## Final version

# **Transfusion**

**Blood transfusion** 

Clinical guideline

Appendices J-L

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Final version

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#### Disclaimer

Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and, where appropriate, their guardian or carer.

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# **Appendices J-L**

# **Appendix J: GRADE tables**

## J.1 Erythropoietin and iron

## J.1.1 Erythropoietin versus placebo

Quality a	ssessment						No. of patien	ts	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Erythropoieti	Placebo/n o erythropo n ietin	Relative (95% CI)	Absolute	Quality	Importance
All-cause	mortality at	30 days										
7	Random ised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	None	24/723 (3.3%)	11/486 (2.3%)	RR 1.55 (0.79 to 3.07)	12 more per 1000 (from 5 fewer to 47 more)	LOW	
Number o	f patients tr	ansfused										
12	Random ised trials	Serious <sup>a</sup>	Very serious <sup>c</sup>	No serious indirectness	No serious imprecision	None	295/971 (30.4%)	348/692 (50.3%)	RR 0.59 (0.53 to 0.67)	206 fewer per 1000 (from 166	VERY LOW	

Quality a	ssessment						No. of patier	nts	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Erythropoieti	Placebo/n o erythropo n ietin	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 236 fewer)		
Number o	f units trans	fused per p	atient (Better indication	ated by lower valu	ies)							
7	Random ised trials	Serious <sup>a</sup>	Very serious <sup>d</sup>	No serious indirectness	Serious <sup>e</sup>	None	501	308	-	MD 0.69 lower (0.89 to 0.49 lower)	VERY LOW	
Serious ad	lverse event	:s										
6	Random ised trials	Serious <sup>a</sup>	Serious <sup>f</sup>	No serious indirectness	Very serious <sup>g</sup>	None	39/541 (7.2%)	25/303 (8.3%)	RR 0.92 (0.57 to 1.5)	7 fewer per 1000 (from 35 fewer to 41 more)	VERY LOW	
Thrombos	is											
5	Random ised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious	None	29/566 (5.1%)	13/410 (3.2%)	RR 1.37 (0.73 to 2.56)	12 more per 1000 (from 9 fewer to 49 more)	VERY LOW	
Infection												
1	Random ised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/158 (0%)	0/162 (0%)	-	-	HIGH	
Length of	hospital sta	y (Better inc	dicated by lower val	ues)								
1	Random	Serious	No serious	No serious	No serious	None	31	32	-	MD 3.00	MODERAT	

Quality a	ıssessmen	t					No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Erythropoietin	Placebo/n o erythropo ietin	Relative (95% CI)	Absolute	Quality	Importance
	ised trials	a,h	inconsistency	indirectness	imprecision					lower (3.36 to 2.64 lower)	E	

- (a) Most information is from studies at high risk of bias
- (b) Confidence interval crosses one default MID (1.25) and line of no effect
- (c) Significant heterogeneity.  $I^2=62\%$ .
- (d) Significant heterogeneity.  $I^2=60\%$ .
- (e) Confidence interval crosses one default MID and line of no effect (f) Heterogeneity.  $l^2$ =30%.
- (g) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect
- (h) Unclear randomisation and allocation concealment

### IV iron versus placebo or no IV iron

	Crous più	10000	110 14 11011									
Quality a	ssessment						No. of patie	ents	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	IV iron	Placebo/no IV iron	Relative (95% CI)	Absolute	Quality	Importance
All-cause	mortality at	30 days										
2	Random ised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	11/140 (7.9%)	10/140 (7.1%)	RR 1.1 (0.49 to 2.47)	7 more per 1000 (from 36 fewer to 105 more)	VERY LOW	
Number o	of patients tr	ansfused										
5	Random ised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	None	67/239 (28%)	85/228 (37.3%)	RR 0.77 (0.59 to 0.99)	86 fewer per 1000 (from 4	LOW	

Quality a	ssessment						No. of patie	ents	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	IV iron	Placebo/no IV iron	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 153 fewer)		
Length of	hospital sta	y (better ind	dicated by lower va	lues)								
1	Random ised trials	Serious <sup>d</sup>	No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	None	100	100	-	MD 0.6 higher (1.34 lower to 2.54 higher)	LOW	
Serious ac	lverse event	:s										
1	Random ised trials	Very serious <sup>e</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/11 (0%)	0/10 (0%)	Not pooled	Not pooled	LOW	
Infections												
1	Random ised trials	Serious <sup>d</sup>	No serious inconsistency	No serious directness	Very serious <sup>b</sup>	None	16/100 (16%)	13/100 (13%)	RR 1.23 (0.63 to 2.42)	30 more per 1000 (from 48 fewer to 185 more)	VERY LOW	

- (a) Most information is from studies at high risk of bias
- (b) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect
- (c) Confidence interval crosses one default MID and line of no effect
- (d) No blinding
- (e) 7/38 (18%) patients missing data. Low frequency of events means this could impact on results. Study reports the trial was underpowered for the outcomes under assessment and that it stopped early because of recruitment problems.

## Oral iron versus placebo or no oral iron

Quality a	ssessment						No. of patie	nts	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Oral iron	Placebo/no oral iron	Relative (95% CI)	Absolute	Quality	Importance
Number o	f patients tr	ansfused										
2	Random ised trials	Serious <sup>a</sup>	Serious <sup>b</sup>	No serious indirectness	Very serious <sup>c</sup>	None	33/77 (42.9%)	39/77 (50.6%)	RR 0.84 (0.6 to 1.19)	81 fewer per 1000 (from 203 fewer to 96 more)	VERY LOW	

- (a) Most information is from studies at high risk of bias (b) Significant heterogeneity.  $I^2=66\%$ .
- (c) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect

### Erythropoietin plus IV iron versus placebo

Quality a	assessment	t					No. of patien	ts	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Erythropoieti + IV iron	in Placek	Relative		Quality	Importance
All-cause	mortality at	30 days										
2	Random ised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	0/77 (0%)	1/77 (1.3%)	RR 0.33 (0.01 to 7.93)	9 fewer per 1000 (from 13 fewer to 90 more)	VERY LOW	
Number o	of patients tr	ansfused										
4	Random ised trials	Serious <sup>a</sup>	Very serious <sup>c</sup>	No serious indirectness	No serious imprecision	None	43/141 (30.5%)	84/142 (59.2%)	RR 0.51 (0.39 to 0.67)	290 fewer per 1000 (from 195 fewer to 361 fewer)	VERY LOW	

Quality a	essessment						No. of patie			Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	+ IV iron	tin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
2	Random ised trials	No serious risk of bias	Very serious <sup>d</sup>	No serious indirectness	No serious imprecision	None	91	91		-	MD 0.76 lower (1 to 0.52 lower)	LOW	
Length of	hospital sta	y (Better ind	dicated by lower val	ues)									
1	Random ised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious <sup>e</sup>	None	37	37		-	MD 2.2 lower (5.1 lower to 0.7 higher)	LOW	
Serious ad	lverse event	:S											
1	Random ised trials	Very serious <sup>f</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/10 (0%)	0/10		Not pooled	Not pooled	LOW	

- (a) Most information is from studies at high risk of bias
- (b) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect
- (c) Significant heterogeneity.  $I^2=69\%$ .
- (d) Significant heterogeneity.  $I^2=93\%$ .
- (e) Confidence interval crosses one default MID and line of no effect
- (f) 7/38 (18%) patients missing data. Low frequency of events means this could impact on results. Study reports the trial was underpowered for the outcomes under assessment and that it stopped early because of recruitment problems.

#### J.1.5 Oral iron versus IV iron

Quality as	ssessment						No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Oral iron	IV iron	Relative (95% CI)	Absolute	Quality	Importance
Number of	lumber of patients transfused											

Quality a	ssessment						No. of patien	ts	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Oral iron	IV iron	Relative (95% CI)	Absolute	Quality	Importance
2	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	None	29/115 (25.2%)	23/113 (20.4%)	RR 1.28 (0.83 to 1.95)	57 more per 1000 (from 35 fewer to 193 more)	LOW	CRITICAL
Length of	hospital stay (bet	tter indicate	ed by lower value	s)								
1	Randomised trials		No serious inconsistency	No serious indirectness	No serious imprecision	None	62	59	-	MD 0.30 lower (0.79 lower to 0.19 higher)	HIGH	
Deep vein	thrombosis									<u>'</u>	<u>'</u>	
1	Randomised trials		No serious inconsistency	No serious indirectness	Very serious <sup>c</sup>	None	0/62 (0%)	1/59 (1.7%)	RR 0.32 (0.01 to 7.64)	12 fewer per 1000 (from 17 fewer to 113 more)	LOW	
Quality of	life (Better indica	ated by low	er values)									
1	Randomised trials		No serious inconsistency	No serious indirectness	No serious imprecision	None	62	59	-	MD 0.00 higher (0.23 lower to 0.23 higher)	HIGH	

<sup>(</sup>a) Unclear randomisation, allocation concealment and unclear missing data (Garrido-Martin 2012).

<sup>(</sup>b) Confidence interval crosses one default MID (1.25) and line of no effect.

<sup>(</sup>c) Confidence interval crosses one default MID and line of no effect.

## Erythropoietin plus IV iron versus IV iron

Quality as	ssessment						No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Erythropoietin + IV iron	IV iron	Relative (95% CI)	Absolute	Quality	Importance
All-cause n	nortality at 30 d	ays										
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/40 (0%)	0/40 (0%)	Not pooled	Not pooled	MODERATE	
Number of	f patients transf	used										
2	Randomised trials	Serious <sup>b</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>c</sup>	None	9/50 (18%)	12/51 (23.5%)	RR 0.76 (0.35 to 1.65)	56 fewer per 1000 (from 153 fewer to 153 more)	VERY LOW	
Serious adv	verse events											
2	Randomised trials	Serious <sup>b</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/48 (0%)	0/51 (0%)	Not pooled	Not pooled	MODERATE	

<sup>(</sup>a) Unclear allocation concealment and blinding

#### Erythropoietin plus oral iron versus oral iron J.1.7

Quality as	ssessment						No. of patients	ı	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		Erythropoietin + Oral iron	Oral iron	Relative (95% CI)	Absolute	Quality	Importance
All-cause n	nortality at 30 da	ays										
2	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	10/437 (2.3%)	12/443 (2.7%)	RR 0.88 (0.39 to 1.96)	3 fewer per 1000 (from 17 fewer to 26	VERY LOW	

<sup>(</sup>b) Most information is from studies at high risk of bias(c) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect

Quality a	ssessment				,		No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Erythropoietin + Oral iron	Oral iron	Relative (95% CI)	Absolute	Quality	Importance
										more)		
Number o	f patients transf	used										
3	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	1/68 (1.5%)	32/73 (43.8%)	RR 0.06 (0.02 to 0.25)	412 fewer per 1000 (from 329 fewer to 430 fewer)	MODERATE	
Length of	hospital stay (be	tter indicat	ed by lower values	s)								
2	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	38	43	-	MD 0.22 lower (0.61 lower to 0.18 higher)	MODERATE	
Infections												
1	Randomised trials	Serious <sup>c</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	1/16 (6.3%)	2/16 (12.5%)	RR 0.5 (0.05 to 4.98)	62 fewer per 1000 (from 119 fewer to 498 more)	VERY LOW	
Deep vein	thrombosis	<u>'</u>	·	·	'					·	,	
1	Randomised trials	Serious <sup>d</sup>	No serious inconsistency	No serious indirectness	Serious <sup>e</sup>	None	16/340 (4.7%)	7/340 (2.1%)	RR 2.29 (0.95 to 5.49)	27 more per 1000 (from 1 fewer to 92 more)	LOW	
Other thro	mbovascular ev	ents										
1	Randomised trials	Serious <sup>d</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	12/340 (3.5%)	7/340 (2.1%)	RR 1.71 (0.68 to 4.3)	15 more per 1000 (from 7 fewer to 68 more)	VERY LOW	

<sup>(</sup>a) Most information is from studies at high risk of bias
(b) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect
(c) Unclear randomisation, blinding and allocation concealment.

- (d) Open label. No blinding.
- (e) Confidence interval crosses one default MID and line of no effect

## J.1.8 Erythropoietin plus oral iron or IV iron versus oral or IV iron

Quality as	ssessment						No. of patients	S	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	EPO+ IV iron or oral iron	Placebo+IV iron or oral iron	Relative (95% CI)	Absolute	Quality	Importance
Mortality												
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/58 (0%)	0/52 (0%)	Not pooled	Not pooled	MODERATE	
Serious adv	verse events											
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	0/58 (0%)	1/52 (1.9%)	RR 0.3 (0.01 to 7.19)	13 fewer per 1000 (from 19 fewer to 119 more)	VERY LOW	
Thrombosi	S											
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/58 (0%)	0/52 (0%)	Not pooled	Not pooled	MODERATE	

<sup>(</sup>a) Allocation concealment not reported.

<sup>(</sup>b) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect.

## J.2 Alternatives to blood transfusion in surgical patients - combinations of cell salvage and tranexamic acid

### J.2.1 Adults - high risk group

	0 - 0	- · ·										
Quality a	assessment						No. of patients	<b>i</b>	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intra- operative cell salvage	Standard treatment	Relative (95% CI)	Absolute	Quality	Importance
No. expos	sed to allogenei	c blood										
4	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	None	49/125 (39.2%)	67/126 (53.2%)	RR 0.74 (0.58 to 0.93)	138 fewer per 1000 (from 37 fewer to 223 fewer)	VERY LOW	
Units of a	llogeneic blood	transfused	d (Better indicate	d by lower value	es)							
4	Randomised trials	Very serious <sup>a</sup>	Serious <sup>c</sup>	No serious indirectness	Serious <sup>b</sup>	None	110	113	-	MD 0.78 lower (1.37 to 0.19 lower)	VERY LOW	
Mortality	at up to 30 day	rs										
7	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>d</sup>	None	15/210 (7.1%)	19/214 (8.9%)	RR 0.97 (0.64 to 1.47)	3 fewer per 1000 (from 32 fewer to 42 more)	VERY LOW	
Any infec	tion											
4	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	None	7/124 (5.6%)	19/126 (15.1%)	RR 0.4 (0.18 to 0.87)	90 fewer per 1000 (from 20 fewer to 124 fewer)	VERY LOW	
Hospital I	ength of stay (E	Better indic	ated by lower val	ues)								
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>d</sup>	None	40	40	-	MD 0.2 lower (1.26 lower to 0.86 higher)	VERY LOW	

<sup>(</sup>a) The majority of the evidence was at very high risk of bias.

<sup>(</sup>b) The confidence interval crosses one MID.

<sup>(</sup>c) Downgraded by one increment due to heterogeneity, 12=65%.

<sup>(</sup>d) The confidence interval crosses both MIDs.

Quality	assessment						No. of patien	ts	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Post Op CS	Standard treatment	Relative (95% CI)	Absolute	Quality	Importance
No. expo	sed to allogene	ic blood										
4	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	None	28/126 (22.2%)	53/136 (39%)	RR 0.6 (0.45 to 0.81)	156 fewer per 1000 (from 74 fewer to 214 fewer)	VERY LOW	
Units of a	Illogeneic blood	l transfuse	d (Better indicate	d by lower value	es)							
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	None	30	30	-	MD 1.02 lower (1.19 to 0.85 lower)	VERY LOW	
Mortality	at up to 30 day	/S								'	'	
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>c</sup>	None	1/25 (4%)	0/25 (0%)	RR 3 (0.13 to 70.3)	-	VERY LOW	
Any infec	tion											
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	None	1/41 (2.4%)	8/49 (16.3%)	RR 0.15 (0.02 to 1.15)	139 fewer per 1000 (from 160 fewer to 24 more)	VERY LOW	
Hospital l	ength of stay (E	Better indic	cated by lower val	lues)								
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	41	49	-	MD 7.13 lower (9.12 to 5.14 lower)	LOW	

<sup>(</sup>a) The majority of the evidence was at very high risk of bias.(b) The confidence interval crosses one MID.(c) The confidence interval crosses both MIDs.

Quality a	assessment						No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intra- operative cell salvage + post- operative cell salvage	Standard treatment	Relative (95% CI)	Absolute	Quality	Importance
No. expo	sed to allogenei	c blood										
2	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	None	49/113 (43.4%)	74/117 (63.2%)	RR 0.69 (0.54 to 0.89)	196 fewer per 1000 (from 70 fewer to 291 fewer)	VERY LOW	
Mortality	at up to 30 day	S										
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>c</sup>	None	1/99 (1%)	3/97 (3.1%)	RR 0.33 (0.03 to 3.09)	21 fewer per 1000 (from 30 fewer to 65 more)	VERY LOW	
Any infec	tion											
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>c</sup>	None	2/99 (2%)	2/97 (2.1%)	RR 0.98 (0.14 to 6.82)	0 fewer per 1000 (from 18 fewer to 120 more)	VERY LOW	
Length of	hospital stay (B	etter indi	cated by lower va	lues)								
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>c</sup>	None	99	97	-	MD 2.8 higher (2.11 lower to 7.71 higher)	VERY LOW	

<sup>(</sup>a) The majority of the evidence is at very high risk of bias.(b) The confidence interval crosses one MID.(c) The confidence interval crosses both MIDs.

Quality	assessment						No. of patients	Intra-	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	operative cell salvage +TXA	operative cell salvage	Relative (95% CI)	Absolute	Quality	Importance
No. expos	sed to allogenei	blood										
5	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	None	100/255 (39.2%)	144/259 (55.6%)	RR 0.71 (0.6 to 0.85)	161 fewer per 1000 (from 83 fewer to 222 fewer)	VERY LOW	
Units of b	lood transfused	(Better in	ndicated by lower	values)								
2	Randomised trials	Very serious <sup>a</sup>	Serious <sup>c</sup>	No serious indirectness	No serious imprecision	None	84	86	-	MD 1.56 lower (1.84 to 1.29 lower)	VERY LOW	
Mortality	at 30 days											
4	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>d</sup>	None	1/143 (0.7%)	2/209 (1%)	RR 1.04 (0.07 to 16.41)	0 more per 1000 (from 9 fewer to 147 more)	VERY LOW	
Length of	stay in hospital	(Better in	dicated by lower	values)								
2	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>d</sup>	None	123	129	-	MD 0.68 higher (0.81 lower to 2.17 higher)	VERY LOW	

<sup>(</sup>a) The majority of the evidence is at very high risk of bias.

<sup>(</sup>b) The confidence interval crosses one MID.

<sup>(</sup>c) Downgraded by one increment due to heterogeneity; I2=61%.

<sup>(</sup>d) The confidence interval crosses both MIDs.

Quality a	assessment						No. of patients	;	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intra- operative cell salvage +TXA	TXA	Relative (95% CI)	Absolute	Quality	Importance
No. expos	sed to allogenei	c blood										
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	12/34 (35.3%)	13/29 (44.8%)	RR 0.79 (0.43 to 1.45)	94 fewer per 1000 (from 256 fewer to 202 more)	VERY LOW	
Mortality	at 30 days											
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	4/34 (11.8%)	0/29 (0%)	RR 7.71 (0.43 to 137.53)	-	VERY LOW	
Infections	;											
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	5/34 (14.7%)	4/29 (13.8%)	RR 1.07 (0.32 to 3.6)	10 more per 1000 (from 94 fewer to 359 more)	VERY LOW	
Length of	stay in hospital	(Better in	dicated by lower	values)								
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	34	29	-	MD 2.1 higher (3.36 lower to 7.56 higher)	VERY LOW	

<sup>(</sup>a) The majority of the evidence is at very high risk of bias.(b) The confidence interval crosses both MIDs.

Quality a	assessment						No. of patients		Effect			
No. of studies	of Risk of less Design bias Inconsistency Indirectness Imprecision Other					Other	Post-operative cell salvage +TXA	ТХА	Relative (95% CI)	Absolute	Quality	Importance
No. of patients with allogeneic blood transfusion												
1	Randomised trials	- /	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/17 (0%)	0/17 (0%)	not pooled	not pooled	LOW	

(a) The majority of the evidence is at very high risk of bias.

Quality	assessmer	nt					No. of patients		Effect			
No. of studies		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intra-operative cell salvage + post- operative cell salvage +TXA	Intra-operative cell salvage + post- operative cell salvage	Relative (95% CI)	Absolute	Quality	Importance
No. expo	sed to allog	eneic bloo	od									
1	Randomis ed trials	,	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	13/50 (26%)	14/50 (28%)	RR 0.93 (0.49 to 1.77)	20 fewer per 1000 (from 143 fewer to 216 more)	VERY LOW	
Units of l	olood transf	used (Bet	ter indicated by	lower values)								
1	Randomise trials		No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	None	13	14	-	MD 0.25 higher (0.32 lower to 0.82 higher)	VERY LOW	
Mortality	at 30 days											
1	Randomise trials		No serious inconsistency		No serious imprecision	None	0/50 (0%)	0/50 (0%)	Not pooled	Not pooled	LOW	

<sup>(</sup>a) The majority of the evidence was at very high risk of bias.

- (b) The confidence interval crosses both MIDs.
- (c) The confidence interval crosses one MID.

Quality a	assessme	nt					No. of patients		Effect			
No. of						Other	Intra-operative cell salvage + post-operative cell salvage +TXA	TXA	Relative (95% CI)	Absolute	Quality	Importance
No. expos	sed to allog	geneic blood										
1	Randomi sed trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	31/102 (30.4%)	33/111 (29.7%)	•	6 more per 1000 (from 95 fewer to 161 more)		
Any infec	tion											
1	Randomi sed trials		No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	6/102 (5.9%)	5/111 (4.5%)	RR 1.31 (0.41 to 4.15)	14 more per 1000 (from 27 fewer to 142 more)	VERY LOW	

- (a) The majority of the evidence is at very high risk of bias.
- (b) The confidence interval crosses both MIDs.

