
Embase (via Embase.com interface) using the following search strategy:
<u>Systematic reviews</u> #1 ((transfus*:ti OP rod coll*:ti OP rod blood coll*:ti OP PPC*:ti OP DPPC*: AND
$\pi \mathbf{I}$ ((trianglet is OR through of the constant is OR through the const
(inggen in OK infestion in OK idiget in OK restrictii OK inderdi in OK
aggressive .u OK conservative .u OK propriyidcuc .u OK IIIIII.".u OK protocol".ti
OK policy.ii OK policies.ii OK practic".ti OK Indicat".ti OK strateg".ti OK
regimentu OK chientu OK siandardtu OK managementu OK programti))
#2 ((nemoglobin:ti UK naemoglobin:ti UK nematocrit:ti UK naematocrit:ti UK
HB:ti OK HCT:ti) AND (polic^:ti OK practic^:ti OK protocol*:ti OK trigger*:ti OR

threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR
standard*:ti))
#3 (blood:ti AND (management:ti OR program*:ti))
#4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and
(critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti))
#5 #1 OR #2 OR #3 OR #4
#6 (systematic reviews) 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR
'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp
OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR
'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti
OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR
'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR
'data extraction':ab,ti
#7 #5 AND #6 (systematic reviews) (Results #hits on 6 July 2017: 227)
Individual experimental (observational studies
#1 (((enthrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR
#1 (((e) y(i)) Cycle .(i) OK block(i) AND (u) it .(i) AND thyger .(i) OK level .(i) OK threshold*ti OR rule*ti OR target*ti OR restrict*ti OR liberal*ti OR requir*ti
OR reduc*ti OR limit*ti)) OR (bemotransfus*ti OR beemotransfus*ti OR
hemotheran*ti OR haemotheran*ti OR "red cell*"ti OR "red hlood cell*"ti OR
RBC*·ti OR transfus*·ti))
#2 (acute ab ti OR massive ab ti) AND (bleeding ab ti OR bemorrhage* ab ti OR
"blood loss" ab ti)
#3 ('clinical study'/exp OR 'cohort analysis'/exp OR 'case control':ab.ti OR 'case-
control':ab.ti OR ((case:ab.ti OR case:ab.ti) AND (control:ab.ti OR controls:ab.ti))
OR 'cohort study':ab.ti OR 'cohort analysis':ab.ti OR 'follow up study':ab.ti OR
'follow-up study':ab,ti OR 'observational study':ab,ti OR 'longitudinal':ab,ti OR
'retrospective':ab,ti OR 'cross sectional':ab,ti OR 'cross-sectional':ab,ti OR
questionnaire:ab,ti OR questionnaires:ab,ti OR survey:ab,ti OR 'epidemiological
study':ab,ti)
#4 ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative
study'/exp OR random*:ab,ti OR control*:ab,ti OR 'intervention study':ab,ti OR
'experimental study':ab,ti OR 'comparative study':ab,ti OR trial:ab,ti OR
evaluat*:ab,ti OR 'before and after':ab,ti OR 'interrupted time series':ab,ti) NOT
('animal'/exp NOT 'human'/exp)
#5 #3 OR #4
#6 #1 AND #2 AND #5 (Results #hits (on 14 July 2017): 1480)
I ransfusion evidence library
#1 Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR
liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit
OR limits OR protocol OR policy OR policies OR practice OR indicator OR
strategy OR strategies OR regimen OR criteria OR standard OR management
OR program OR programme) OR Red Cells AND title:(critical OR critically OR
intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging
OR haemorrhaging OR bleed OR bleeding)
#2 systematic review filter #3 #1 AND #2 (results #bits on 6 July 2017: 427 SPc)
$\pi J \pi T \cap V \pi Z (\text{ICSUILS } \pi \text{IIILS OFF } 0 \text{ July } 2017. 427 \text{ SKS})$
Individual experimental studies
#1 restrict* OR liberal OR trigger* OR threshold* OR hemoglobin OR
haemoglobin OR hematocrit [*] OR haematocrit [*] OR hb OR ht