Quality	assessme	nt					No. of pat	tients	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	TXA	Standard treatment or placebo- High risk- adults	Relative (95% CI)	Absolute	Quality	Importance
No. of pa	tients need	ding blood trai	nsfusions									
38	Randomi sed trials	Serious <sup>a</sup>		No serious indirectness	Serious <sup>c</sup>	None	684/2065 (33.1%)	968/2040 (47.5%)	RR 0.71 (0.63 to 0.81)	138 fewer per 1000 (from 90 fewer to 176 fewer)	VERY LOW	

Quality a	assessme	nt					No. of par	tients	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	TXA	Standard treatment or placebo- High risk- adults	Relative (95% CI)	Absolute	Quality	Importance
No. of un	its of bloo	d transfused -	All Patients (Bet	ter indicated by	lower values)							
17	Randomi sed trials	Serious <sup>a</sup>	Serious <sup>b</sup>		No serious imprecision	None	953	965	-	MD 0.0.83 lower (1.17 to 0.5 lower)	LOW	
Mortality		,	'	,	'		<u>'</u>	·	,		,	'
31	Randomi sed trials	Serious <sup>a</sup>	Serious <sup>d</sup>	No serious indirectness	Serious <sup>c</sup>	None	17/1891 (0.9%)	35/1880 (1.9%)	RR 0.52 (0.31 to 0.87)	9 fewer per 1000 (from 2 fewer to 13 fewer)	VERY LOW	
Length of	hospital s	tay (Better inc	licated by lower	values)								
3	Randomi sed trials				No serious imprecision	None	89	93	-	MD 0.08 lower (0.35 lower to 0.18 higher)	MODERATE	
Infections	5							·				
1	Randomi sed trials			No serious indirectness	Serious <sup>c</sup>	None	10/50 (20%)	16/50 (32%)	RR 0.62 (0.31 to 1.24)	122 fewer per 1000 (from 221 fewer to 77 more)	LOW	
Thrombo	tic complic	cations										
10	Randomi sed trials		No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	None	5/503 (1%)	12/483 (2.5%)	RR 0.48 (0.18 to 1.23)	13 fewer per 1000 (from 20 fewer to 6 more)	LOW	

<sup>(</sup>a) Majority of the evidence was at high risk of bias.

<sup>(</sup>b) Downgraded by one increment due to heterogeneity, 12=72%.

<sup>(</sup>c) Confidence interval crosses one MID.

<sup>(</sup>d) Downgraded by one increment as the point estimate varies widely across studies, unexplained by subgroup analysis.

## J.2.2 Adults - moderate risk group

Quality a	assessment						No. of patien	ts	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Othe		Standard treatment	Relative (95% CI)	Absolute	Quality	Importance
No. expos	sed to allogenei	c blood										
3	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>		37/192 (19.3%)	48/192 (25%)	•	65 fewer per 1000 (from 125 fewer to 30 more)	VERY LOW	

<sup>(</sup>a) Majority of the evidence was at very high risk of bias.

<sup>(</sup>b) Confidence interval crosses one MID.

Quality asse	essment						No. of patients	;	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Post-operative cell salvage	Standard treatment	Relative (95% CI)	Absolute	Quality	Importance
No. exposed	d to allogeneic	blood										
14	Randomised trials	Very serious <sup>a</sup>	Serious <sup>b</sup>	No serious indirectness	Serious <sup>c</sup>	None	152/1264 (12%)	224/1377 (16.3%)	RR 0.58 (0.41 to 0.83)	68 fewer per 1000 (from 28 fewer to 96 fewer)	VERY LOW	
Units of allo	geneic blood t	transfused	(Better indicate	ed by lower val	ues)							
7	Randomised trials	Very serious <sup>a</sup>	Serious <sup>d</sup>	No serious indirectness	Serious <sup>c</sup>	None	50421	83122	_	MD 0.82 lower (1.31 to 0.33 lower)	VERY LOW	
Infection												
4	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>e</sup>	None	9/613 (1.5%)	3/412 (0.7%)	RR 1.79 (0.53 to 6.07)	6 more per 1000 (from 3 fewer to 37 more)	VERY LOW	
Hospital len	gth of stay (Be	etter indica	ated by lower va	alues)								

3	Randomised	Very	No serious	No serious	Very serious <sup>e</sup> No	one	115	90	-	MD 0.37 lower (1.73 lower VERY LOW
	trials	serious <sup>a</sup>	inconsistency	indirectness						to 0.99 higher)

- (a) Majority of the evidence was at very high risk of bias. (b) Downgraded by one increment due to heterogeneity,  $l^2 = 67\%$ .
- (c) Confidence interval crosses one MID.
   (d) Downgraded by one increment due to heterogeneity, l<sup>2</sup>=88%.
- (e) Confidence interval crosses both MIDs.

Quality as	sessment						No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider ations	Intra-operative cell salvage + post-operative cell salvage	Standard treatment	Relative (95% CI)	Absolute	Quality	Importance
No. expose	d to allogene	eic blood										
2	Randomise d trials	, ,	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>		25/377 (6.6%)	58/720 (8.1%)	to 1.33)	13 fewer per 1000 (from 37 fewer to 27 more)		
Units of allo	ogeneic bloo	d transfused	(Better indicated	by lower values)								
1	Randomise d trials		No serious inconsistency	No serious indirectness	No serious imprecision	None	23	54		MD 0.81 higher (0.49 higher to 1.13 higher)	LOW	
Infection												
1	Randomise d trials	, ,	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>		1/56 (1.8%)	0/62 (0%)	RR 3.32 (0.14 to 79.77)	_	VERY LOW	
Length of s	tay (Better ir	ndicated by l	ower values)									
1	Randomise d trials	, ,	No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	None	56	62		MD 0.2 higher (0.2 lower to 0.6 higher)	VERY LOW	
Mortality												

Quality as	ssessment						No. of patients		Effect			
No. of studies		Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider	•	Standard treatment	Relative (95% CI)	Absolute	Quality	Importance
1	Randomise d trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>		/56 1.8%)	0/62 (0%)	RR 3.32 (0.14 to 79.77)	-	VERY LOW	_

- (a) Majority of the evidence is at very high risk of bias
- (b) Confidence interval crosses both MIDs.
- (c) Confidence interval crosses one MID.

Quality a	assessment						No. of patients	3	Effect			
No. of studies	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other	Intra- operative cell salvage +TXA	Intra- operative cell salvage	Relative (95% CI)	Absolute	Quality	Importance
No. expos												
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency		Serious <sup>b</sup>	None	23/73 (31.5%)	30/74 (40.5%)	RR 0.78 (0.5 to 1.2)	89 fewer per 1000 (from 203 fewer to 81 more)	VERY LOW	
Units of b	lood transfused	l (Better ir	ndicated by lowe	er values)								·
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency		Very serious <sup>c</sup>	None	73	74	-	MD 0.46 lower (1.1 lower to 0.18 higher)	VERY LOW	
Length of	stay in hospital	(Better in	dicated by lowe	er values)								
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency		Very serious <sup>c</sup>	None	73	74	-	MD 0.72 higher (0.85 lower to 2.29 higher)	VERY LOW	

- (a) Majority of the evidence was at very high risk of bias.
- (b) Confidence interval crosses one MID.(c) Confidence interval crosses both MIDs.

Quality a	ssessment	:					No. of patie	ents	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecisio n		_	Post-operative cell salvage		Absolute	Quality	Importance
No. expos	ed to alloge	neic blood										
2	Randomise d trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	None	4/95 (4.2%)	(11.2%)	RR 0.37 (0.12 to 1.14)	71 fewer per 1000 (from 99 fewer to 16 more)	VERY LOW	
Thrombo	tic complicat	tions		·								·
1	Randomise d trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>c</sup>	None	0/49 (0%)		RR 0.2 (0.01 to 4.06)	33 fewer per 1000 (from 40 fewer to 125 more)		

- (a) Majority of the evidence is at very high risk of bias.(b) Confidence interval crosses one MID.(c) Confidence interval crosses both MIDs.

Quality a	ssessment						No. of patients		Effect			
No. of		Risk of					Intra-operative cell salvage + post- operative cell		Relative			
studies	Design	bias	Inconsistency	Indirectness	Imprecision	Other	salvage +TXA	TXA	(95% CI)	Absolute	Quality	Importance
No. expos	ed to alloge	neic blood					,					
1	Randomis ed trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	9/96 (9.4%)	•	RR 0.73 (0.33 to 1.63)	35 fewer per 1000 (from 86 fewer to 81 more)	VERY LOW	

Quality a	ssessment						No. of patients		Effect			
No. of		Risk of	In a maintain and	In discount of the	. Imaga da la	n Otho	Intra-operative cell salvage + post- operative cell		Relative	Absolute	Ovalia.	
studies	Design	bias	Inconsistency	Indirectness	imprecisio	n Otne	r salvage +TXA	TXA	(95% CI)	Absolute	Quality	Importance
1	Randomise trials	, ,		No serious indirectness		None 96		101	-	Not pooled	LOW	

- (a) Majority of the evidence was at very high risk of bias.(b) Confidence interval crosses both MIDs.

Quality a	assessment	ı					No. of patien	ts	Effect			
No. of studies		Risk of bias	Inconsistency	Indirectnes s	Imprecisio n	Other	TXA	Standard treatment- Adults- moderate risk	Relative (95% CI)	Absolute	Quality	Importance
No. expos	sed to alloge	neic transfu	ısions									
52	Randomise d trials	Serious <sup>a</sup>	Serious <sup>b</sup>	No serious indirectness	No serious imprecision	None	384/2397 (16%)	766/2180 (35.1%)	RR 0.45 (0.38 to 0.53)	193 fewer per 1000 (from 165 fewer to 218 fewer)	LOW	
No. of uni	its of blood t	transfused -	All Patients (Bett	er indicated b	y lower value	s)						
9	Randomise d trials	Serious <sup>a</sup>	Serious <sup>c</sup>	No serious indirectness		None	325	319	-	MD 0.88 lower (1.22 to 0.54 lower)	LOW	
Mortality												
9	Randomise d trials	Serious <sup>a</sup>	Serious <sup>d</sup>	No serious indirectness	Very serious <sup>e</sup>	None	1/550 (0.2%)	2/521 (0.4%)	RR 0.73 (0.15 to 3.66)	1 fewer per 1000 (from 3 fewer to 10 more)	VERY LOW	

Quality a	assessment						No. of patien	ts	Effect			
No. of studies		Risk of bias	Inconsistency	Indirectnes s	_	Other	TXA	Standard treatment- Adults- moderate risk	Relative (95% CI)	Absolute	Quality	Importance
Length of	hospital stay	(Better in	dicated by lower v	values)								
9	Randomised trials	l Serious <sup>a</sup>	Serious <sup>f</sup>	No serious indirectness	Serious <sup>g</sup>	None	667	665	-	MD 0.5 lower (1.09 lower to 0.09 higher)	VERY LOW	
Infections	S			,								
6	Randomised trials	l Serious <sup>a</sup>	Serious <sup>d</sup>	No serious indirectness	Very serious <sup>e</sup>	None	3/296 (1%)	3/290 (1%)	RR 0.93 (0.22 to 3.93)	1 fewer per 1000 (from 8 fewer to 30 more)	VERY LOW	
Thrombo	tic complicati	ons										
48	Randomised trials	l Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Serious <sup>f</sup>	None	44/2708 (1.6%)	46/2471 (1.9%)	RR 0.67 (0.43 to 1.04)	6 fewer per 1000 (from 11 fewer to 1 more)	LOW	

<sup>(</sup>a) Majority of the evidence was at high risk of bias.

- (b) Downgraded by one increment due to heterogeneity,  $l^2=55\%$ . (c) Downgraded by one increment due to heterogeneity,  $l^2=77\%$ .
- (d) Downgraded by one increment due to heterogeneity; the point estimate varies widely across studies, unexplained by subgroup analysis.
- (e) Confidence interval crosses both MIDs.
- (f) Downgraded by one increment due to heterogeneity,  $l^2=61\%$ .
- (g) Confidence interval crosses one MID.

Quality	assessment						No of patient	ts	Effect			Im
No of studie s	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration s	Intraop CS+Post op CS	Post op CS	Relative (95% CI)	Absolute	Qual ity	por tan ce
Number	of patients t	ransfused	d									
1	randomis ed trials	seriou s1	no serious inconsistency	no serious indirectness	serious2	none	23/321 (7.2%)	33/32 1 (10.3 %)	RR 0.70 (0.42 to 1.16)	31 fewer per 1000 (from 60 fewer to 16 more)	LOW	
Units of	allogeneic bl	ood trans	sfused (Better ind	icated by lower	values)							
1	randomis ed trials	seriou s1	no serious inconsistency	no serious indirectness	no serious imprecision	none	23	33	-	MD 2.23 higher (1.92 to 2.54 higher)	MO DER ATE	

<sup>1</sup> Majority of the evidence was at high risk of bias.2 Confidence interval crosses one MID.

#### Adults - low risk group J.2.3

Quality a	assessment						No. of patien	ts	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectnes s	-	Other	TXA	Placebo- Low risk- adults	Relative (95% CI)	Absolute	Quality	Importance
No. of pa	tients receiving	g allogene	ic transfusions (ro	oute)								
4	Randomised trials		No serious inconsistency	No serious indirectness	, ,	None	6/315 (1.9%)	7/311 (2.3%)	2.29)	4 fewer per 1000 (from 16 fewer to 29 more)	VERY LOW	
No. of pa	tients receiving	g allogene	ic transfusions (ro	oute) - Topical	TXA							
1	Randomised trials		No serious inconsistency	No serious indirectness	, p	None	0/200 (0%)	2/200 (1%)	4.14)	8 fewer per 1000 (from 10 fewer to 31 more)	VERY LOW	

Quality a	assessment						No. of patien	ts	Effect			
No. of studies		Risk of bias	Inconsistency	Indirectnes s	-	Other	TXA	Placebo- Low risk- adults	Relative (95% CI)	Absolute	Quality	Importance
1	Randomised trials		No serious inconsistency	No serious indirectness	Very serious <sup>2</sup>	None	6/70 (8.6%)	5/66 (7.6%)	RR 1.13 (0.36 to 3.53)	10 more per 1000 (from 48 fewer to 192 more)	VERY LOW	
Blood los	s (type of surg	ery-topica	al TXA)) - Orthogn	athic surgery (	Better indicat	ed by lo	ower values)					
1	Randomised trials		No serious inconsistency	No serious indirectness		None	0	-	-	MD 0.93 higher (0.73 to 1.2 higher)	MODERATE	
Blood los	s (type of surg	ery-topica	al TXA)) - Otolaryn	geal surgery (	Better indicate	ed by lo	wer values)					
2	Randomised trials		No serious inconsistency	No serious indirectness		None	0	-	-	MD 0.74 higher (0.73 to 0.76 higher)	MODERATE	

<sup>(</sup>a) Majority of the evidence was at high risk of bias.(b) Confidence interval crosses both MIDs.

#### J.2.4 Children - high risk group

Quality a	ssessment						No. of patien	ts	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectnes s				Intra-operative cell salvage- type of surgery	Relative (95% CI)	Absolute	Quality	Importance
Number o	f patients tra	nsfused -	Post 2003									
1	Randomised trials			No serious indirectness	Very serious <sup>2</sup>	None	14/23 (60.9%)	15/21 (71.4%)	RR 0.85 (0.56 to 1.3)	107 fewer per 1000 (from 314 fewer to 214	VERY LOW	

Quality a	ssessment						No. of patien	ts	Effect			
No. of studies		Risk of bias	Inconsistency	Indirectnes s	-	Other	cells salvage	Intra-operative cell salvage- type of surgery	Relative (95% CI)	Absolute	Quality	Importance
Total bloo	d transfused -	Post 200	3 (Better indicate	d by lower val	lues)							
1	Randomised trials	•	No serious inconsistency	No serious indirectness	, .	None	23	21	-	MD 325 lower (685.06 lower to 35.06 higher)	VERY LOW	
Total bloo	d loss - Post 2	.003 (Bett	er indicated by lo	wer values)	,		,		,		,	·
1	Randomised trials		No serious inconsistency	No serious indirectness	- /	None	23	21	-	MD 855 lower (1408.15 to 301.85 lower)	VERY LOW	

- (a) Majority of the evidence was at very high risk of bias.(b) Confidence interval crosses both MIDs.

Quality a	ssessment						No. of patie	nts	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectne ss	-	Other	TXA		Relative (95% CI)	Absolute	Quality	Importance
Post-opera	ative blood lo	ss - Post	2003 (Better indi	cated by low	er values)							
1	Randomise d trials			No serious indirectness		None	96	24	-	MD 16 lower (21.13 to 10.87 lower)	MODERATE	
Length of	stay (Better ir	ndicated	by lower values)									
1	Randomise d trials			No serious indirectness		None	36	47	-	MD 0.1 higher (0.37 lower to 0.57 higher)	LOW	

- (a) Majority of the evidence was at high risk of bias.
- (b) Confidence interval crosses one MID.

## J.3 Red blood cells

### J.3.1 RBC thresholds

J.3.1.1 Restrictive strategy versus liberal strategy (adults)

Quality	assessment						No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistenc y	Indirectness	Imprecision	Other considerations	Blood transfusions (adults)	Contro I	Relative (95% CI)	Absolute	Quality	Importanc e
Number	of patients need	ding transf	usion									
24	Randomised trials	Serious <sup>a</sup>	Very serious <sup>b</sup>	No serious indirectness	No serious imprecision	None	2499/4981 (50.2%)	92%	RR 0.65 (0.59 to 0.73)	322 fewer per 1000 (from 248 fewer to 377 fewer)	LOW	
Number	of patients nee	ding trans	fusion (sub-grou	ps) - Peri-operat	ive surgical patie	ents						
14	Randomised trials	Serious <sup>a</sup>	Serious <sup>e</sup>	No serious indirectness	No serious imprecision	None	1462/3256 (44.9%)	87.8%	RR 0.61 (0.52 to 0.72)	342 fewer per 1000 (from 246 fewer to 421 fewer)	LOW	
Number	of patients need	ding transf	usion (sub-grou	ps) - Critical care								
5	Randomised trials	Serious <sup>a</sup>	Serious <sup>f</sup>	No serious indirectness	Serious <sup>d</sup>	None	711/1105 (64.3%)	100%	RR 0.73 (0.6 4 to 0.84)	270 fewer per 1000 (from 160 fewer to 360 fewer)	VERY LOW	
Number	of patients need	ding transf	usion (sub-grou	ps) - Acute blood	loss/trauma							
4	Randomised trials	Serious <sup>a</sup>	Serious <sup>g</sup>	No serious indirectness	No serious imprecision	None	300/591 (50.8%)	95.2%	RR 0.58 (0.46 to 0.74)	400 fewer per 1000 (from 248 fewer to 514 fewer)	LOW	

Quality a	assessment						No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistenc y	Indirectness	Imprecision	Other considerations	Blood transfusions (adults)	Contro I	Relative (95% CI)	Absolute	Quality	Importanc e
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	26/29 (89.7%)	93.6%	RR 0.96 (0.82 to 1.12)	37 fewer per 1000 (from 168 fewer to 112 more)	HIGH	
Number o	of units of blood	d transfuse	ed in those trans	fused (Better ind	licated by lower	values)						
10	Randomised trials	Serious <sup>a</sup>	Very serious <sup>c</sup>	No serious indirectness	Serious <sup>d</sup>	None	964	1179	-	MD 1.13 lower (1.67 to 0.59 lower)		
Number o	of units of blood	d transfuse	ed in those trans	fused (sub-group	os) - Peri-operativ	e surgical patients	(Better indicated b	y lower v	alues)			
5	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	172	225	-	MD 0.55 lower (0.91 to 0.18 lower)	MODER ATE	
Number o	of units of blood	d transfuse	ed in those trans	fused (sub-group	os) - Critical care	(Better indicated by	lower values)					
1	Randomised trials	Serious <sup>h</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	280	420	-	MD 1.72 lower (2.45 to 0.99 lower)	MODER ATE	
Number o	of units of blood	d transfuse	ed in those trans	fused (sub-group	os) - Acute blood	loss/trauma (Bette	r indicated by lowe	r values)				
3	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	457	479	-	MD 2.19 lower (2.58 to 1.8 lower)	MODER ATE	
Number o	of units of blood	d transfuse	ed in those trans	fused (sub-group	s) - Acute corona	ary syndrome (ACS)	(Better indicated l	y lower	values)			
1	Randomised trials	Serious <sup>i</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	55	55	-	MD 1.09 lower (1.49 to 0.69 lower)	MODER ATE	

<sup>(</sup>a) Majority of the evidence is from studies at high risk of bias.

<sup>(</sup>b) Evidence of high heterogeneity with I2 value of 91%.

<sup>(</sup>c) Evidence of high heterogeneity, 12=84%.

<sup>(</sup>d) Confidence interval crosses one MID.

<sup>(</sup>a) Confident (e)  $I^2 = 91\%$ . (f)  $I^2 = 83\%$ . (g)  $I^2 = 76\%$ .

- (h) Unclear randomisation. No blinding.
- (i) Unclear randomisation and allocation concealment.

Quality a	ssessment						No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistenc y	Indirectness	Imprecisio n	Other considerations	Length of hospital stay (adults)	Contro I	Relativ e (95% CI)	Absolute	Quality	Importanc e
Hospital le	ength of stay- su	bgroups (b	etter indicated b	y lower values)								•
12	Randomised trials	Serious <sup>a</sup>	Serious <sup>b</sup>	No serious indirectness	Serious <sup>c</sup>	None	2697	2699	-	MD 0.52 lower (1.11 lower to 0.06 higher)	VERY LOW	
Hospital le	ength of stay- su	bgroups - I	Peri-operative su	irgical patients (Be	tter indicated	by lower values)						
9	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	1811	1813	-	MD 0.01 higher (0.30 lower to 0.32 higher)	MODERA TE	
Hospital le	ength of stay- su	bgroups - (	Critical care (Bet	ter indicated by lov	wer values)			·			·	
1	Randomised trials	Serious <sup>d</sup>	No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	None	24	21	-	MD 4.2 lower (6.93 to 1.47 lower)	LOW	
Hospital le	ength of stay- su	bgroups –	ACS (Acute MI)	(Better indicated b	y lower value	s)						
1	Randomised trials	Serious <sup>d</sup>		No serious indirectness	Serious <sup>c</sup>	None	24	21	-	MD 4.2 lower (6.93 to 1.47 lower)	LOW	
Hospital le	ength of stay- su	bgroups - /	Acute blood loss,	/trauma (Better in	dicated by lov	ver values)						
1	Randomised trials	Serious <sup>e</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	444	445	-	MD 1.9 lower (3.34 to 0.46 lower)	MODERA TE	

- (a) Majority of the evidence is from studies at high risk of bias.
- (b)  $I^2 = 55\%$ .
- (c) Confidence interval crosses one MID.
- (d) Unclear randomisation and allocation concealment.
- (e) Unclear blinding.

Quality	assessment						No. of patie	ents	Effect			
No. of studie s	Design	Risk of bias	Inconsiste ncy	Indirectness	Imprecisi on	Other consideration s	Mortality (adults)	Cont	Relative (95% CI)	Absolute	Quali ty	Importa nce
30-day m	ortality											
21	Randomised trials	Serious a	Serious <sup>b</sup>	No serious indirectness	Serious <sup>c</sup>	None	423/4798 (8.8%)	5.1%	RR 0.95 (0.77 to 1.17)	3 fewer per 1000 (from 12 fewer to 9 more)	VERY LOW	
30-day m	ortality (sub-gro	oups) - Peri	operative surgio	al patients								
12	Randomised trials	Serious a	No serious inconsistenc	No serious indirectness	Serious <sup>c</sup>	None	102/3145 (3.2%)	2.4%	RR 0.99 (0.75 to 1.3)	0 fewer per 1000 (from 6 fewer to 7 more)	LOW	
30-day m	ortality (sub-gro	oups) - Crit	ical care									
5	randomised trials	Serious a	no serious inconsistenc y	no serious indirectness	Serious <sup>e</sup>	None	289/1105 (26.2%)	25%	RR 0.98 (0.73 to 1.31)	5 fewer per 1000 (from 67 fewer to 77 more)	LOW	
30-day m	ortality (sub-gro	oups) – ACS	(Acute MI)									
2	randomised trials	Serious a	no serious inconsistenc y	no serious indirectness	very serious <sup>d</sup>	None	9/78 (11.5%)	4.8%	RR 3.85 (0.82 to 18)	137 more per 1000 (from 9 fewer to 816 more)	VERY LOW	
30-day m	ortality (sub-gro	oups) - Acu	te blood loss/tra	auma								
2	randomised trials	Serious a	no serious inconsistenc y	no serious indirectness	Serious <sup>c</sup>	None	23/470 (4.9%)	8.8%	RR 0.55 (0.34 to 0.89)	40 fewer per 1000 (from 10 fewer to 58 fewer)	LOW	

<sup>(</sup>a) Majority of the evidence is from studies at high risk of bias.

<sup>(</sup>b) Effect sizes on forest plot are not consistent with each other.

<sup>(</sup>c) Confidence interval crosses one MID.

<sup>(</sup>d) Confidence interval crosses both default MIDs and line of no effect.

<sup>(</sup>e) Confidence interval crosses one default MID and line of no effect.

Quality a	assessment						No. of patient	ts	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	New cardiac events (adults)		Relative (95% CI)	Absolute	Quality	Importanc e
New Card	iac events (MI,	CHF) - sub-	total analysis - My	ocardial infarction								
16	Randomised trials	Serious	No serious inconsistency	No serious indirectness	Very serious <sup>a</sup>	None	80/4184 (1.9%)	1.8%	RR 1.13 (0.79 to 1.61)	2 more per 1000 (from 4 fewer to 11 more)	VERY LOW	
New Card	iac events (MI,	CHF)- sub-	total analysis - Con	gestive heart failur	e							
7	Randomised trials	Serious <sup>b</sup>	Serious <sup>c</sup>	No serious indirectness <sup>d</sup>	Very serious <sup>a</sup>	None	83/2106 (3.9%)	4.2%		0 fewer per 1000 (from 19 fewer to 35 more)	VERY LOW	

- (a) Confidence interval crosses both MIDs.
- (b) Majority of the evidence was from studies at high risk of bias.
- (c)  $I^2 = 61\%$ .
- (d) Pulmonary oedema reported in 3 studies which is a surrogate outcome.

Quality assessment							No. of patients		Effect			
No. of studies		Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio	Other consideratio ns	Infection - adults		Relative (95% CI)	Absolute	Quality	Importance
Infection (Pneumonia, surgical site infection, septicaemia, UTI, infections not specified) – Pneumonia												
8	Randomised trials		No serious inconsistency		Serious <sup>b</sup>		146/1725 (8.5%)	4.1%	,	4 fewer per 1000 (from 11 fewer to 5 more)	LOW	
Infection (Pneumonia, surgical site infection, septicaemia, UTI, infections not specified) - Surgical site/Wound infection												
2	randomised trials			no serious indirectness	serious <sup>2</sup>		56/1069 (5.2%)		,	17 fewer per 1000 (from 30 fewer to 1 more)	LOW	

Quality a	assessment						No. of pa	tients	Effect			
No. of studies	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other considerations	Infection - adults		Relative (95% CI)	Absolute	Quality	Importance
nfection	(Pneumonia, su	rgical site	infection, seption	caemia, UTI, ir	nfections not :	specified) - Sept	icaemia/Ba	cteraemia				
2	randomised trials	Serious <sup>a</sup>		no serious indirectness	Serious <sup>b</sup>	None	1/114 (0.88%)		RR 1 (0.06 to 15.62)	0 fewer per 1000 (from 8 fewer to 117 more)	LOW	
nfection	(Pneumonia, su	rgical site	infection, seption	caemia, UTI, ir	nfections not	specified) - Infe	ction (not s	pecified)				
4	randomised trials	Serious <sup>a</sup>		no serious indirectness	Serious <sup>b</sup>	None	172/1204 (14.3%)		RR 0.89 (0.74 to 1.07)	11 fewer per 1000 (from 26 fewer to 7 more)	LOW	
Infection	(overall)											
17	randomised trials	Serious <sup>a</sup>	no serious inconsistency	no serious indirectness	Serious <sup>b</sup>	None	613/5048 (12.1%)	675/5080 (13.3%)	RR 0.92 (0.83 to 1.01)	11 fewer per 1000 (from 23 fewer to 1 more)	LOW	
nfection	(Sepsis or wour	nd infection	n)									
1	randomised trials	Serious <sup>a</sup>	no serious inconsistency	no serious indirectness	Serious <sup>b</sup>	None	238/936 (25.4%)		RR 1.01 (0.87 to 1.18)	3 more per 1000 (from 33 fewer to 45 more)	LOW	

<sup>(</sup>a) Majority of the evidence was from studies at high risk of bias.(b) Confidence interval crosses one MID.

Quality a	Quality assessment								Effect			
No. of studies	Design	Risk of bias	Inconsistenc Y	Indirectnes s	Imprecisio	Other consideratio ns	Adverse events (adults)		Relative (95% CI) Absolute		Quality	Importance
All advers	All adverse events (as defined by the study)											
3	Randomised trials	Serious <sup>a</sup>	No serious inconsistency		Serious <sup>b</sup>	None	179/957 (18.7%)			0 fewer per 1000 (from 0 fewer to 1 fewer)	LOW	

Quality a	uality assessment								Effect			
No. of studies	No. of Risk studies Design bias		Inconsistenc y	Indirectnes s	Imprecisio	Other	No. of patients  Adverse events (adults)		Relative	Absolute	Quality	Importance
Transfusi	on associated o	circulatory	overload (TAC	0)								
2	Randomised trials		No serious inconsistency	No serious indirectness		None	2/932 (0.21%)		RR 0.13 (0.03 to 0.54)	16 fewer per 1000 (from 8 fewer to 17 fewer)	MODERATE	
Transfusion Related Acute Lung Injury (TRALI)												
2	Randomised trials		No serious inconsistency			None	0/932 (0%)	0%	Not pooled	Not pooled	MODERATE	

<sup>(</sup>a) Majority of the evidence is from studies at high risk of bias.

# J.3.1.2 Restrictive strategy versus liberal strategy (children)

	Ī	-										
Quality	assessment	t					No. of patients		Effect			
No. of studie	Design	Risk of bias	Inconsistenc Y	Indirectness	Imprecisio n	Other	Blood transfusion (children)	Control	Relative (95% CI)	Absolute	Quality	Importanc e
Total RE	BC ml/patient	(Better indi	cated by lower	values)							,	
1	Randomised trials	Serious <sup>a</sup>	serious inconsistency <sup>b</sup>	No serious indirectness	No serious imprecision	None	53	54	-	MD 73.0 lower (1.0352 to 0.4248 lower)	MODERATE	
Number	of patients n	eeding tran	sfusion –childre	n							'	
2	Randomised trials	Serious <sup>c</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	157/350 (44.9%)	97.2%	RR 0.46 (0.41 to 0.52)	525 fewer per 1000 (from 467 fewer to 573 fewer)	MODERATE	
Number	of patients n	eeding tran	sfusion (sub-gro	oup)-children - C	Critical care						·	
1	Randomised	Serious <sup>d</sup>	No serious	No serious	No serious	None	146/320	97.8%	RR 0.47	518 fewer per 1000 (from	MODERATE	

<sup>(</sup>b) Confidence interval crosses one MID.

Quality	<i>ı</i> assessment						No. of patients		Effect			
No. of studie		Risk of bias	Inconsistenc y	Indirectness	Imprecisio n		Blood transfusion (children)	Control	Relative (95% CI)	Absolute	Quality	Importanc e
	trials		inconsistency	indirectness	imprecision		(45.6%)		(0.41 to 0.53)	460 fewer to 577 fewer)		
Numbei	r of patients n	eeding tran	sfusion (sub-gro	oup)-children - C	Congenital card	diac disea	se					
1	Randomised trials	Serious <sup>e</sup>	No serious inconsistency <sup>f</sup>		No serious imprecisiond	None	11/30 (36.7%)	96.7%	RR 0.38 (0.24 to 0.61)	600 fewer per 1000 (from 377 fewer to 735 fewer)	MODERATE	
Numbei	of units trans	fused-child	ren (Better indi	cated by lower v	values)	•						
2	Randomised trials	Serious <sup>c</sup>	Very serious <sup>b</sup>		No serious imprecision	None	350	340	-	MD 0.65 lower (0.98 to 0.33 lower)	VERY LOW	

- (a) Unclear sequence generation and unclear blinding.
- (b)  $I^2 = 97\%$ .
- (c) Most information comes from studies with high risk of bias
- (d) Unclear randomisation. No blinding of clinical staff and patients.
- (e) Unclear randomisation and allocation concealment.
- (f)  $I^2 = 93\%$ .

Quality a	uality assessment						No. of patie	ents	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecisio n		Mortality (children)		Relative (95% CI)	Absolute	Quality	Importance
Mortality	(30 days)											
2	randomised trials		no serious inconsistency	serious <sup>2</sup>	very serious <sup>3</sup>	none	14/350 (4%)		RR 0.93 (0.46 to 1.87)	3 fewer per 1000 (from 21 fewer to 34 more)	VERY LOW	

- (a) Most information is from studies at high risk of bias.
- (b) Lacroix 2007- Included infants <1 year.

Quality ass	uality assessment						No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectnes s	-		Length of hospital stay (children)		Relative Il (95% CI) Absolute		o !!!	Importanc e
ICU length of stay (Better indicated by lower values)												
1	Randomised trials		No serious inconsistency	Serious <sup>b</sup>	Serious <sup>c</sup>	None	320	317	-	MD 0.4 lower (1.59 lower to 0.79 higher)	VERY LOW	

<sup>(</sup>a) Unclear randomisation sequence generation.

<sup>(</sup>b) Not protocol outcome. Length of hospital stay not reported. Study included infants <1 year.</li>(c) Confidence interval crosses one default MID and line of no effect.

Quality a	uality assessment  o. of Risk of Indirectnes Imprecisio						No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectnes s			New cardiac events (children)		Relative ol (95% CI) Absolute		Quality	Importance
Pulmonar	ry oedema											
1	Randomised	Serious <sup>a</sup>	No serious	Serious <sup>b</sup>	Very serious <sup>c</sup>	None	0/320	1.6%	RR 0.09 (0.01	15 fewer per 1000 (from	VERY LOW	

- (a) Unclear randomisation sequence generation.
- (b) Pulmonary oedema not protocol specified new cardiac event. Included children less than 1 year.
- (c) Confidence interval crosses both default MIDs and line of no effect.

Quality a	Quality assessment No. of Inconsistenc Indirectnes Imprecisio							ients	Effect			
No. of studies	Design	Risk of bias		Indirectnes s			Infection (children)		Relative I (95% CI) Absolute		Quality	Importance
	(Nosocomial i		7				(4111411)		(00% 01)	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	<b></b>	
1	randomised trials		no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	65/320 (20.3%)		•	45 fewer per 1000 (from 97 fewer to 22 more)	VERY LOW	

- (a) Unclear randomisation and blinding.
- (b) Not specified type of nosocomial infection. Included infants (<1 year).
- (c) Confidence interval crosses one default MID and line of no effect.

# J.3.2 RBC targets

# **Blood transfusions (adults)**

Quality assessment	No of patients	Effect	Quality I	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness		Other considerations	Blood transfusions (adults)		Relative (95% CI)	Absolute			
Number o	f patients nee	ding trans	fusion (all studie	s)									
5	randomised trials	serious <sup>1</sup>			no serious imprecision	none	644/1169 (55.1%)		RR 0.61 (0.55 to 0.67)	358 fewer per 1000 (from 303 fewer to 413 fewer)	LOW		
Number of patients needing transfusion (sub-groups) - Peri-operative surgical patients													
1	randomised trials					none	118/249 (47.4%)	198/253 (78.3%)		305 fewer per 1000 (from 235 fewer to 376 fewer)			
								78.3%		305 fewer per 1000 (from 235 fewer to 376 fewer)			
Number o	f units of bloo	d transfus	ed in those trans	sfused (Better inc	licated by lower	values)							
3	randomised trials	serious <sup>1</sup>			no serious imprecision	none	748	886	-	MD 1.72 lower (2.41 to 1.02 lower)	LOW		

 $<sup>^{1}</sup>$  Majority of the evidence was from studies at high risk of bias.  $^{2\ 12}$  value=64%  $^{3\ 12}$  value=68%

#### Length of hospital stay (adults)

Length	i ilospitai st	ay (addin										
Quality as	ssessment					No of patients		Effect				
No of studies	Design	Risk of bias	Inconsistency	Indirectness		Other considerations	Length of hospital stay (adults)		Relative (95% CI)	Absolute	Quality	Importance
Hospital le	ngth of stay (B	etter indica	ated by lower value	s)								
3	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	886	886		MD 2.16 lower (3.81 to 0.5 lower)	⊕⊕OO LOW	

# Mortality (adults)

Quality a	ssessment					No of patien	ts	Effect				
No of studies	Design	Risk of bias	Inconsistency	Indirectness		Other considerations	Mortality (adults)		Relative (95% CI)	Absolute	Quality	Importance
30-day mc	ortality											
6	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	126/1193 (10.6%)		to 0.97)	20 fewer per 1000 (from 3 fewer to 34 fewer)	⊕⊕OO LOW	

<sup>&</sup>lt;sup>1</sup> Majority of the evidence is from studies at high risk of bias. <sup>2</sup> Confidence interval crosses one MID.

#### New cardiac events (adults)

reer ca.	uiac events	(uuu.to,										
Quality a	ssessment						No of patients		Effect			
No of studies		Risk of bias	Inconsistency	Indirectness		Other considerations	New cardiac events (adults)	Control	Relative (95% CI)	Absolute	Quality	Importance
New Card	iac events (MI,	CHF)- sub	-total analysis - My	ocardial infarction	า							
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	3/418 (0.72%)			22 fewer per 1000 (from 3 fewer to 27 fewer)	⊕⊕OO LOW	
New Card	iac events (MI,	CHF)- sub	o-total analysis - Co	ngestive heart fail	ure	,	·		,	·	,	
2	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>3</sup>	serious <sup>2</sup>	none	22/461 (4.8%)		•	40 fewer per 1000 (from 17 fewer to 54 fewer)	⊕OOO VERY LOW	

<sup>&</sup>lt;sup>1</sup> Majority of the evidence is from studies at high risk of bias. <sup>2</sup> Confidence interval crosses MID

# Infection - adults for guiding allogeneic red blood cell transfusion

Quality a	ssessment						No of patie	nts	Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness		Other considerations	Infection - adults		Relative	Absolute	Quality	Importance
Infection (	Pneumonia, surgi	cal site inf	ection, septicemia,	UTI) - Pneumonia								
2 r	no methodology chosen					none	90/443 (20.3%)		to 1.22)	10 fewer per 1000 (from 54 fewer to 44 more)		
								20.5%		10 fewer per 1000 (from 55 fewer to 45 more)		
Infection (	Pneumonia, surgi	cal site inf	ection, septicemia,	UTI) - Infection (n	ot specified)							
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	30/249 (12%)	9.9%	to 2.01)	22 more per 1000 (from 26 fewer to 100 more)	???? VERY LOW	

<sup>&</sup>lt;sup>1</sup> Evidence from study at high risk of bias. <sup>2</sup> Confidence interval crosses both MIDs.

#### Adverse events (adults)

Quality a	Quality assessment								Effect			
							Adverse					
No of		Risk of				Other	events		Relative			
studies	Design	bias	Inconsistency	Indirectness	Imprecision	considerations	(adults)	Control	(95% CI)	Absolute	Quality	Importance

Majority of the evidence is from studies at high risk of bias.
 Confidence interval crosses one MID.
 One study reports acute pulmonary oedema which is a surrogate outcome for congestive heart failure.

Quality a	ssessment						No of patients	i	Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness		Other considerations	Adverse events (adults)		Relative (95% CI)	Absolute	Quality	Importance
All adverse	e events (as de	fined by th	ne study)									
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	179/444 (40.3%)		to 0.97)	77 fewer per 1000 (from 14 fewer to 135 fewer)	⊕OOO VERY LOW	

Evidence from study at high risk of bias.
 Adverse event not defined in study.
 Confidence interval crosses one MID.

### **Blood transfusion (children)**

	ansiusion (		·,									
Quality a	assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Blood transfusion (children)		Relative (95% CI)	Absolute	Quality	Importance
Total RBC	ml/patient (B	etter indi	cated by lower val	ues)								
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	146	310	-	MD 0.2 higher (0.4 lower to 0.8 higher)	⊕OOO VERY LOW	
Number o	of patients nee	ding tran	sfusion -children (	critical care)	,		·		,		,	,
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	146/320 (45.6%)		RR 0.47 (0.41 to 0.53)	518 fewer per 1000 (from 460 fewer to 577 fewer)		

<sup>&</sup>lt;sup>1</sup> Evidence from study at high risk of bias. <sup>2</sup> Confidence interval crosses both MIDs.

### Mortality (children)

Quality a	ssessment					No of patient	·s	Effect				
No of studies	Design	Risk of bias	Inconsistency	Indirectness		Other considerations	Mortality		Relative	Absolute	Quality	Importance
Mortality	(30 days)											
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	14/320 (4.4%)		•	0 fewer per 1000 (from 23 fewer to 46 more)	⊕OOO VERY LOW	

<sup>&</sup>lt;sup>1</sup> Evidence from study at high risk of bias. <sup>2</sup> Confidence interval crosses both MIDs.

## Length of hospital stay (children)

Quality a	ssessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness		Other considerations	Length of hospital stay (children)		Relative (95% CI)	Absolute	Quality	Importance
ICU length	of stay (Bette	r indicated	by lower values)			'						
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	320	317		MD 0.4 lower (1.59 lower to 0.79 higher)		

<sup>&</sup>lt;sup>1</sup> Evidence from study at high risk of bias. <sup>2</sup> Confidence interval crosses both MIDs.

# New cardiac events (children)

0!	· · · · · · · · · · · · · · · · · · ·	N	F## A	0	/
Quali	ity assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness		Other considerations	New cardiac events (children)		Relative (95% CI)	Absolute		
Pulmonary	Pulmonary oedema											
1	randomised trials		no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	None	0/320 (0%)		to 1.62)	15 fewer per 1000 (from 16 fewer to 10 more)	⊕OOO VERY LOW	

# Infection (children)

	r(ciliarell)											
Quality a	ssessment						No of patient	ts	Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness		Other considerations	Infection (children)		Relative (95% CI)	Absolute	Quality	Importance
Infection (	Nosocomial in	fections)										
1	randomised trials	serious <sup>1</sup>		no serious indirectness	serious <sup>2</sup>	none	65/320 (20.3%)		to 1.09)	45 fewer per 1000 (from 97 fewer to 22 more)	⊕⊕OO LOW	

<sup>&</sup>lt;sup>1</sup> Evidence from study at high risk of bias. <sup>2</sup> Confidence interval crosses one MID.

#### J.3.3 **RBC** doses

None.

<sup>&</sup>lt;sup>1</sup> Evidence from study at high risk of bias.
<sup>2</sup> Study reports acute pulmonary oedema which is a surrogate outcome for congestive heart failure.
<sup>3</sup> Confidence interval crosses one MID.