	#2 (acute OR massive) AND (bleeding OR hemorrhage* OR "blood loss")
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson
	2018)
	26/01/2018 (update after latest search date Carson review)
In/Exclusion criteria	Population: <u>Included:</u> patients with acute bleeding: clinically instable bleeding patients undergoing massive transfusion: a.) trauma-induced bleeding; b.) non-trauma induced bleeding
	Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL.
	Comparison: the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL.
	Outcomes: <i>Primary:</i> Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and <i>Secondary</i> : Morbidity-related outcomes that occurred during hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction, congestive heart failure, stroke, renal injury, pneumonia, septic shock, rebleeding, infection, and fatigue).
	Study design: <u>Included:</u> The following study designs were included: 1) (cluster) randomized controlled trials included in the Cochrane review by Carson et al (May 2016) or other systematic reviews identified in the update and 2) individual (cluster) randomized controlled trials not included in a systematic review or 3) observational studies if no experimental studies were identified. To examine the evidence for the effect of transfusion threshold on the use of RBC transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or haematocrit level (without hemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic or autologous red blood cells, or both, at higher haemoglobin or haematocrit levels (transfusion threshold) than the intervention group, or transfused in accordance with current transfusion practices, which may not have included a well-defined transfusion threshold, but involved liberal rather than restrictive transfusion practices. We excluded trials that were not designed to include any clinical outcomes.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Study funding, financial COI and remarks
Fisher, 1956, United Kingdom	Experimental: randomised controlled trial	22 trauma participants were randomly allocated to 1 of 2 groups: • Liberal group: n = 10 • Restrictive group: n = 12 NB: no demographic data were reported.	Restrictive RBC transfusion trigger: an attempt was made to leave the RBC volume at the end of resuscitation at 70% to 80% of normal. Liberal RBC transfusion trigger: the aim was to achieve 100% or more of the RBC volume at the end of resuscitation.	The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, #	Reference						
			participants							
PRIMARY OUTCOMES										
Blood usage	Restrictive vs liberal	Statistically significant:	1, 12 vs 10 §	Fisher 1956						
(units)		4.8±6.7 vs 11.3±6.9								
		MD: -6.50 [95%CI: -12.21;-0.79]								
		(p=0.03)* (Figure 1)								
		In favour of restrictive								
		transfusion trigger								
Number of	Restrictive vs liberal	Not statistically significant:	1, 12 vs 10 §	Fisher 1956						
participants		8/12 vs 10/10								
transfused		RR: 0.68 [95%CI: 0.45;1.04] ¥								
		(p=0.07)* (Figure 2)								

Mean \pm SD (unless otherwise indicated), MD: mean difference, RR: risk ratio, OR: odds ratio, SD: standard deviation

* Calculations done by the reviewer using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Forest plots

Study or Subgroup	Restric	tive gr	oup	Liber	al gro	up Total	Woight	Mean Difference	Mean Difference	Risk of Bias
Study of Subgroup	Weall	30	TULAI	Weall	30	TUtal	weight	IV, Rahuom, 95% Ci	IV, Raiuoin, 95% Ci	ADCDEFO
Fisher 1956	4.8	6.7	12	11.3	6.9	10	100.0%	-6.50 [-12.21, -0.79]		? 🛨 ? ? 🛨 🖶 🛨
Total (95% CI)			12			10	100.0%	-6.50 [-12.21, -0.79]	•	
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 2.23 (I	P = 0.0	3)						-100 -50 0 50 100	
									Favours resultitive group Favours liberal group	
Risk of bias legend										
(A) Random sequenc	e generat	ion (se	election	bias)						
(B) Allocation conceal	ment (sel	ection	bias)							
(C) Blinding of particip	(C) Blinding of participants and personnel (performance bias)									
(D) Blinding of outcome assessment (detection bias)										
(E) Incomplete outcome data (attrition bias)										
(F) Selective reporting	(reporting	j bias)								
(G) Other bias										

Figure 93: Forest plot of outcome: Blood usage (units).



Figure 2: Forest plot of outcome: Number of participants transfused.

Quality of evidence

Author, Year	Lack of allocation concealment and random sequence generation (selection bias)	Lack of blinding (performance bias)	Incomplete accounting of outcome events (attrition bias)	Selective outcome reporting (reporting bias)	Other limitations
Fisher, 1956	Randomization: Unclear The use of random sequence generation was not described Allocation concealment: No The trial used sealed envelopes. When the participant was considered eligible for the trial, they were placed in a severity grade and an envelope was opened to decide which transfusion schedule was to be used.	Participants and personnel: Unclear Blinding of participants and personnel was not addressed Outcome assessors: Unclear Blinding of outcome assessment was not addressed	No The data set appeared to be complete	Yes No pre- registration of study protocol	No

Certainty of the body of evidence: see GRADE evidence tables

Conclusion	See Evidence-to-Decision template
Reference(s)	Articles Fisher 1956 Fisher MR and Topley ET. The illness of trauma. British Journal of Clinical Practice 1956, 10(11): 770-776. Systematic reviews Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev. 2016, 10:CD002042. Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, Goodman SG, Rao SV, Doree C, Hebert PC. Clinical trials evaluating red blood cell transfusion thresholds: an updated systematic review and with additional focus on patients with cardiovascular disease. In peer-review [February 2018]
Evidence used for	Consensus meeting PBM
Project	PBM
Reviewer(s)	Hans Van Remoortel