# J.4 Platelets

# J.4.1 Platelet thresholds and targets

J.4.1.1 Prophylactic transfusion versus no prophylactic transfusion - adults who are haematology patients (non-bleeding patients)

Quality	assessment						No of patie	nts	Effect			
No of studies		Risk of bias	Inconsistenc Y	Indirectnes s		Other	Prophylacti	haematology	Relative (95% CI)	Absolute		Importanc e
Number	of patients w	ith bleeding	g events (WHO ¿	grade 2 or hig	her)							
2	Randomised trials	Serious <sup>a</sup>	Very serious <sup>b</sup>	No serious indirectness	Serious <sup>c</sup>	None	193/493 (39.1%)	57.3%	RR 0.7 (0.61 to 0.8)	172 fewer per 1000 (from 115 fewer to 223 fewer)	VERY LOW	
Number	of patients w	ith major b	leeding events (	WHO grade 3	or 4)							
2	Randomised trials		No serious inconsistency			None	8/493 (1.6%)	6.3%	·	44 fewer per 1000 (from 22 fewer to 54 fewer)	MODERATE	
Serious a	dverse event	s (including	sepsis and resp	oiratory deteri	oration)							
1	Randomised trials		No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	None	20/298 (6.7%)	6%	RR 1.12 (0.6 to 2.07)	7 more per 1000 (from 24 fewer to 64 more)	LOW	
Transfus	ion related se	rious adver	rse event (urtica	rial and angio	edema)							
1	Randomised trials			No serious indirectness	Very serious <sup>e</sup>	None	1/299 (0.33%)	0%	RR 3.02 (0.12 to 73.84)	_	VERY LOW	
Number	of patients ne	eeding plate	elet transfusion									
1	Randomised trials			No serious indirectness		None	266/299 (89%)	58.5%	RR 1.52 (1.37 to 1.69)	304 more per 1000 (from 216 more to 404 more)	MODERATE	

Quality	assessment						No of patie	ate.	Effect			
No of studies			Inconsistenc y	Indirectnes s	•	Other	Prophylacti	No prophylactic transfusion - adults who are haematology	Relative (95% CI)	Absolute	Quality	Importanc e
Number	of units (plate	elets) transf	used per patier	nt (better indi	cated by lowe	r values	)					
	Randomised trials			No serious indirectness		None	299	301	-	MD 1.3 higher (0.75 to 1.85 higher)	MODERATE	
Mortality	y (all cause)											
	Randomised trials			No serious indirectness	Very serious <sup>e</sup>	None	5/194 (2.6%)	3.6%	RR 0.73 (0.23 to 2.25)	10 fewer per 1000 (from 28 fewer to 45 more)	LOW	
Side effe	cts of transfu	sion (not sp	ecified)									
	Randomised trials		No serious inconsistency	Serious <sup>f</sup>	Very serious <sup>e</sup>	None	25/194 (12.9%)	13.7%	RR 0.94 (0.57 to 1.56)	8 fewer per 1000 (from 59 fewer to 77 more)	VERY LOW	

<sup>(</sup>a) Most information is from studies at high risk of bias.

#### Prophylactic transfusion versus no prophylactic transfusion - children who are haematology patients (non-bleeding patients) J.4.1.2

,	Quality	assessment						No of patier	nts	Effect			
	No of		Risk of			Imprecisio		Prophylacti	No prophylactic transfusion - children who are haematology	Relative			
	studies	Design	bias	Inconsistency	Indirectness	n	Other	transfusion	patients	(95% CI)	Absolute	Quality	Importance

<sup>(</sup>b)  $^{12}=92\%$ .

<sup>(</sup>c) Confidence interval crosses one default MID and line of no effect.

<sup>(</sup>d) Study at high risk of bias.

<sup>(</sup>e) Confidence interval crosses both default MIDs and line of no effect.(f) No pre-specified definition of side-effects.

Quality	assessment						No of patie	nts	Effect			
No of studies		Risk of bias	Inconsistency	Indirectness	Imprecisio n		Prophylacti	No prophylactic transfusion - children who are haematology patients	Relative (95% CI)	Absolute	Quality	Importance
Number	of patients wi	th major	bleeding events (	WHO grade 3 o	r 4)							
1	Randomised trials			No serious indirectness	Serious <sup>b</sup>	None	10/35 (28.6%)	52.4%	RR 0.55 (0.28 to 1.06)	236 fewer per 1000 (from 377 fewer to 31 more)	LOW	
Mortality	(all cause) (3	years)										
1	Randomised trials		No serious inconsistency	Serious <sup>c</sup>	Very serious <sup>d</sup>	None	12/35 (34.3%)	33.3%	RR 1.03 (0.48 to 2.2)	10 more per 1000 (from 173 fewer to 400 more)	VERY LOW	
Mortality	Mortality from bleeding (3 years)											
1	Randomised trials		No serious inconsistency	Serious <sup>e</sup>	Very serious <sup>d</sup>	None	1/35 (2.9%)	9.5%	RR 0.3 (0.03 to 3.11)	67 fewer per 1000 (from 92 fewer to 200 more)	VERY LOW	

<sup>(</sup>a) Study is at high risk of bias.

- (b) Confidence interval crosses one default MID and line of no effect.
- (c) Mortality assessed at 3 years, our protocol outcome was mortality at 30 days.
- (d) Confidence interval crosses both default MIDs and line of no effect.
- (e) Mortality assessed at 3 years, our protocol outcome was mortality at 30 days.

# J.4.1.3 Low platelet thresholds versus high platelet thresholds - adults who are haematology patients (non-bleeding patients)

Quality assessment	No of patients	Effect	Quality	Importance

No of studie		Risk of bias	Inconsistenc Y	Indirectnes s	Imprecisio n	Other	Low platelet thresholds	High platelet thresholds - Adults who are haematology patients	Relative (95% CI)	Absolute		
Mortalit	y (all cause)										'	
4	Randomised trials	Serious <sup>a</sup>	No serious inconsistency		Serious <sup>b</sup>	None	83/329 (25.2%)	23.3%	RR 1.14 (0.9 to 1.45)	33 more per 1000 (from 23 fewer to 105 more)	LOW	
Mortalit	y (all cause) -	Patients (	undergoing cher	notherapy								
2	Randomised trials	Serious <sup>a</sup>	Serious <sup>c</sup>	No serious indirectness	No serious imprecision	None	43/172 (25%)	39.1%	RR 1.17 (0.85 to 1.6)	66 more per 1000 (from 59 fewer to 235 more)	LOW	
Mortalit	y (all cause) -	Patients (	undergoing sten	n-cell transpla	nt							
2	Randomised trials		No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	None	40/157 (25.5%)	22.6%	RR 1.12 (0.78 to 1.6)	27 more per 1000 (from 50 fewer to 136 more)	LOW	
Number	of patients w	ith bleedi	ing events (WHO	O grade 2 or h	igher)							
2	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	Serious <sup>d</sup>	No serious imprecision	None	88/157 (56.1%)	97.5%	RR 0.97 (0.91 to 1.04)	29 fewer per 1000 (from 88 fewer to 39 more)	LOW	
Numbei	of patients w	ith major	bleeding event	s (WHO grade	3 or 4)							
4	Randomised trials	Serious <sup>a</sup>	Serious <sup>e</sup>	Serious <sup>f</sup>	Serious <sup>b</sup>	None	60/329 (18.2%)	17.2%	RR 1.17 (0.84 to 1.64)	29 more per 1000 (from 28 fewer to 110 more)	VERY LOW	
Number	of patients w	ith major	bleeding event	s - Patients un	dergoing che	mothera	ару					
2	Randomised trials	Serious <sup>a</sup>	Serious <sup>g</sup>	Serious <sup>h</sup>	Serious <sup>b</sup>	None	46/172 (26.7%)	18.5%	RR 1.41 (0.95 to 2.1)	76 more per 1000 (from 9 fewer to 203 more)	VERY LOW	
Number	of patients w	ith major	bleeding event	s - Patients un	dergoing ster	n-cell tr	ansplant					
2	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	Serious <sup>d</sup>	Very serious <sup>i</sup>	None	14/157 (8.9%)	11.7%	RR 0.76 (0.4 to 1.45)	28 fewer per 1000 (from 70 fewer to 53 more)	VERY LOW	
Infectio	ns (Bacteraem	iia)										
1	Randomised trials	Serious <sup>j</sup>	No serious inconsistency		Serious <sup>b</sup>	None	31/79 (39.2%)	34.5%	RR 1.14 (0.76 to 1.7)	48 more per 1000 (from 83 fewer to 242 more)	LOW	
Adverse	events											

Quality	<i>r</i> assessment						No of patie	nts	Effect			
No of studie		Risk of bias	Inconsistenc y	Indirectnes s	· ·	Other	Low platelet thresholds	High platelet thresholds - Adults who are haematology patients	Relative (95% CI)	Absolute	Quality	Importance
1	Randomised trials	Serious <sup>j</sup>	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	None	0/37 (0%)	19.5%	RR 0.07 (0 to 1.09)	181 fewer per 1000 (from 195 fewer to 18 more)	LOW	
Number	of units (plate	elets) trar	nsfused per pati	ent (Better in	dicated by lov	ver valu	es)		·		,	
3	Randomised trials	Serious <sup>a</sup>	No serious inconsistency			None	250	242	-	MD 1.96 lower (3.03 to 0.89 lower)	MODERATE	
Number	of units (plate	elets) trar	nsfused per pati	ent - Patients	undergoing c	hemoth	erapy (Better	indicated by lower value	s)			
2	Randomised trials	Serious <sup>a</sup>	No serious inconsistency			None	172	161	-	MD 2.09 lower (3.2 to 0.99 lower)	MODERATE	
Number	of units (plate	elets) trar	nsfused per pati	ent - Patients	undergoing st	tem-cell	transplant (B	etter indicated by lower	values)			
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency			None	78	81	-	MD 0.2 higher (4.27 lower to 4.67 higher)	MODERATE	

- (a) Most information is from studies at high risk of bias.
- (b) Confidence interval crosses one default MID and line of no effect.
- (c)  $I^2 = 66\%$ .
- (d) Zumberg 2002 assigned bleeding scores based on modified GIMEMA criteria.
- (e) 12=54%
- (f) Heckman 1997 did not use WHO bleeding criteria, but used a standardised toxicity scale (no details reported). Zumberg 2002 assigned bleeding scores based on modified GIMEMA criteria.
- (q)  $I^2 = 75\%$ .
- (h) Heckman 1997 used a standardised toxicity scale to assess severity of bleeding.
- (i) Confidence interval crosses both default MIDs and line of no effect.
- (j) Study at high risk of bias.

### J.4.2 Platelet doses

### J.4.2.1 Low platelet dose versus medium platelet dose

Quality	, assessment						No. of pat	ients	Effect			
No. of studie		Risk of bias	Inconsistenc Y	Indirectnes s	Imprecisio n	Other		Mediu	Relative (95% CI)	Absolute	Quality	Importance
Number	of patients w	ith bleed	ing (WHO grade	2 and above)								
3	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	332/531 (62.5%)	49.2%	RR 1.04 (0.95 to 1.13)	20 more per 1000 (from 25 fewer to 64 more)	MODERATE	
Mortali	ty at 30 days		·	'			,	'	,	·		
3	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	10/531 (1.9%)	1%	RR 2.04 (0.7 to 5.93)	10 more per 1000 (from 3 fewer to 49 more)	VERY LOW	
Infectio	ns		'	'	'		'	'	'	,		
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	5/417 (1.2%)	1.2%		0 more per 1000 (from 8 fewer to 30 more)	VERY LOW	
Serious	adverse event	t	·	'			,	'	,	·		
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	None	35/417 (8.4%)	6.4%		20 more per 1000 (from 12 fewer to 72 more)	LOW	

<sup>(</sup>a) Majority of the evidence was from one study where a significant percentage of patients in each group did not receive transfusions within the assigned dose range.

# J.4.2.2 High platelet dose versus medium platelet dose

Quality a	Quality assessment							ationts	Effect			
No. of							No. of pa		Relative			
studies	Design	bias	у			Other		dose	(95% CI)	Absolute	Quality	Importance

<sup>(</sup>b) Confidence interval crosses both MIDs.

<sup>(</sup>c) Confidence interval crosses one MID.

Quality as	ssessment						No. of p	atients	Effect			
No. of studies	Design	Risk of bias	Inconsistenc y			Other	High dose	Medium dose	Relative (95% CI)	Absolute	Quality	Importance
Number of	patients with	bleeding (	WHO grade 2 a	nd above)								
2	Randomised trials	Serious <sup>a</sup>	No serious inconsistency		No serious imprecision	None	305/480 (63.5%)	36.6%	RR 1.02 (0.93 to 1.11)	7 more per 1000 (from 26 fewer to 40 more)	MODERATE	
Mortality a	at 30 days											
2	Randomised trials	Serious <sup>a</sup>		No serious indirectness	Very serious <sup>b</sup>	None	7/432 (1.6%)	1%	•	7 more per 1000 (from 5 fewer to 48 more)	VERY LOW	
Infections												
1	Randomised trials	Serious <sup>a</sup>		No serious indirectness	Very serious <sup>b</sup>	None	7/432 (1.6%)	1.2%	RR 1.37 (0.44 to 4.29)	4 more per 1000 (from 7 fewer to 39 more)	VERY LOW	
Serious ad	verse event											
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency		Serious <sup>c</sup>	None	36/432 (8.3%)	6.4%	RR 1.31 (0.81 to 2.11)	20 more per 1000 (from 12 fewer to 71 more)	LOW	

<sup>(</sup>a) Majority of the evidence was from one study where a significant percentage of patients in each group did not receive transfusions within the assigned dose range.

### J.4.2.3 Low platelet dose versus high platelet dose

Quality a	Quality assessment								Effect			
No. of studies	Design	Risk of bias	Inconsistenc Y	Indirectness	Imprecisio	Other conside rations	Low dose		Relative (95% CI)	Absolute	Quality	Importance
Number o	of patients with	bleeding (	WHO grade 2 a	nd above)								'
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	None	71/417 (17%)	16.2%	RR 1.05 (0.78 to	8 more per 1000 (from 36 fewer to 68 more)	LOW	

<sup>(</sup>b) Confidence interval crosses both MIDs.

<sup>(</sup>c) Confidence interval crosses one MID.

Ouality a	assessment						No. of pat	ients	Effect			
No. of studies	Design	Risk of bias	Inconsistenc Y	Indirectness	Imprecisio	Other conside			Relative	Absolute	Quality	Importance
									1.42)			
Mortality	at 30 days											
1	Randomised trials	Serious <sup>a</sup>		No serious indirectness	Very serious <sup>c</sup>	None	9/417 (2.2%)	1.6%	RR 1.33 (0.5 to 3.54)	5 more per 1000 (from 8 fewer to 41 more)	VERY LOW	
Infections	3											
1	Randomised trials	Serious <sup>a</sup>		No serious indirectness	Very serious <sup>c</sup>	None	5/417 (1.2%)	1.6%	RR 0.74 (0.24 to 2.31)	4 fewer per 1000 (from 12 fewer to 21 more)	VERY LOW	
Serious ac	dverse event											
1	Randomised trials			No serious indirectness	Very serious <sup>c</sup>	None	35/417 (8.4%)	8.3%	RR 1.01 (0.65 to 1.57)	1 more per 1000 (from 29 fewer to 47 more)	VERY LOW	

<sup>(</sup>a) Majority of the evidence was from one study where a significant percentage of patients in each group did not receive transfusions within the assigned dose range.

# J.5 PCC

#### J.5.1 PCC thresholds

None

# J.5.2 PCC targets

None

<sup>(</sup>b) Confidence interval crosses one MID.

<sup>(</sup>c) Confidence interval crosses both MIDs.

### J.5.3 PCC doses

2 J.5.3.1 Low dose PCC (25 IU/kg) versus high dose PCC (40 IU/kg)

Quality	assessment	t					No. of pat	ients	Effect			
No. of studie s	Design	Risk of bias	Inconsistenc y	Indirectness	Imprecisio n	Other	Low dose (25 IU /kg)	High dose (40 IU /kg) [RCT]	Relative (95% CI)	Absolute	Quality	Importance
Mortali	ty											
1	Randomised trials	Serious <sup>a</sup>		No serious indirectness	Very serious <sup>b</sup>	None	4/29 (13.8%)	20%	RR 0.69 (0.22 to 2.19)	62 fewer per 1000 (from 156 fewer to 238 more)	VERY LOW	
Patients	with at least	one adve	rse event									
1	Randomised trials	Serious <sup>a</sup>		No serious indirectness	Very serious <sup>b</sup>	None	24/29 (82.8%)	83.3%	RR 0.99 (0.79 to 1.25)	8 fewer per 1000 (from 175 fewer to 208 more)	VERY LOW	
Patients	with at least	one serio	us adverse even	nt								
1	Randomised trials	Serious <sup>a</sup>		No serious indirectness	Very serious <sup>b</sup>	None	11/29 (37.9%)	40%	RR 0.95 (0.5 to 1.8)	20 fewer per 1000 (from 200 fewer to 320 more)	VERY LOW	
Patients	with at least	one thron	mbotic event									
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	2/29 (6.9%)	6.9%	RR 1 (0.15 to 6.63)	0 fewer per 1000 (from 59 fewer to 388 more)	VERY LOW	
Target I	NR (<1.2) achi	ieved										
1	Randomised trials			No serious indirectness	Serious <sup>c</sup>	None	13/29 (44.8%)	76.7%	RR 0.58 (0.37 to 0.92)	322 fewer per 1000 (from 61 fewer to 483 fewer)	LOW	

<sup>(</sup>a) Allocation concealment not reported. Open label study.

<sup>(</sup>b) Confidence interval crosses both default MIDs and line of no effect.

<sup>(</sup>c) Confidence interval crosses one default MID.

# J.5.3.2 Low fixed dose PCC (1040 IU FIX) versus PCC variable dosing regimen (modified GRADE profile)

Quality	assessment						No. of patie	ents	Effect			
No. of studie	Design	Risk of bias	Inconsistenc Y	Indirectnes s	Imprecisio n		Fixed dose (1040 IU)	Variable dose (cohort study)	Relative (95% CI)	Absolute	Quality	Importance
Target I	NR reached (<1.5)											
1	Observational studies	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	88/101 (87.1%)	89.2%	RR 0.98 (0.89 to 1.07)	18 fewer per 1000 (from 98 fewer to 62 more)	VERY LOW	
Deep ve	in thrombosis		•									
1	Observational studies	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	0/101 (0%)	0.7%	RR 0.46 (0.02 to 11.12)	4 fewer per 1000 (from 7 fewer to 71 more)	VERY LOW	
Mortali	ty (all cause)											
1	Observational studies	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	None	14/101 (13.9%)	25.9%	RR 0.54 (0.31 to 0.94)	119 fewer per 1000 (from 16 fewer to 179 fewer)	VERY LOW	

<sup>(</sup>a) Observational study and is therefore more prone to selection bias.

### J.5.3.3 Standard dose PCC (500 IU FIX/7 IU FIX/kg) versus PCC individualised dosing regimen

Quality	assessmen	t					No. of patients		Effect			
No. of studie		Risk of	Inconsistenc	Indirectnes	•		Standard dose (500 IU FIX/7		Relative			
	Design	bias	<b>y</b>		n	Other	IU/kg)	regimen [RCT]	(95% CI)	Absolute	Quality	Importanc
rarget i	NK at 15 minu	ites after	the first dosage	OF PCC								
1	Randomised trials	Serious <sup>a</sup>		No serious indirectness	No serious imprecision	None	20/47 (42.6%)	89.1%	RR 0.48 (0.34 to 0.68)	463 fewer per 1000 (from 285 fewer to 588 fewer)	MODERATE	

<sup>(</sup>b) Confidence interval crosses both default MIDs and line of no effect.

<sup>(</sup>c) Confidence interval crosses one default MID.

Quality	<i>ı</i> assessment						No. of patients		Effect			
No. of studie		Risk of	Inconsistenc	Indirectnes	-		Standard dose (500 IU FIX/7		Relative			
S	Design	bias	У	S	n	Other	IU/kg)	regimen [RCT]	(95% CI)	Absolute	Quality	Importance
serious	adverse event	:S										

<sup>(</sup>a) Allocation concealment not reported. Open label study.

# J.6 Monitoring for acute reactions

None

# J.7 Electronic decision support

None

# J.8 Electronic patient identification

None

# J.9 Patient information

None

<sup>(</sup>b) Confidence interval crosses both default MIDs and line of no effect.

# **Appendix K: Forest plots**

# K.1 Erythropoietin and iron

#### K.1.1 Erythropoietin versus placebo

Figure 1: All-cause mortality at 30 days

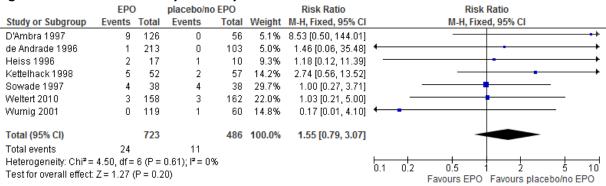


Figure 2: Number of patients transfused

•		•						
	EPO	)	placebo/no	EPO		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Anon 1993	64	130	52	78	16.3%	0.74 [0.58, 0.93]		
D'Ambra 1997	36	119	25	52	8.7%	0.63 [0.42, 0.93]		
Faris 1996	25	118	36	67	11.5%	0.39 [0.26, 0.60]		<del></del>
Feagan 2000	23	123	35	78	10.8%	0.42 [0.27, 0.65]		<del></del>
Heiss 1996	9	17	4	10	1.3%	1.32 [0.55, 3.20]		<del></del>
Kettelhack 1998	16	48	15	54	3.5%	1.20 [0.67, 2.16]		<del></del>
Kosmadakis 2003	10	31	28	32	6.9%	0.37 [0.22, 0.62]		
Qvist 1999	13	38	23	43	5.4%	0.64 [0.38, 1.08]		
Scott 2002	19	29	24	29	6.0%	0.79 [0.58, 1.08]		-
Sowade 1997	4	36	19	36	4.8%	0.21 [0.08, 0.56]	•	
Weltert 2010	35	158	59	162	14.6%	0.61 [0.43, 0.87]		
Wurnig 2001	41	124	28	51	10.0%	0.60 [0.42, 0.86]		
Total (95% CI)		971		692	100.0%	0.59 [0.53, 0.67]		<b>•</b>
Total events	295		348					
Heterogeneity: Chi²=	29.24, df	= 11 (F	$P = 0.002); I^2$	= 62%			-	02 05 1 2 5 10
Test for overall effect:	Z= 8.56 (	(P < 0.0	00001)				0.1	0.2 0.5 1 2 5 10 Favours EPO Favours placebo/no EPO
								FAVOUIS EFU FAVOUIS DIACEDU/IIU EFU

Figure 1: Number of patients transfused – sub-grouped by presence/absence of anaemia at baseline

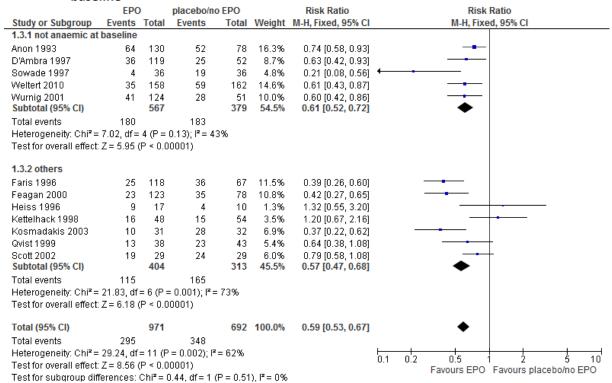


Figure 4: Number of units transfused per patient

		EPO		place	bo/no E	PO		Mean Difference		Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI	
D'Ambra 1997	1.546	3.247	119	1.33	2.01	52	6.0%	0.22 [-0.58, 1.02]		+	
de Andrade 1996 (1)	0.436	1.093	57	1.14	1.432	29	10.9%	-0.70 [-1.30, -0.11]			
Faris 1996	0.484	1.072	118	1.42	1.67	67	19.5%	-0.94 [-1.38, -0.49]		*	
Feagan 2000	0.364	0.835	123	1	1.2	78	41.5%	-0.64 [-0.94, -0.33]		•	
Heiss 1996	1.82	0.8	17	1.8	0.97	10	7.6%	0.02 [-0.69, 0.73]		+	
Qvist 1999	0.3	1	38	1.6	1.5	43	12.7%	-1.30 [-1.85, -0.75]		-	
Scott 2002	3.16	2.87	29	4.12	2.86	29	1.8%	-0.96 [-2.43, 0.51]			
Total (95% CI)			501			308	100.0%	-0.69 [-0.89, -0.49]		•	
Heterogeneity: Chi² = 1	14.92, df	= 6 (P =	0.02);	$I^2 = 60\%$	6				10	<u> </u>	<del></del>
Test for overall effect: 2	Z = 6.91 (	(P < 0.0	0001)						-10	Favours EPO Favours placebo	10 /no E

<sup>(1)</sup> deAndrade 1996 data analysed for patients with Hb >10 <13 g/dL

Figure 2: Number of units transfused per patient – sub-grouped by presence/absence of anaemia at baseline

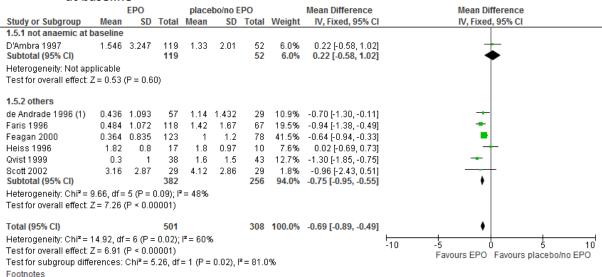


Figure 3: Serious adverse events

(1) deAndrade 1996 data analysed for patients with Hb >10 <13 g/dL

	EPO	)	placebo/no	EPO		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
D'Ambra 1997	13	126	2	56	9.0%	2.89 [0.67, 12.38]	-
de Andrade 1996	13	213	8	103	34.9%	0.79 [0.34, 1.84]	
Faris 1996	5	125	6	67	25.3%	0.45 [0.14, 1.41]	<del></del>
Karkouti 2006	0	10	0	10		Not estimable	
Scott 2002	2	29	0	29	1.6%	5.00 [0.25, 99.82]	<del></del>
Sowade 1997	6	38	9	38	29.2%	0.67 [0.26, 1.69]	
Total (95% CI)		541		303	100.0%	0.92 [0.57, 1.50]	•
Total events	39		25				
Heterogeneity: Chi²=	5.72, df=	4 (P=	$0.22$ ); $I^2 = 30$	1%			0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z = 0.33 (	P = 0.7	'4)				Favours EPO Favours placebo/no E

Figure 4: Thrombosis

	EPC	)	placebo/no	EPO		Risk Ratio		Risk Ra	atio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed,	95% CI	
Anon 1993	16	130	5	78	37.4%	1.92 [0.73, 5.04]		+	-	
Feagan 2000	7	123	6	78	43.9%	0.74 [0.26, 2.12]		-	_	
Kosmadakis 2003	2	31	1	32	5.9%	2.06 [0.20, 21.63]			•	
Weltert 2010	0	158	1	162	8.9%	0.34 [0.01, 8.33]		•		
Wurnig 2001	4	124	0	60	4.0%	4.39 [0.24, 80.27]			•	
Total (95% CI)		566		410	100.0%	1.37 [0.73, 2.56]		4	<b>&gt;</b>	
Total events	29		13							
Heterogeneity: Chi <sup>2</sup> =	3.25, df=	4 (P =	$0.52$ ); $I^2 = 0\%$	)			0.04		40	400
Test for overall effect	Z= 0.99	(P = 0.3)	32)				0.01	0.1 1 Favours EPO F	10 avours placebo/n	100 o EPO

Figure 5: Length of hospital stay

	E	PO		placel	oo/no E	PO		Mean Difference		Mean I	Differ	ence		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fix	ed, 95	% CI		
Kosmadakis 2003	10	0.5	31	13	0.9	32	100.0%	-3.00 [-3.36, -2.64]						
Total (95% CI) Heterogeneity: Not ap Test for overall effect:	•		<b>31</b> < 0.000	001)		32	100.0%	-3.00 [-3.36, -2.64]	-100	-50 Favours EP	0 D Fav	50 yours place	100 cebo/no F	

Figure 6: Infection (pneumonia)

	EPC	)	placebo/no	EPO		Risk Ratio		Risl	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% CI	
Weltert 2010	0	158	0	162		Not estimable				
Total (95% CI)		158		162		Not estimable				
Total events	0		0							
Heterogeneity: Not ap Test for overall effect:	•	cable					0.01	0.1 Favours EPC	1 10 Favours palc	100 ebo

## K.1.2 IV iron versus placebo or no IV iron

Figure 7: All-cause mortality at 30 days

	IV iro	n	placebo/no	IV iron		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
Madi-Jebara 2004	0	40	0	40		Not estimable	<u>L</u>
Serrano-Trenas 2011	11	100	10	100	100.0%	1.10 [0.49, 2.47]	<del></del>
Total (95% CI)		140		140	100.0%	1.10 [0.49, 2.47]	
Total events	11		10				
Heterogeneity: Not appli	cable						0.1 0.2 0.5 1 2 5 10
Test for overall effect: Z	= 0.23 (P	= 0.82	)				Favours IV iron Favours placebo/no IV in

Figure 8: Number of patients transfused

rigule o. Inullibe	ti vi pa	ueni	s cialistus	Eu			
	IV iro	n	placebo/no l'	V iron		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Edwards 2009	2	34	5	26	6.6%	0.31 [0.06, 1.45]	<del></del>
Garrido-Martin 2012	20	54	26	52	30.7%	0.74 [0.48, 1.15]	<del></del>
Karkouti 2006	2	11	4	10	4.9%	0.45 [0.10, 1.97]	•
Madi-Jebara 2004	10	40	9	40	10.4%	1.11 [0.51, 2.44]	<del></del>
Serrano-Trenas 2011	33	100	41	100	47.5%	0.80 [0.56, 1.16]	<del></del>
Total (95% CI)		239		228	100.0%	0.77 [0.59, 0.99]	•
Total events	67		85				
Heterogeneity: Chi² = 2.	77, df = 4	(P = 0.	60); I² = 0%				0.1 0.2 0.5 1 2 5 10
Test for overall effect: Z	= 2.02 (P	= 0.04)	ı				Favours IV iron Favours placebo/no IV i

Figure 9: Length of hospital stay

	IV iron			placebo/no IV iron				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	I IV, Fixed, 95% CI
Serrano-Trenas 2011	13.5	7.1	100	12.9	6.9	100	100.0%	0.60 [-1.34, 2.54]	•
Total (95% CI)			100			100	100.0%	0.60 [-1.34, 2.54]	· · · · · · · · · · · · · · · · · · ·
Heterogeneity: Not appl Test for overall effect: Z		(P = 0	0.54)						-100 -50 0 50 100 Favours IV iron Favours placebo/no IV ir

Figure 10: Serious adverse events

	IV iro				placebo/no IV iron Risk Ratio					Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fix	ed, 95%	CI			
Karkouti 2006	0	11	0	10		Not estimable								
Total (95% CI)		11		10		Not estimable								
Total events	0		0											
Heterogeneity: Not app Test for overall effect:		able					0.1	0.2 Favo	0.5 ours IV iron	1 2 Favour	s place	5 00/1	10 no IV	

Figure 11: Infections

	IV iron	placebo/no IV i	iron		Risk Ratio	Risk Ratio
Study or Subgroup	Events Tota	I Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Serrano-Trenas 2011	16 10	) 13	100	100.0%	1.23 [0.63, 2.42]	-
Total (95% CI)	10	)	100	100.0%	1.23 [0.63, 2.42]	<b>*</b>
Total events	16	13				
Heterogeneity: Not appl Test for overall effect: Z		5)				0.01 0.1 1 10 100 Favours IV iron Favours placebo/no IV i

#### K.1.3 Oral iron versus placebo or no oral iron

Figure 12: Number of patients transfused

_	Oral ir	on	placebo/no ora	ıl iron		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	CI M-H, Fixed, 95% CI
Garrido-Martin 2012	27	53	26	52	67.3%	1.02 [0.70, 1.49]	_ <b></b>
Lidder 2007	6	24	13	25	32.7%	0.48 [0.22, 1.06]	
Total (95% CI)		77		77	100.0%	0.84 [0.60, 1.19]	•
Total events	33		39				
Heterogeneity: Chi <sup>2</sup> = 2	2.91, df = 1	1 (P = 0	0.09); I <sup>2</sup> = 66%				0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z = 0.98 (I	P = 0.3	3)				Favours Oral iron Favours placebo/no oral ir

# K.1.4 Erythropoietin plus IV iron versus placebo

Figure 13: All-cause mortality at 30 days

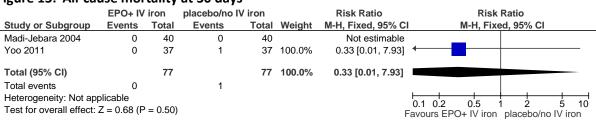


Figure 14: Number of patients transfused

	EPO+ IV	iron	place	bo		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% C	1 M-H, Fixed, 95% CI			
Karkouti 2006	2	10	2	11	2.3%	1.10 [0.19, 6.41	] -			
Madi-Jebara 2004	7	40	9	40	10.7%	0.78 [0.32, 1.88	· · ·			
Na 2011	12	54	41	54	48.9%	0.29 [0.17, 0.49	] ———			
Yoo 2011	22	37	32	37	38.1%	0.69 [0.51, 0.92	]			
Total (95% CI)		141		142	100.0%	0.51 [0.39, 0.67]	1 ◆			
Total events	43		84							
Heterogeneity: Chi <sup>2</sup> =	9.79, df=	3(P = 0)	$1.02$ ); $I^2 =$	69%			01 02 05 1 2 5 10			
Test for overall effect:	Z = 4.90 (1	P < 0.00	0001)				0.1 0.2 0.5 1 2 5 10 Favours EPO+ IV iron Favours placebo			

Figure 15: Number of units transfused per patient

•						•	•						
	EPO-	+ IV ir	on	pla	aceb	0		Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI				
Na 2011	0.2	0.5	54	0.8	0.8	54	89.5%	-0.60 [-0.85, -0.35]					
Yoo 2011	1.6	0.9	37	3.7	2.1	37	10.5%	-2.10 [-2.84, -1.36]	<del></del>				
Total (95% CI)			91			91	100.0%	-0.76 [-1.00, -0.52]	<b>•</b>				
Heterogeneity: Chi² = Test for overall effect		,			= 939	%			-10 -5 0 5 10 Favours EPO+ IV iron Favours placebo				

Figure 16: Number of units transfused per patient- sub-grouped by presence/absence of anaemia at baseline

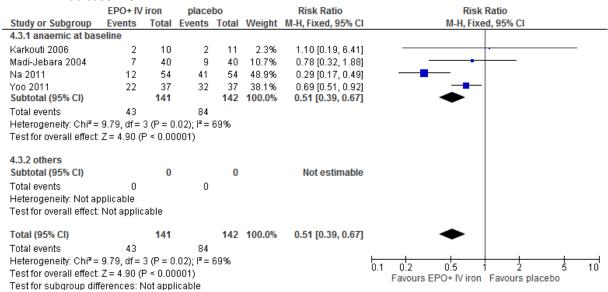


Figure 17: Length of hospital stay

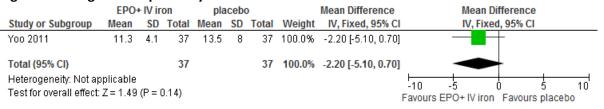


Figure 18: Serious adverse events

	EPO	)	place	bo		Risk Ratio	Risk Ratio					
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% CI			M-H, Fixe	d, 95% CI		
Karkouti 2006	0	10	0	10		Not estimable						
Total (95% CI)		10		10		Not estimable						
Total events	0		0									
Heterogeneity: Not ap Test for overall effect:	•	cable					0.1	0.2	0.5 Favours EPO	1 2 Favours	5 Placebo	10

#### K.1.5 Oral iron versus IV iron

Figure 19: Number of patients transfused

_	Oral in	on	IV iro	on		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Bisbe 2014	2	62	3	59	13.4%	0.63 [0.11, 3.66]	_	• -	
Garrido-Martin 2012	27	53	20	54	86.6%	1.38 [0.89, 2.13]		+	
Total (95% CI)		115		113	100.0%	1.28 [0.83, 1.95]		-	
Total events	29		23						
Heterogeneity: Chi² = 1 Test for overall effect: 2	•	•		0%			0.1	0.2 0.5 1 2 5 1 Favours Oral iron Favours IV iron	ō

Figure 20: Length of hospital stay

•				•									
	Or	al iro	n	IV	iron			Mean Difference		Mean D	ifferenc	е	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixe	d, 95% C	1	
Bisbe 2014	7.6	0.9	62	7.9	1.7	59	100.0%	-0.30 [-0.79, 0.19]					
Total (95% CI)			62			59	100.0%	-0.30 [-0.79, 0.19]					
Heterogeneity: Not ap Test for overall effect:			0.23)						-100	-50 Favours Oral iron	0 Favour	50 s IV iron	100

Figure 21: Deep vein thrombosis (DVT)

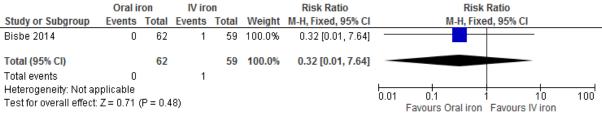
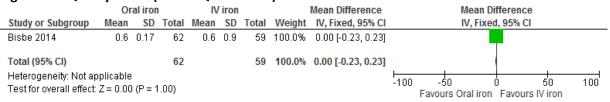


Figure 22: Quality of life (Total EQ-5D scores)



#### K.1.6 Erythropoietin plus IV iron versus IV iron

Figure 23: All-cause mortality at 30 days

	EPO+ IV	iron	IV iro	n		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Madi-Jebara 2004	0	40	0	40		Not estimable	
Total (95% CI)		40		40		Not estimable	
Total events	0		0				
Heterogeneity: Not app	olicable						0.1 0.2 0.5 1 2 5 10
Test for overall effect: I	Not applica	able				Fa	0.1 0.2 0.5 1 2 5 10 vours EPO+ IV iron Favours IV iron

Figure 24: Number of patients transfused

	EPO+ IV	iron	IV iro	n		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Karkouti 2006	2	10	2	11	19.2%	1.10 [0.19, 6.41]	
Madi-Jebara 2004	7	40	10	40	80.8%	0.70 [0.30, 1.66]	<del></del>
Total (95% CI)		50		51	100.0%	0.76 [0.35, 1.65]	
Total events	9		12				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 0.20, 0	df = 1 (P =	= 0.65);	$I^2 = 0\%$		0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z = 0.68 (P	r = 0.49	)				vours EPO+ IV iron Favours IV iron

Figure 25: Serious adverse events

	EPO+ IV	iron	IV iro	on		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	I M-H, Fixed, 95% CI
Karkouti 2006	0	10	0	10		Not estimable	9
Kateros 2010	0	38	0	41		Not estimable	e
Total (95% CI)		48		51		Not estimable	9
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not applic	able					0.1 0.2 0.5 1 2 5 10
1001101 0101411 011001	or alalam						Favours FPO+IV iron Favours IV iron

#### K.1.7 Erythropoietin plus oral iron versus oral iron

Figure 26: All-cause mortality at 30 days

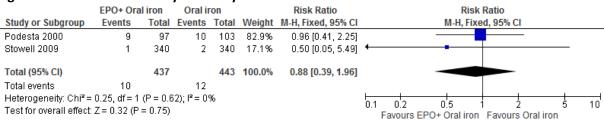


Figure 27: Number of patients transfused

	EPO+ Oral iron Oral iron					Risk Ratio		Risk Ratio				
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI			
Dousias 2003	0	23	5	27	15.6%	0.11 [0.01, 1.82]	+					
Larson 2001	0	15	1	16	4.5%	0.35 [0.02, 8.08]	<del></del>	•			_	
Podesta 2000	1	30	26	30	79.9%	0.04 [0.01, 0.27]	←—					
Total (95% CI)		68		73	100.0%	0.06 [0.02, 0.25]						
Total events	1		32									
Heterogeneity: Chi²=	1.55, df = 2	(P = 0.4)	$(6); I^2 = 0$	%			N1 N2	0.5	<del>  </del>	<del></del> _	10	
Test for overall effect:	Z=3.94 (P	< 0.000	1)			F	avours EPO		Favours O	ral iron		

Figure 28: Length of hospital stay

	EPO+	Oral i	ron	Or	al iro	n		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% (	IV, Fixed, 95% CI
Dousias 2003	7.6	0.5	23	7.8	0.9	27	98.9%	-0.20 [-0.60, 0.20	0]
Larson 2001	6.4	2.4	15	8.1	7.1	16	1.1%	-1.70 [-5.38, 1.98	7
Total (95% CI)			38			43	100.0%	-0.22 [-0.61, 0.18	1
Heterogeneity: Chi² = Test for overall effect		•		; I² = 0%	)				-100 -50 0 50 100 Favours EPO+ Oral iron Favours Oral iron

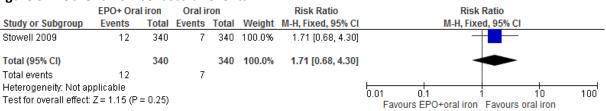
Figure 29: Infections

	EPO+ Ora	l iron	Oral iron			Risk Ratio	Risk		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	d, 95% CI	
Larson 2001	1	16	2	16	100.0%	0.50 [0.05, 4.98]	<b>—</b>		-
Total (95% CI)		16		16	100.0%	0.50 [0.05, 4.98]			
Total events	1		2						
Heterogeneity: Not applicable Test for overall effect: Z = 0.59 (P = 0.55)							0.1 0.2 0.5 1 Favours EPO+oral iron	2 Favours oral iron	5 10

Figure 30: Deep vein thrombosis (DVT)

	EPO+ Ora	al iron	Oral i	ron		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fix	ed, 95% CI	
Stowell 2009	16	340	7	340	100.0%	2.29 [0.95, 5.49]			
Total (95% CI)		340		340	100.0%	2.29 [0.95, 5.49]		<b>◆</b>	
Total events	16		7						
Heterogeneity: Not a Test for overall effect		= 0.06)					0.01 0.1 Favours EPO+Oral iron	1 10 Favours Oral iron	100

Figure 31: Other thrombovascular events



#### K.1.8 Erythropoietin plus oral iron or IV iron versus oral iron or IV iron

Figure 32: Mortality (all-cause)

	EPO+oral or IV iron			/ iron		Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI		
Olijhoek 2001	0	58	0	52		Not estimable					
Total (95% CI)		58		52		Not estimable					
Total events	0		0								
Heterogeneity: Not ap Test for overall effect:	•						0.01	0.1 Favours EPO+oral or IV	1 10 Favours oral or IV iron	100	

Figure 33: Serious adverse events

	EPO+oral or IV iron			/ iron		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI			
Olijhoek 2001	0	58	1	52	100.0%	0.30 [0.01, 7.19]				
Total (95% CI)		58		52	100.0%	0.30 [0.01, 7.19]				
Total events	0		1							
Heterogeneity: Not ap Test for overall effect		16)					0.01 0.1 10 10 Favours EPO+oral or IV Favours Oral or IV iron	ΠÖ		

Figure 34: Thrombosis

	EPO+oral or I'	V iron	Oral or IV iron			Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fix	red, 95% CI		
Olijhoek 2001	0	58	0	52		Not estimable				
Total (95% CI)		58		52		Not estimable				
Total events	0		0							
Heterogeneity: Not ap Test for overall effect:							0.01 0.1 Favours EPO+oral or IV iron	1 10 Favours oral or IV iron	100	

# K.2 Alternatives to blood transfusion in surgical patientscombinations of cell salvage and tranexamic acid

#### K.2.1 Adults - high risk

Figure 35: ICS versus standard treatment- Number exposed to allogeneic blood

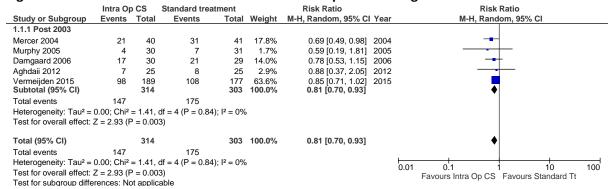


Figure 36: ICS versus standard treatment- Units of allogeneic blood transfused

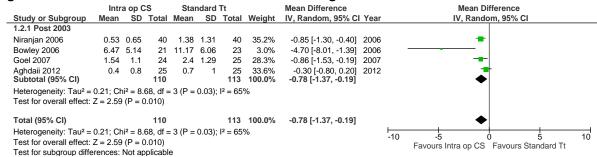


Figure 37: ICS versus standard treatment- Mortality at up to 30 days

•								, ,		•
	Intr	a op C	s	Sta	ndard	Tt		Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.2.1 Post 2003										
Niranjan 2006	0.53	0.65	40	1.38	1.31	40	35.2%	-0.85 [-1.30, -0.40]	2006	<b>-</b>
Bowley 2006	6.47	5.14	21	11.17	6.06	23	3.0%	-4.70 [-8.01, -1.39]	2006	<del></del>
Goel 2007	1.54	1.1	24	2.4	1.29	25	28.3%	-0.86 [-1.53, -0.19]	2007	<del></del>
Aghdaii 2012 Subtotal (95% CI)	0.4	8.0	25 110	0.7	1	25 113	33.6% 100.0%	-0.30 [-0.80, 0.20] -0.78 [-1.37, -0.19]	2012	<u>.</u>
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:				= 3 (P =	0.03);	l <sup>2</sup> = 65	%			
Total (95% CI)			110			113	100.0%	-0.78 [-1.37, -0.19]		•
Heterogeneity: Tau <sup>2</sup> =	= 0.21; CI	ni² = 8.	68, df =	3 (P =	0.03);	$I^2 = 65^\circ$	%		10	-5 0 5 10
Test for overall effect:	: Z = 2.59	(P = 0	0.010)						-10	Favours Intra op CS Favours Standard Tt
Test for subgroup diffe	erences:	Not an	plicable	е						r avours mina op oo ir avours standard it

Figure 38: ICS versus standard treatment- Infection

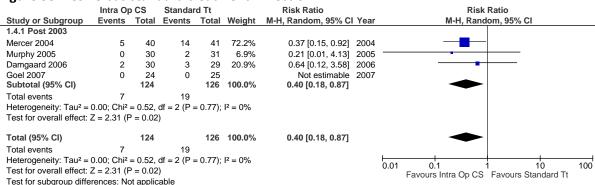


Figure 39: ICS versus standard treatment- Length of stay in hospital

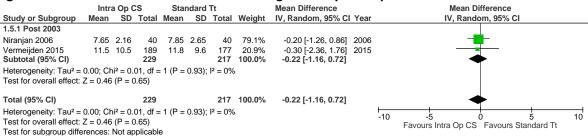


Figure 40: PCS versus standard treatment- Number exposed to allogeneic blood

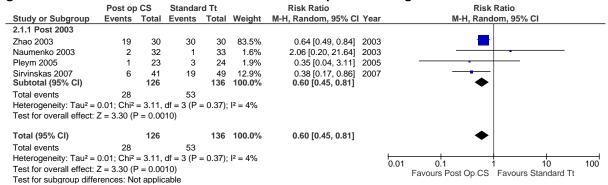


Figure 41: PCS versus standard treatment- Units of allogeneic blood transfused

	Pos	st op (	cs	Star	ndard	Tt		Mean Difference		Mean D	ifference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI Yea		IV, Rando	om, 95% CI	
2.2.1 Post 2003												
Zhao 2003	1.2	0.27	30	2.22	0.4	30	100.0%	-1.02 [-1.19, -0.85] 2003	;			
Subtotal (95% CI)			30			30	100.0%	-1.02 [-1.19, -0.85]		▼		
Heterogeneity: Not ap	plicable											
Test for overall effect:	Z = 11.5	8 (P <	0.0000	)1)								
Total (95% CI)			30			30	100.0%	-1.02 [-1.19, -0.85]		•		
Heterogeneity: Not ap	plicable								-10	-	<u> </u>	10
Test for overall effect:	Z = 11.5	8 (P <	0.0000	)1)					-10	Favours Post op CS	Favours Standard	
Test for subgroup diffe	erences:	Not an	policable	e						1 avours 1 ost op Co	i avouis stanuaru	11

Figure 42: PCS versus standard treatment- Mortality at up to 30 days

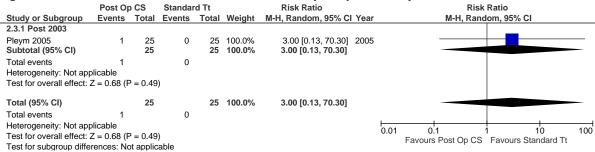
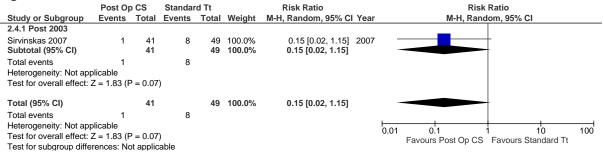


Figure 43: PCS versus standard treatment- Infection



#### Figure 44: PCS versus standard treatment- Length of stay in hospital

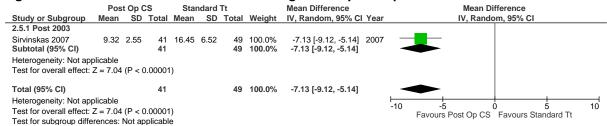


Figure 45: ICS plus PCS versus standard treatment- Number exposed to allogeneic blood

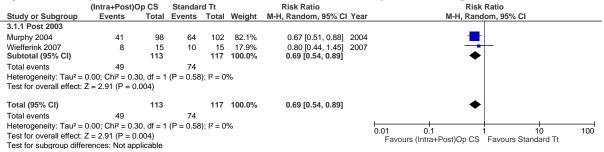


Figure 46: ICS plus PCS versus standard treatment- Mortality at up to 30 days

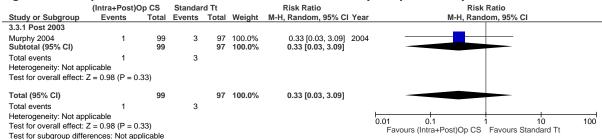


Figure 47: ICS plus PCS versus standard treatment- Infection

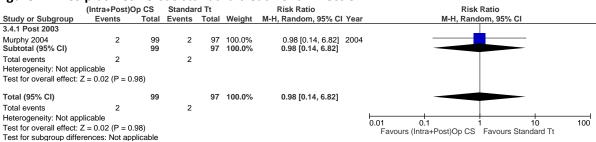


Figure 48: ICS plus PCS versus standard treatment- Length of stay in hospital

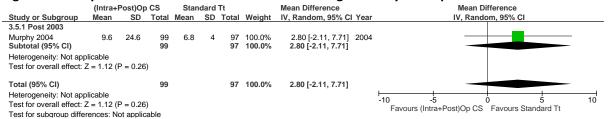


Figure 49: ICS plus TXA versus ICS- Number exposed to allogeneic blood

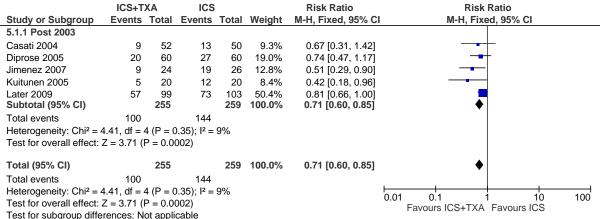


Figure 50: ICS plus TXA versus ICS - Units of allogeneic blood transfused

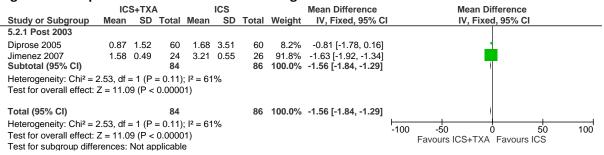


Figure 51: ICS plus TXA versus ICS- Mortality at up to 30 days

	ICS+T	XΑ	ICS		•	Risk Ratio	Risk Ratio
Study or Subgroup	Events				Weight	M-H, Fixed, 95% C	
5.3.1 Post 2003							
Diprose 2005	0	0	1	60		Not estimable	
Jimenez 2007	0	24	0	26		Not estimable	
Kuitunen 2005	0	20	0	20		Not estimable	<u>L</u>
Later 2009	1	99	1	103	100.0%	1.04 [0.07, 16.41]	
Subtotal (95% CI)		143		209	100.0%	1.04 [0.07, 16.41]	
Total events	1		2				
Heterogeneity: Not app	licable						
Test for overall effect: 2	Z = 0.03 (F	P = 0.98	3)				
Total (95% CI)		143		209	100.0%	1.04 [0.07, 16.41]	
Total events	1		2				
Heterogeneity: Not app	licable						0.01 0.1 1 10 100
Test for overall effect: Z = 0.03 (P = 0.98)		3)				Favours ICS +TXA Favours ICS	
Test for subgroup differ	rences: No	ot appli	cable				1 400413 100 11701 1 400413 100

Figure 52: ICS plus TXA versus ICS- Length of stay in hospital

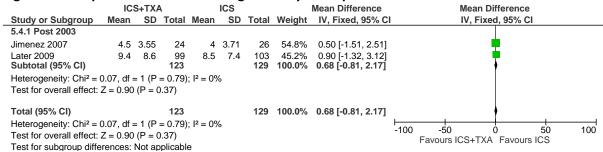


Figure 53: ICS plus TXA versus TXA- Number exposed to allogeneic blood

	Intra op CS	+TXA	TXA		_	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI	
6.1.1 Post 2003							
Reyes 2011 Subtotal (95% CI)	12	34 <b>34</b>	13	29 <b>29</b>	100.0% 100.0%	0.79 [0.43, 1.45] <b>0.79 [0.43</b> , <b>1.45</b> ]	
Total events Heterogeneity: Not app	12 licable		13				
Test for overall effect: Z	Z = 0.77 (P = 0)	0.44)					
Total (95% CI)		34		29	100.0%	0.79 [0.43, 1.45]	•
Total events	12		13				
Heterogeneity: Not app Test for overall effect: Z Test for subgroup differ	Z = 0.77 (P = 0)	,					0.01 0.1 1 10 100 Favours Intra op CS +TXA Favours TXA

Figure 54: ICS plus TXA versus TXA- Mortality at up to 30 days

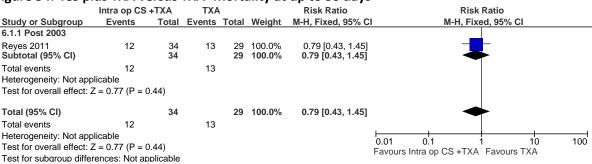


Figure 55: ICS plus TXA versus TXA- Infections

	Intra op CS	+TXA	TXA			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
6.3.1 Post 2003							<u>L</u>
Reyes 2011 Subtotal (95% CI)	5	34 <b>34</b>	4	29 <b>29</b>	100.0% <b>100.0</b> %	1.07 [0.32, 3.60] 1.07 [0.32, 3.60]	<del></del>
Total events	5		4				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.10 (P = 0)	0.92)					
Total (95% CI)		34		29	100.0%	1.07 [0.32, 3.60]	
Total events	5		4				
Heterogeneity: Not app	plicable						0.01 0.1 1 10 100
Test for overall effect:	Z = 0.10 (P = 0)	0.92)					Favours Intra Op CS+TXA Favours TXA
Test for subaroup diffe	rancas. Not ar	nlicable					Tavodio initia op oo i i/ot i avodio i/ot

Figure 56: ICS+TXA versus TXA- Length of stay in hospital

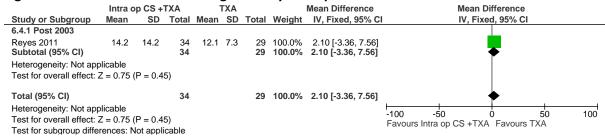


Figure 57: PCS plus TXA versus TXA- No. exposed to allogeneic blood

•	Post OP CS	+TXA	TXA		•	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI	
8.1.1 Post 2003							
Westerberg 2004 Subtotal (95% CI)	0	17 17	0	17 17		Not estimable Not estimable	
Total events Heterogeneity: Not app Test for overall effect:		<b>)</b>	0				
Total (95% CI)		17		17		Not estimable	
Total events Heterogeneity: Not app Test for overall effect: Test for subgroup diffe	Not applicable		0				0.01 0.1 1 10 100 Favours Poat Op CS+TXA Favours TXA

Figure 58: ICS plus PCS plus TXA versus ICS plus PCS- Number exposed to allogeneic blood

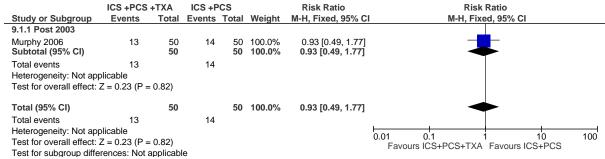


Figure 59: ICS plus PCS plus TXA versus ICS plus PCS- Units of allogeneic blood transfused

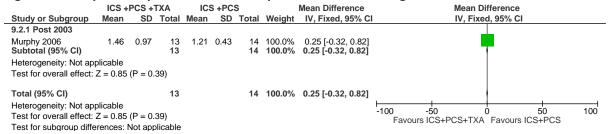


Figure 60: ICS plus PCS plus TXA versus ICS plus PCS- Mortality at up to 30 days

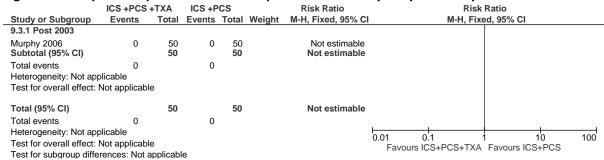
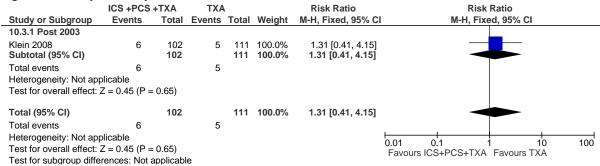


Figure 61: ICS plus PCS plus TXA versus TXA- Number exposed to allogeneic blood

	ICS +PCS +TXA TXA					Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
10.1.1 Post 2003							
Klein 2008 Subtotal (95% CI)	31	102 <b>102</b>	33	111 111	100.0% <b>100.0</b> %	1.02 [0.68, 1.54] 1.02 [0.68, 1.54]	<b>#</b>
Total events	31		33				
Heterogeneity: Not app	olicable						
Test for overall effect:	Z = 0.11 (P =	0.92)					
Total (95% CI)		102		111	100.0%	1.02 [0.68, 1.54]	<b>*</b>
Total events	31		33				
Heterogeneity: Not app	olicable						0.01 0.1 1 10 100
Test for overall effect: 2	Z = 0.11 (P =	0.92)					0.01
Test for subgroup diffe	rences: Not a	applicabl	е				1 avodis 10011 0011/At 1 avodis 1/A

Figure 62: ICS plus PCS plus TXA versus TXA- Infection



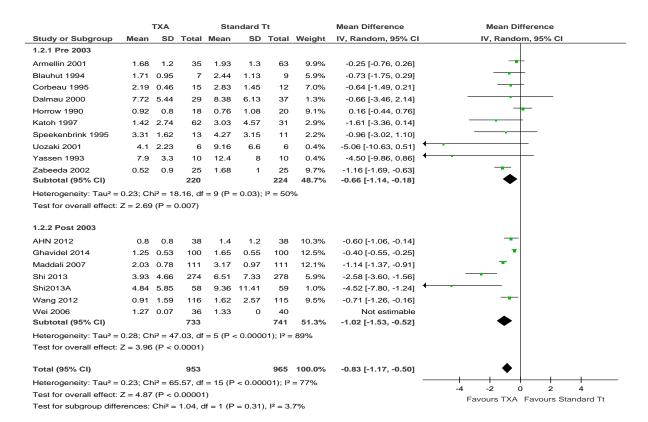
Standard Tt Risk Ratio Risk Ratio TXAM-H, Random, 95% CI Study or Subgroup **Events Total Events** Total Weight M-H, Random, 95% CI 1.1.1 Pre 2003 Armellin 2001 140 0.54 [0.39, 0.77] 3.9% Blauhut 1994 0.73 [0.37, 1.41] 15 9 14 2.1% 2 0.50 [0.10, 2.43] Casati 2001 20 4 20 0.5% Coffey 1995 9 8 2.3% 0.98 [0.53, 1.84] 16 14 Corbeau 1995 15 41 12 20 2.7% 0.61 [0.36, 1.05] Dalmau 2000 29 42 37 40 4.8% 0.75 [0.60, 0.93] Debonis 2000 3 20 4 20 0.7% 0.75 [0.19, 2.93] Fawzy 2009 14 19 13 19 3.5% 1.08 [0.72, 1.62] Hardy 1998 28 42 27 44 4.1% 1.09 [0.79, 1.49] Horrow 1991 12 37 44 2.3% 0.89 [0.49, 1.64] 16 Katoh 1997 31 1.5% 0.35 [0.15, 0.83] 62 10 Katsaros 1996 27 0.42 [0.22, 0.79] 11 104 106 2 2% Krohn 2002 2 16 9 14 0.7% 0.19 [0.05, 0.75] Menichetti 1996 12 24 18 24 3.1% 0.67 [0.42, 1.06] Pugh 1995 22 22 23 23 5.6% 1.00 [0.92, 1.09] Speekenbrink 1995 13 15 11 15 3.8% 1.18 [0.82, 1.70] Subtotal (95% CI) 638 588 43.8% 0.74 [0.58, 0.95] Total events 221 291 Heterogeneity:  $Tau^2 = 0.17$ ;  $Chi^2 = 91.69$ , df = 15 (P < 0.00001);  $I^2 = 84\%$ Test for overall effect: Z = 2.35 (P = 0.02) 1.1.2 Post 2003 AHN 2012 20 38 27 38 3.8% 0.74 [0.51, 1.07] Andreasen 2004 1.02 [0.38, 2.76] 6 20 5 17 1.2% Baric 2007 51 97 51 96 4.5% 0.99 [0.76, 1.29] Dell Amore 2012 8 44 10 43 1.6% 0.78 [0.34, 1.79] 0.51 [0.34, 0.76] 22 Esfandiari 2013 75 43 75 3.5% Ghaffari 2012 15 2.8% 50 23 50 0.65 [0.39, 1.10] Ghavidel 2014 60 100 74 100 5.0% 0.81 [0.67, 0.99] Jares 2003 2 22 7 25 0.6% 0.32 [0.08, 1.40] Karski 2005 147 0.66 [0.42, 1.03] 165 3.2% Lundin 2014 15 50 22 50 2.7% 0.68 [0.40, 1.15] Mansour 2004 2.0% 0.58 [0.29, 1.17] 7 20 12 20 5 0.63 [0.23, 1.71] Mehr-Aein 2007 8 1.2% 33 33 Nouraei 2013 15 21 40 2.9% 0.71 [0.43, 1.17] 40 Pleym 2003 40 8 39 1.3% 0.85 [0.34, 2.13] Saberi 2010 0 50 0 50 Not estimable Santos 2006 29 12 31 1.7% 0.62 [0.29, 1.36] Shi 2013 0.76 [0.68, 0.85] 166 274 221 278 5.5% Shi2013A 5.1% 0.79 [0.66, 0.94] 42 58 54 59 Taghaddomi 2009 27 8 50 50 2.0% 0.30 [0.15, 0.59] Vanek 2005 32 30 0.8% 0.47 [0.13, 1.71] 3 6 Wang 2012 37 116 54 115 4.0% 0.68 [0.49, 0.94] Wei 2006 3 36 8 40 0.8% 0.42 [0.12, 1.45] Wu 2006 106 108 0.2% 0.03 [0.00, 0.48] 17 Subtotal (95% CI) 1527 1552 56.2% 0.72 [0.65, 0.80] Total events 523 751 Heterogeneity:  $Tau^2 = 0.01$ ;  $Chi^2 = 29.00$ , df = 21 (P = 0.11);  $I^2 = 28\%$ Test for overall effect: Z = 6.05 (P < 0.00001) Total (95% CI) 2140 100.0% 0.72 [0.64, 0.81] 2165 Total events 744 1042 Heterogeneity:  $Tau^2 = 0.07$ ;  $Chi^2 = 125.33$ , df = 37 (P < 0.00001);  $I^2 = 70\%$ 0.1 0.2 0.5 Test for overall effect: Z = 5.30 (P < 0.00001)

Figure 63: TXA versus standard treatment- Number exposed to allogeneic transfusions

Test for subgroup differences:  $Chi^2 = 0.04$ , df = 1 (P = 0.85),  $I^2 = 0\%$ 

Favours TXA Favours standard tt.

Figure 64: TXA versus standard treatment- Units of allogeneic blood transfused



**TXA** Standard Tt **Risk Ratio Risk Ratio** Study or Subgroup **Events Total Events Total Weight** M-H, Fixed, 95% CI M-H, Fixed, 95% CI 1.3.1 Pre 2003 Armellin 2001 150 7.4% 0.33 [0.04, 3.17] 150 3 1 Blauhut 1994 0 15 0 14 Not estimable 9.6% Boylan 1996 0 25 20 0.12 [0.01, 2.11] 3 Coffey 1995 0 16 14 4.0% 0.29 [0.01, 6.69] Dalmau 2000 3 42 4 40 10.2% 0.71 [0.17, 2.99] De Bonis 2000 0 20 0 20 Not estimable Dryden 1997 22 4 19 10.6% 0.22 [0.03, 1.77] 1 Hardy 1998 0 0 Not estimable 43 45 0 16 1.2% 3.00 [0.13, 68.57] Kaspar 1997 1 16 Katoh 1997 1 62 0 31 1.6% 1.52 [0.06, 36.36] Katsaros 1996 0 104 2 106 6.1% 0.20 [0.01, 4.19] Misfeld 1998 0 14 0 14 Not estimable Nuttall 2000 0 45 2 45 6.2% 0.20 [0.01, 4.05] Zabeeda 2002 0 25 0 25 Not estimable Subtotal (95% CI) 599 559 57.0% 0.40 [0.19, 0.84] Total events 19 Heterogeneity: Chi<sup>2</sup> = 4.39, df = 8 (P = 0.82);  $I^2 = 0\%$ Test for overall effect: Z = 2.41 (P = 0.02) 1.3.2 Post 2003 Abul-Azm 2006 50 50 9.9% 0.25 [0.03, 2.16] Andreasen 2004 0 23 1.2% 3.27 [0.14, 76.21] 1 21 Baric 2007 97 3 96 7.5% 0.33 [0.03, 3.12] Dell Amore 2012 0 0 44 43 Not estimable Esfandiari 2013 2 75 2 75 5.0% 1.00 [0.14, 6.91] 0 0 Fawzy 2009 19 19 Not estimable Ghaffari 2012 0 50 0 50 Not estimable Jares 2003 0 22 25 Not estimable 0 Karski 2005 147 165 2.3% 3.37 [0.35, 32.02] 3 1 Maddali 2007 0 111 0 111 Not estimable Mehr-Aein 2007 0 33 0 33 Not estimable Nouraei 2013 0 40 0 40 Not estimable Santos 2006 0 29 2 31 6.0% 0.21 [0.01, 4.26] Shi 2013 2 274 3 278 7.4% 0.68 [0.11, 4.02] Shi2013A 0 58 1 59 3.7% 0.34 [0.01, 8.15] Wang 2012 0 116 0 115 Not estimable Wu 2006 106 108 Not estimable 0 0 Subtotal (95% CI) 43.0% 1321 0.68 [0.33, 1.41] 1292 10 Total events Heterogeneity: Chi<sup>2</sup> = 5.03, df = 7 (P = 0.66);  $I^2 = 0\%$ Test for overall effect: Z = 1.04 (P = 0.30) Total (95% CI) 1880 100.0% 0.52 [0.31, 0.87] Total events 17 35 Heterogeneity:  $Chi^2 = 10.05$ , df = 16 (P = 0.86);  $I^2 = 0\%$ 0.05 20 Test for overall effect: Z = 2.47 (P = 0.01) Favours TXA Favours standard ti Test for subgroup differences:  $Chi^2 = 0.96$ , df = 1 (P = 0.33),  $I^2 = 0\%$ 

Figure 65: TXA versus standard treatment- Mortality

Figure 66:	TXA versus	standard treat	ment-Length	of hospita	l stav
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0					_		0 -		
		TXA		Star	dard	Tt		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
1.4.2 Post 2003									
Mansour 2004	5.8	2.2	20	6.4	3	20	2.7%	-0.60 [-2.23, 1.03]	<del> -</del>
Mehr-Aein 2007	4.8	0.4	33	4.8	0.9	33	62.9%	0.00 [-0.34, 0.34]	•
Wei 2006	7.1	8.0	36	7.3	1.2	40	34.4%	-0.20 [-0.65, 0.25]	<del>-</del>
Subtotal (95% CI)			89			93	100.0%	-0.08 [-0.35, 0.18]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; CI	ni² = (	0.87, df	= 2 (P =	0.65	); $I^2 = 0$	%		
Test for overall effect:	Z = 0.62	(P =	0.53)						
Total (95% CI)			89			93	100.0%	-0.08 [-0.35, 0.18]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; CI	ni² = (	0.87, df	= 2 (P =	0.65	); $I^2 = 0$	%		10 5 10
Test for overall effect:	Z = 0.62	(P =	0.53)						-10 -5 0 5 10 Favours TXA Favours Standard
Test for subgroup diffe	erences:	Not a	applicat	ole					Tavouis TAA Favouis Statiuatu

Figure 67: TXA versus standard treatment- Thrombotic complications

	TXA	4	Standa	d Tt		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% CI
1.6.1 Pre 2003							
Horrow 1990	0	18	0	20		Not estimable	
Horrow 1991	0	37	1	44	9.0%	0.39 [0.02, 9.41]	<del></del>
Katoh 1997	0	62	0	31		Not estimable	
Katsaros 1996	0	104	1	106	8.9%	0.34 [0.01, 8.24]	
Subtotal (95% CI)		221		201	17.9%	0.37 [0.04, 3.47]	
Total events	0		2				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	$^{2} = 0.00$	, df = 1 (P)	= 0.95)	$I^2 = 0\%$		
Test for overall effect:	Z = 0.88 (	P = 0.3	8)				
1.6.2 Post 2003							
Ahn2012	0	38	0	38		Not estimable	
Dell Amore 2012	0	44	0	43		Not estimable	
Esfandiari 2013	3	75	5	75	46.5%	0.60 [0.15, 2.42]	<del></del>
Hosseini 2014	0	35	0	36		Not estimable	
Lundin 2014	2	50	5	50	35.7%	0.40 [0.08, 1.97]	<del></del>
Nouraei 2013	0	40	0	40		Not estimable	
Subtotal (95% CI)		282		282	82.1%	0.50 [0.18, 1.44]	<b>◆</b>
Total events	5		10				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	$^{2} = 0.14$	, df = 1 (P	= 0.71)	$I^2 = 0\%$		
Test for overall effect:	Z = 1.28 (	P = 0.2	0)				
Total (95% CI)		503		483	100.0%	0.48 [0.18, 1.23]	•
Total events	5		12				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	$^{2} = 0.21$	, df = 3 (P)	= 0.98)	$; I^2 = 0\%$		0.004 0.4 4 40 4000
Test for overall effect:	Z = 1.53 (	P = 0.1	3)	,			0.001
Test for subgroup diffe	rences: C	$hi^2 = 0.$	06, df = 1	(P = 0.8)	30), $I^2 = 0$	%	i avouis ina Favouis Stalluatu

Figure 68: Infections

gare ooeetio							
	TXA		Standar	rd Tt		Risk Ratio	Risk Ratio
Study or Subgroup	<b>Events</b>	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
1.5.1 Post 2003							
Lundin 2014 Subtotal (95% CI)	10	50 <b>50</b>	16	50 <b>50</b>	100.0% <b>100.0</b> %	0.63 [0.31, 1.24] <b>0.63 [0.31</b> , <b>1.24</b> ]	
Total events	10		16				
Heterogeneity: Not app	plicable						
Test for overall effect:	Z = 1.34 (F	P = 0.18	8)				
Total (95% CI)		50		50	100.0%	0.63 [0.31, 1.24]	•
Total events	10		16				
Heterogeneity: Not app	plicable						
Test for overall effect:	Z = 1.34 (F	P = 0.18	8)				0.01 0.1 1 10 100 Favours TXA Favours Standard
Test for subgroup diffe	rences: N	ot appli	cable				i avouis IAA Favouis Staildaid I

# K.2.2 Adults - moderate risk

Figure 69: ICS versus standard treatment- Number exposed to allogeneic blood

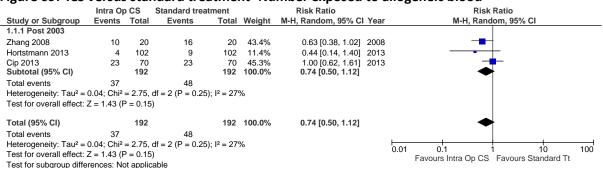


Figure 70: ICS versus standard treatment- Units of allogeneic blood transfused

	Intra	ор С	cs	Star	ndard	Tt		Mean Difference		Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI	
1.2.1 Post 2003											
Thomasson 2012	2.33	0	96	2.54	0	101		Not estimable	2012		
Hortstmann 2013	2	0	102	2	0	102		Not estimable	2013		
Subtotal (95% CI)			198			203		Not estimable			
Heterogeneity: Not app	plicable										
Test for overall effect:	Not appli	cable	:								
Total (95% CI)			198			203		Not estimable			
Heterogeneity: Not app	plicable								<del> </del>		-
Test for overall effect:	Not appli	cable							-10	-5 0 5 Favours Intra op CS Favours Standard Tt	10
Test for subgroup diffe	erences: I	Not a	oplicab	le						r avours intra op 00 Favours Standard Tt	

Figure 71: PCS versus standard treatment- Number exposed to allogeneic blood

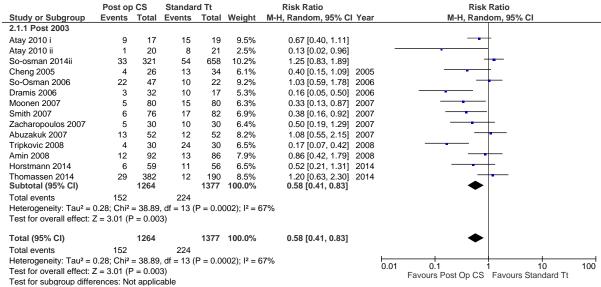


Figure 72: PCS versus standard treatment- Units of allogeneic blood transfused

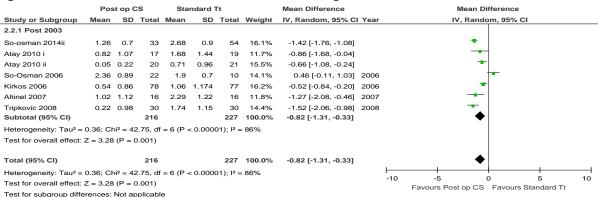


Figure 73: PCS versus standard treatment-Infection

	Post Op	CS	Standar	d Tt		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% C	Year	M-H, Random, 95% CI
2.3.1 Post 2003								
Moonen 2007	1	80	1	80	19.7%	1.00 [0.06, 15.71]	2007	<del></del>
Amin 2008	3	92	2	86	48.0%	1.40 [0.24, 8.19]	2008	<del>-   •</del>
Horstmann 2014	1	59	0	56	14.8%	2.85 [0.12, 68.53]	2014	<del></del>
Thomassen 2014 Subtotal (95% CI)	4	382 <b>613</b>	0	190 <b>412</b>	17.6% <b>100.0</b> %	4.49 [0.24, 82.93] 1.79 [0.53, 6.07]	2014	
Total events Heterogeneity: Tau <sup>2</sup> = 0	,		,	= 0.87);	l² = 0%			
Test for overall effect: 2	Z = 0.93 (P)	r = 0.35	)					
Total (95% CI)		613		412	100.0%	1.79 [0.53, 6.07]		
Total events	9		3					
Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z Test for subgroup differ	Z = 0.93 (P	0.35	)	= 0.87);	I <sup>2</sup> = 0%		0.0	10 0.1 10 100 Favours Post Op CS Favours Standard Tt

Figure 74: PCS versus standard treatment- Length of hospital stay

	Pos	t Op (	cs	Star	ndard	Tt		Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
2.4.1 Post 2003										
So-Osman 2006	7.85	3.57	47	9	2.8	22	39.5%	-1.15 [-2.70, 0.40]	2006	<del></del>
Abuzakuk 2007	8.1	2.4	52	8.3	2.8	52	56.3%	-0.20 [-1.20, 0.80]	2007	<del>-</del> ■-
Altinel 2007	21.2	11.3	16	16.5	6.9	16	4.2%	4.70 [-1.79, 11.19]	2007	<del>-  </del>
Subtotal (95% CI)			115			90	100.0%	-0.37 [-1.73, 0.99]		<b>*</b>
Heterogeneity: Tau2 =	= 0.59; Ch	$ni^2 = 3.$	42, df =	= 2 (P =	0.18);	$I^2 = 42$	%			
Test for overall effect:	Z = 0.53	(P = 0	).59)							
Total (95% CI)			115			90	100.0%	-0.37 [-1.73, 0.99]		•
Heterogeneity: Tau <sup>2</sup> =	0.59; Ch	ni² = 3.	42, df =	2 (P =	0.18);	$I^2 = 42$	%		<u> </u>	
Test for overall effect:				,	,				-1	0 -5 0 5 10 Favours Post Op CS Favours Standard Tt
Test for subgroup diffe	erences:	Not an	plicable	e						ravours rost op 00 ravours Standard It

Figure 75: ICS plus PCS versus standard treatment- Number exposed to allogeneic blood

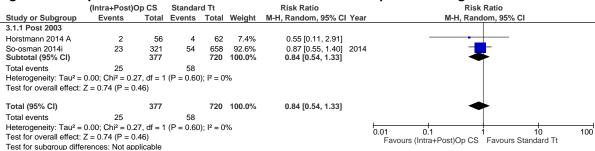


Figure 76: ICS plus PCS versus standard treatment- Units of allogeneic blood transfused

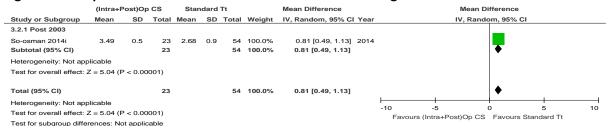


Figure 77: ICS plus PCS versus standard treatment- Mortality

	(Intra+Post)Op			S Standard Tt		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% C	<b>:</b>	
Horstmann 2014 A	1	56	0	62	100.0%	3.32 [0.14, 79.77]					
Total (95% CI)		56		62	100.0%	3.32 [0.14, 79.77]					
Total events	1		0								
Heterogeneity: Not ap Test for overall effect:		.46)					0.0.	ICS+PCS	1 Favours	10 Stan	100 dard Tt

Figure 78: ICS plus PCS versus standard treatment- Infection

	(Intra+Post)	Op CS	Standar	rd Tt		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Yea	ar M-H, Random, 95% CI
3.3.1 Post 2003							
Horstmann 2014 A Subtotal (95% CI)	1	56 <b>56</b>	0	62 <b>62</b>	100.0% <b>100.0</b> %	3.32 [0.14, 79.77] 3.32 [0.14, 79.77]	
Total events Heterogeneity: Not app	1 olicable		0				
Test for overall effect:	Z = 0.74 (P = 0)	.46)					
Total (95% CI)		56		62	100.0%	3.32 [0.14, 79.77]	
Total events	1		0				
Heterogeneity: Not app	olicable						0.01 0.1 1 10 100
Test for overall effect:	Z = 0.74 (P = 0)	.46)					Favours (Intra+Post)Op CS Favours Standard Tt
Test for subgroup diffe	rences: Not ap	plicable					Tavodio (ililia il ootjop oo Tavodio Otalidaid It

Figure 79: ICS plus PCS versus standard treatment- Length of hospital stay

	(Intra+P	Intra+Post)Op CS Standard Tt			Tt	Mean Difference			Mea	an Differe	nce		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV,	Fixed, 95°	% CI	
Horstmann 2014 A	4.5	1.2	56	4.3	1	62	100.0%	0.20 [-0.20, 0.60]					
Total (95% CI)			56			62	100.0%	0.20 [-0.20, 0.60]				,	1
Heterogeneity: Not app Test for overall effect: 2		9 = 0.33	)						-100 Favo	-50 urs ICS+l	0 PCS Fav	50 ours Stand	100 dard Tt

Figure 80: ICS plus PCS versus PCS- No. of patients receiving allogeneic transfusions

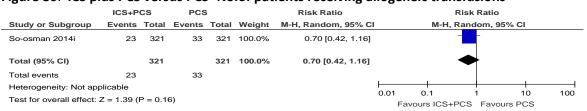


Figure 81: ICS plus PCS versus PCS- Units of allogeneic blood transfused

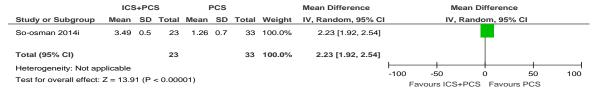


Figure 82: ICS plus TXA versus ICS- Number exposed to allogeneic blood

	ICS+T	XΑ	ICS	i		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI		
4.1.1 Post 2003									
Wong 2008 Subtotal (95% CI)	23	73 <b>73</b>	30	74 <b>74</b>		0.78 [0.50, 1.20] <b>0.78 [0.50</b> , 1. <b>20</b> ]	•		
Total events	23		30						
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 1.13 (	P = 0.2	6)						
Total (95% CI)		73		74	100.0%	0.78 [0.50, 1.20]	•		
Total events	23		30						
Heterogeneity: Not ap	plicable					F	.01 0.1 1 10	100	
Test for overall effect:	Z = 1.13 (	P = 0.2	6)			U	Favours ICS+TXA Favours ICS	100	
Test for subgroup diffe	erences: N	lot appli	cable				1 4/04/3 1001 1/1/4 1 4/04/3 100		

Figure 83: ICS plus TXA versus ICS- Units of allogeneic blood transfused

	ICS	S+TX	Α		ICS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	I IV, Fixed, 95% CI
4.2.1 Post 2003									
Wong 2008	0.89	1.8	73	1.35	2.16	74	100.0%	-0.46 [-1.10, 0.18]	•
Subtotal (95% CI)			73			74	100.0%	-0.46 [-1.10, 0.18]	T
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 1.40	(P =	0.16)						
Total (95% CI)			73			74	100.0%	-0.46 [-1.10, 0.18]	
Heterogeneity: Not ap	plicable								-100 -50 0 50 100
Test for overall effect:	Z = 1.40	(P =	0.16)						Favours ICS+TXA Favours ICS
Test for subgroup diffe	erences:	Not a	applicat	ole					1 4/04/3 1001 17/1/ 1 4/04/3 100

Figure 84: ICS plus TXA versus ICS- Length of hospital stay

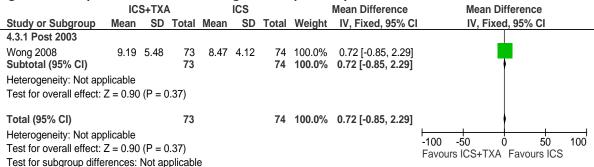


Figure 85: PCS plus TXA versus PCS- Number exposed to allogeneic blood

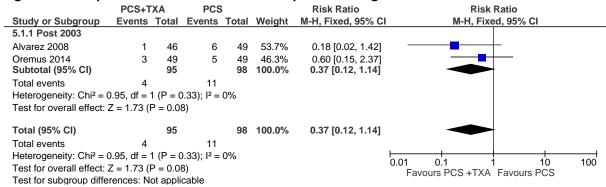


Figure 86: PCS plus TXA versus PCS- Thrombotic complications

	PCS+T	XΑ	PCS	3		Risk Ratio	Risk Ratio
Study or Subgroup	<b>Events</b>	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
Oremus 2014	0	49	2	49	100.0%	0.20 [0.01, 4.06]	<b>←</b>
Total (95% CI)		49		49	100.0%	0.20 [0.01, 4.06]	
Total events	0		2				
Heterogeneity: Not app	olicable						0.01 0.1 1 10 100
Test for overall effect:	Z = 1.05 (	P = 0.2	9)			1	Favours PCS+TXA Favours PCS

Figure 87: ICS plus PCS plus TXA versus TXA- No. exposed to allogeneic blood

	ICS +PCS +TXA		TXA			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
7.1.1 Post 2003							
Thomasson 2012 Subtotal (95% CI)	9	96 <b>96</b>	13	101 <b>101</b>	100.0% <b>100.0</b> %	0.73 [0.33, 1.63] <b>0.73 [0.33, 1.63]</b>	-
Total events Heterogeneity: Not ap Test for overall effect:		0.44)	13				
Total (95% CI)		96		101	100.0%	0.73 [0.33, 1.63]	
Total events Heterogeneity: Not ap Test for overall effect: Test for subgroup diffe	Z = 0.77 (P =	,	13 le				0.01 0.1 1 10 100 Favours ICS+PCS+TXA Favours TXA

Figure 88: ICS plus PCS plus TXA versus TXA- Units of allogeneic blood transfused

	ICS +P	CS+TXA		TXA			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD Tota	l Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
7.2.1 Post 2003								
Thomasson 2012	2.33	0 9	2.54	0	101		Not estimable	
Subtotal (95% CI)		9	5		101		Not estimable	
Heterogeneity: Not ap	plicable							
Test for overall effect:	Not appli	cable						
Total (95% CI)		9	6		101		Not estimable	
Heterogeneity: Not ap	plicable							-100 -50 0 50 100
Test for overall effect:	Not appli	cable					Fav	ours ICS+PCS+TXA Favours TXA
Test for subgroup diffe	erences:	Not applica	ble				rav	ouis ioo i co in Pavouis in

Standard Tt Risk Ratio TXAM-H, Random, 95% CI M-H, Random, 95% CI Study or Subgroup **Events Total Events** Total Weight 1.1.1 Pre 2003 Benoni 1996 2.8% 0.33 [0.17, 0.66] 8 43 24 43 Benoni 2000 9 20 15 19 3.5% 0.57 [0.33, 0.98] Benoni 2001 4 18 8 20 1.7% 0.56 [0.20, 1.54] Ellis 2001 1 10 7 10 0.6% 0.14 [0.02, 0.96] Engel 2001 0 12 3 12 0.3% 0.14 [0.01, 2.50] 12 Hiipala 1995 10 15 13 4.2% 0.72 [0.49, 1.07] Hiipala 1997 17 39 34 38 4.3% 0.49 [0.34, 0.71] Jansen 1999 2 21 13 21 1.1% 0.15 [0.04, 0.60] Sorin 1999 2 21 13 21 1.1% 0.15 [0.04, 0.60] 0.65 [0.55, 0.78] **0.46 [0.32, 0.65]** Tanaka 2001 47 73 26 26 5.3% Subtotal (95% CI) 272 24.9% Total events 100 155 Heterogeneity:  $Tau^2 = 0.16$ ;  $Chi^2 = 29.02$ , df = 9 (P = 0.0006);  $I^2 = 69\%$ Test for overall effect: Z = 4.33 (P < 0.0001) 1.1.2 Post 2003 Aguilera 2013 12 42 1.0% 0.17 [0.04, 0.72] Alshryda 2013 79 13 78 0.6% 0.08 [0.01, 0.57] Bidolegui 2014 0 25 8 25 0.3% 0.06 [0.00, 0.97] Bradshaw 2012 0 26 20 0.2% 0.26 [0.01, 6.05] Caglar 2008 15 50 10 50 2.7% 1.50 [0.75, 3.01] Charoench 2012 57 120 102 120 5.2% 0.56 [0.46, 0.68] Charoench2011 28 50 45 50 4.9% 0.62 [0.48, 0.81] Claeys 2007 20 6 20 0.6% 0.17 [0.02, 1.26] Crescenti 2011 34 100 55 100 4.6% 0.62 [0.45, 0.86] Dakir 2014 0 2 0.3% 0.20 [0.01, 3.46] Eftekharian 2015 0 28 28 Not estimable Farrokhi 2011 10 15 38 2.9% 0.67 [0.34, 1.29] 1.14 [0.72, 1.80] Garneti 2004 16 14 25 3.9% 0 4 51 0.3% 0.11 [0.01, 2.05] Georgiadis 2013 50 Gill 2009 5 0.25 [0.04, 1.52] 5 0.7% Good 2003 3 2 27 14 24 1.5% 0.19 [0.06, 0.58] 330 Gungorduk 2011 330 0.9% 0.29 [0.06, 1.37] Husted 2003 20 20 1.0% 0.29 [0.07, 1.21] 0 0 Imai2012 95 22 Not estimable Ishida 2011 0 50 50 0.2% 0.33 [0.01, 7.99] 8 Johansson 2005 47 23 53 2.7% 0.39 [0.19, 0.79] 0 Karimi 2012 16 16 0.2% 0.33 [0.01, 7.62] Kazemi 2010 11 0.36 [0.13, 1.02] 32 32 1.7% Kim 2014 i 90 6 90 0.5% 0.17 [0.02, 1.36] Kim 2014 ii 5 73 20 73 2.0% 0.25 [0.10, 0.63] 9 20 Lee 2013 34 34 3.0% 0.45 [0.24, 0.84] Lemay 2004 0 20 19 0.3% 0.06 [0.00, 0.91] 8 13 MacGillivray 2010 40 10 20 3.0% 0.65 [0.35, 1.22] 50 10 50 2.1% 0.70 [0.29, 1.69] Martin 2014 5 19 8 20 Niskanen 2005 2.0% 0.66 [0.26, 1.66] Orpen 2006 15 3 14 0.5% 0.31 [0.04, 2.65] 1 Rajesparan 2009 0.31 [0.09, 1.03] 3 36 10 37 1.3% 7 18 7 Ravirai2012 88 88 2.3% 0.39 [0.17, 0.88] 2 25 25 0.29 [0.07, 1.24] Rov 2012 1.0% Sa-Ngasoongsong 2011 1 24 8 24 0.6% 0.13 [0.02, 0.92] 6 10 45 0.30 [0.12, 0.77] Sa-ngasoongsong 2013 90 1.9% 12 32 0.66 [0.39, 1.12] Sadeghi 2007 20 35 3.5% 10 0.21 [0.12, 0.37] Seo 2013 50 47 50 3.3% 3 Shahid 2013 38 12 36 1.4% 0.24 [0.07, 0.77] 7 45 18 45 2.4% Vijay 2013 0.39 [0.18, 0.84] Wong 2010 5 64 9 35 1.7% 0.30 [0.11, 0.84] Yamasaki 2004 0 20 0 20 Not estimable 3.0% Yang 2015 10 40 19 40 0.53 [0.28, 0.99] 49 Yue 2015 3 52 11 1.3% 0.26 [0.08, 0.87] Zohar 2004 3 20 12 20 1.5% 0.25 [0.08, 0.75] 0.44 [0.36, 0.53] Subtotal (95% CI) 75.1% 2245 2074 Total events 297 641 Heterogeneity:  $Tau^2 = 0.12$ ;  $Chi^2 = 79.34$ , df = 41 (P = 0.0003);  $I^2 = 48\%$ Test for overall effect: Z = 8.71 (P < 0.00001) Total (95% CI) 2517 2297 100.0% 0.45 [0.38, 0.52] Total events 397 796 Heterogeneity:  $Tau^2 = 0.12$ ;  $Chi^2 = 109.71$ , df = 51 (P < 0.00001);  $I^2 = 54\%$ 0.1 0.2 0.5 Test for overall effect: Z = 9.90 (P < 0.00001) Favours TXA Favours Standard tt Test for subgroup differences: Chi<sup>2</sup> = 0.06, df = 1 (P = 0.81), I<sup>2</sup> = 0%

Figure 89: TXA versus standard treatment- Number exposed to allogeneic transfusions

Figure 90: TXA versus standard treatment- Units of allogeneic blood transfused

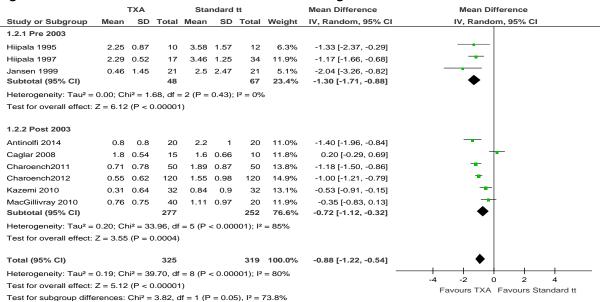


Figure 91: TXA versus standard treatment- Mortality

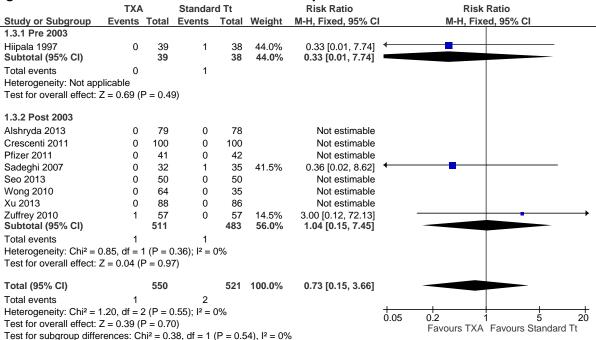


Figure 92: TXA versus standard treatment- Length of hospital stay

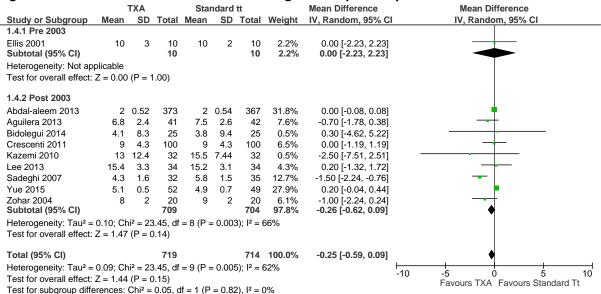


Figure 93: TXA versus standard treatment- Infections

	TXA		Standard Tt		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% C	CI M-H, Fixed, 95% CI	
1.5.1 Post 2003								
Bidolegui 2014	0	25	0	25		Not estimable	e	
Bradshaw 2012	0	26	1	20	45.8%	0.26 [0.01, 6.05]	]	
Charoench2011	1	50	1	50	27.1%	1.00 [0.06, 15.55]	] ← 💮 🕴	+
Charoench2012	2	120	1	120	27.1%	2.00 [0.18, 21.76]	] -	+
Eftekharian 2015	0	28	0	28		Not estimable		
Malhotra 2011	0	25	0	25		Not estimable		
Martin 2014	0	50	0	50		Not estimable		
Subtotal (95% CI)		324		318	100.0%	0.93 [0.22, 3.93]		
Total events	3		3					
Heterogeneity: Chi <sup>2</sup> = 1	.03, df = 2	2(P = 0)	).60); I <sup>2</sup> =	0%				
Test for overall effect: 2	Z = 0.10 (F	P = 0.92	2)					
Total (95% CI)		324		318	100.0%	0.93 [0.22, 3.93]		
Total events	3		3					
Heterogeneity: Chi <sup>2</sup> = 1	.03, df = 2	2(P = 0)	).60); I <sup>2</sup> =	0%				Ă
Test for overall effect: 2	Z = 0.10 (F	P = 0.92	2)				0.1 0.2 0.5 1 2 5 1 Favours TXA Favours Standard Tt	0
Test for subgroup differ	rences: No	ot appli	cable				Tavouis TAA Tavouis Standard It	

Figure 94: TXA versus standard treatment- Thrombotic complications Standard Tt Risk Ratio Risk Ratio TXAStudy or Subgroup **Events Total Events** Total Weight M-H, Random, 95% CI M-H, Random, 95% CI 1.6.1 Pre 2003 Benoni 1996 1.33 [0.32, 5.61] 43 3 43 9 4% Engel 2001 5.00 [0.27, 94.34] 0 2 12 12 2.3% 2 Hiipala 1995 0 2.2% 0.17 [0.01, 3.34] 15 13 Hiipala 1997 2 39 38 5.3% 0.97 [0.14, 6.57] 0 Jansen 1999 21 2 21 2.2% 0.20 [0.01, 3.93] Sorin 1999 0 21 21 2.2% 0.20 [0.01, 3.93] Subtotal (95% CI) 151 23.6% 0.82 [0.33, 2.03] 148 11 Total events 8 Heterogeneity:  $Tau^2 = 0.00$ ;  $Chi^2 = 4.74$ , df = 5 (P = 0.45);  $I^2 = 0\%$ Test for overall effect: Z = 0.43 (P = 0.66) 1.6.2 Post 2003 Abdal-aleem 2013 0 373 0 367 Not estimable Alshryda 2013 79 0 78 2.1% 4.94 [0.24, 101.22] Antinolfi 2014 0 20 0 20 Not estimable Bidolegui 2014 0 25 0 25 Not estimable Bradshaw 2012 0 26 20 2.0% 0.26 [0.01, 6.05] Charoench2011 0 50 0 50 Not estimable Charoench2012 0 120 0 120 Not estimable Claeys 2007 0 20 0 20 Not estimable Crescenti 2011 100 3 100 3.8% 0.33 [0.04, 3.15] Dakir 2014 0 0 Not estimable Farrokhi 2011 0 38 0 38 Not estimable Garneti 2004 0 25 0 25 Not estimable Georgiadis 2013 4 9 15.7% 0.45 [0.15, 1.38] 50 51 Gill 2009 0 5 0 5 Not estimable Good 2003 2 27 2 24 0.89 [0.14, 5.83] 5.5% Gungorduk 2011 0 330 0 330 Not estimable Husted 2003 0 0 20 20 Not estimable 3 0.77 [0.23, 2.57] Imai2012 10 95 22 13.4% Johansson 2005 0 47 0 53 Not estimable Kakar 2009 0 25 0 25 Not estimable 0 Kazemi 2010 32 32 1.9% 0.33 [0.01, 7.89] 1 0 Kim 2014 i 90 90 1.9% 0.33 [0.01, 8.08] 1 Kim 2014 ii 0 73 0 73 Not estimable Lee 2013 0 34 0 34 Not estimable 0 0 19 Lemay 2004 20 Not estimable Malhotra 2011 0 0 25 Not estimable 25 Martin 2014 0 50 0 50 Not estimable Niskanen 2005 0 19 0 20 Not estimable 0 Orpen 2006 15 0 Not estimable 14 3 0 40 2.3% 6.83 [0.36, 128.20] Pfizer 2011 41 2 0.51 [0.05, 5.42] Raiesparan 2009 36 37 3.5% Raviraj2012 0 88 87 0.33 [0.01, 7.98] 1 1.9% 0 25 0 25 Rov 2012 Not estimable 0 0 Sa-Ngasoongsong 2011 24 24 Not estimable 3 9.2% 0.38 [0.09, 1.60] Sa-ngasoongsong 2013 90 4 45 Seo 2013 0 50 2 50 0.20 [0.01, 4.06] 2.1% 0 Shahid 2013 0 38 36 Not estimable 0 O Van Elst 2013 41 26 Not estimable 0 0 Vijay 2013 45 45 Not estimable 3 2 Wong 2010 64 35 3.9% 1.64 [0.18, 15.19] 1 Xu 2013 0.98 [0.14, 6.78] 88 2 86 5.2% 0 Yang 2015 O 40 40 Not estimable 0 49 2.83 [0.12, 67.87] Yue 2015 1 52 1.9% Zhang 2007 0 51 0 51 Not estimable Zuffrey 2010 5 57 3 Not estimable Subtotal (95% CI) 2432 76.4% 0.65 [0.39, 1.07] 2669 37 35 Total events Heterogeneity:  $Tau^2 = 0.00$ ;  $Chi^2 = 8.88$ , df = 15 (P = 0.88);  $I^2 = 0\%$ Test for overall effect: Z = 1.68 (P = 0.09) Total (95% CI) 2820 2580 100.0% 0.69 [0.44, 1.07] Total events 45 46 Heterogeneity:  $Tau^2 = 0.00$ ;  $Chi^2 = 13.73$ , df = 21 (P = 0.88);  $I^2 = 0\%$ 0.001 0.1 10 1000 Test for overall effect: Z = 1.68 (P = 0.09) Favours TXA Favours Standard Tt Test for subgroup differences: Chi<sup>2</sup> = 0.19, df = 1 (P = 0.66), I<sup>2</sup> = 0%

# K.2.3 Adult- Low risk group

Figure 95: TXA versus standard treatment- Number exposed to allogeneic blood

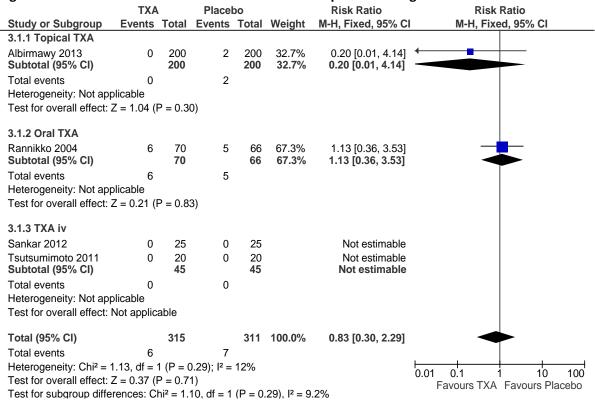


Figure 96: TXA versus standard treatment- Blood loss

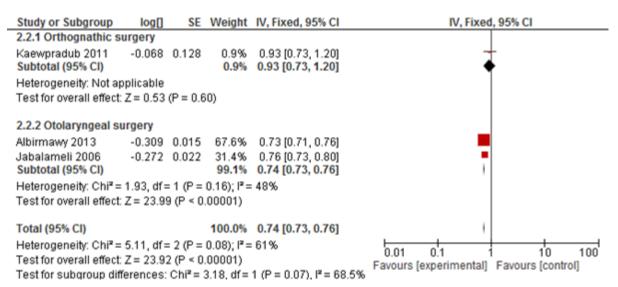


Figure 97: Thrombotic complications

	TXA	١	Place	bo		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% C	l M-H, Fixe	ed, 95% CI	
3.3.1 TXA iv									
Sankar2012	0	25	0	25		Not estimable			
Tsutsumimoto 2011	0	20	0	20		Not estimable			
Subtotal (95% CI)		45		45		Not estimable			
Total events	0		0						
Heterogeneity: Not app	olicable								
Test for overall effect: I	Not applic	able							
							0.01 0.1	<del>     </del> 1 10	100
							0.0.	Favours Plac	

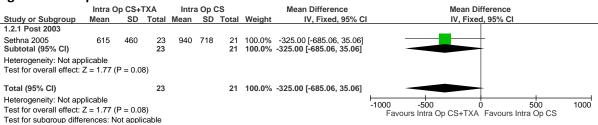
Test for subgroup differences: Not applicable

### K.2.4 Children - high risk

Figure 98: ICS plus TXA versus ICS- Number exposed to allogeneic blood

	Intra Op CS	+TXA	Intra O	CS CS		Risk Ratio	Risk Ratio
Study or Subgroup	Events Total		Events	Events Total		M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
1.1.1 Post 2003							
Sethna 2005 Subtotal (95% CI)	14	23 <b>23</b>	15	21 <b>21</b>	100.0% 100.0%	0.85 [0.56, 1.30] <b>0.85 [0.56, 1.30]</b>	
Total events Heterogeneity: Not ap Test for overall effect:	•	0.46)	15				
Total (95% CI)		23		21	100.0%	0.85 [0.56, 1.30]	
Total events Heterogeneity: Not ap Test for overall effect: Test for subgroup diffe	Z = 0.74 (P =	,	15				0.1 0.2 0.5 1 2 5 10 Favours Intra Op CS+TXA Favours Intra Op CS

Figure 99: ICS plus TXA versus ICS- Total blood transfused





	Intra Op CS+TXA Intra Op CS				S		Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	IV, Fixed, 95% CI
1.3.1 Post 2003									
Sethna 2005	1,230	535	23	2,085	1,188	21	100.0%	-855.00 [-1408.15, -301.85]	<b>←</b>
Subtotal (95% CI)			23			21	100.0%	-855.00 [-1408.15, -301.85]	
Heterogeneity: Not app	olicable								
Test for overall effect: 2	Z = 3.03 (	P = 0.0	02)						
Total (95% CI)			23			21	100.0%	-855.00 [-1408.15, -301.85]	
Heterogeneity: Not app	olicable								1000 500 1000
Test for overall effect: 2	Z = 3.03 (	P = 0.0	02)						-1000 -500 0 500 1000 Favours Intra Op CS+TXA Favours Intra Op CS
Test for subgroup diffe	rences: N	ot appli	icable						ravours initia Op CS+TAA Favours initia Op CS

Figure 101: TXA versus standard treatment- Post-operative blood loss

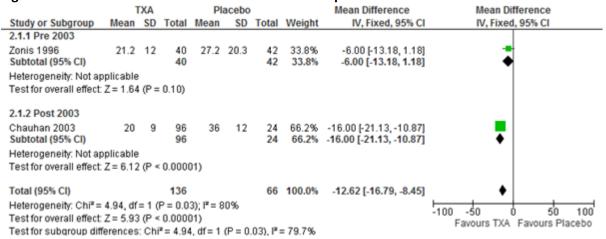


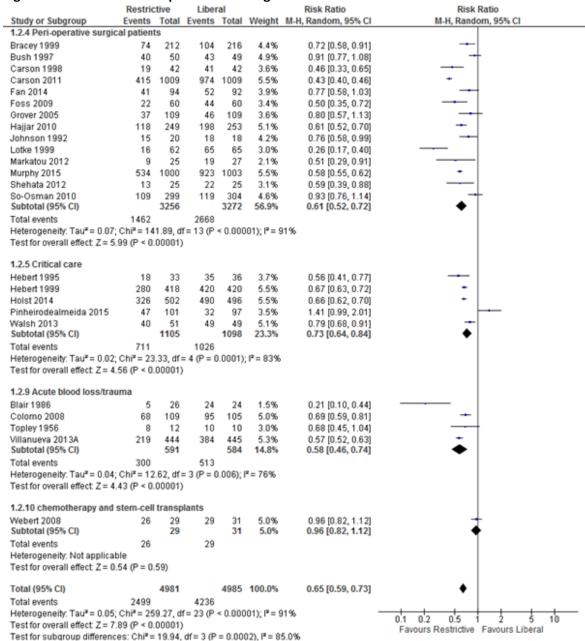
Figure 102: Length of hospital stay

		ГХА	•	Stan	dard	Tt		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Verma 2014	5.4	1.2	36	5.3	0.9	47	100.0%	0.10 [-0.37, 0.57]	
Total (95% CI)			36			47	100.0%	0.10 [-0.37, 0.57]	
Heterogeneity: Not app Test for overall effect:	•	! (P =	0.68)						-100 -50 0 50 100 Favours TXA Favours standard tt

# K.3 Red blood cells

### K.3.1 RBC thresholds - adults

Figure 103: Number of patients needing transfusion



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Figure 104: Number of units of blood transfused in those transfused (adults)

	Res	strictiv	е	L	iberal			Mean Difference	Mean Difference
Study or Subgroup	Mean			Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.5.1 Peri-operative	surgical	patier	its						
Bracey 1999	2.58	1.45	74	2.91	1.53	104	13.0%	-0.33 [-0.77, 0.11]	=
Bush 1997	3.5	3.09	40	4.22	3.43	43	7.2%	-0.72 [-2.12, 0.68]	<del></del>
Carson 1998	1.84	1.12	19	2	0.89	39	12.2%	-0.16 [-0.74, 0.42]	*
Cooper 2011	1.6	2	24	2.5	1.3	21	9.7%	-0.90 [-1.87, 0.07]	
Johnson 1992	1	0.86	15	2.05	0.93	18	12.0%	-1.05 [-1.66, -0.44]	• 1
Subtotal (95% CI)			172			225	54.1%	-0.55 [-0.91, -0.18]	•
Heterogeneity: Tau² =				= 4 (P =	0.22);	$I^2 = 30^{\circ}$	%		
Test for overall effect:	Z = 2.93	8(P=0)	).003)						
1.5.2 Critical care									
			000			400	44.00	4 70 10 45 0 00	
Hebert 1999 Subtotal (95% CI)	3.88	4.49	280 <b>280</b>	5.6	5.3	420 <b>420</b>	11.3% <b>11.3%</b>	-1.72 [-2.45, -0.99] - <b>1.72</b> [- <b>2.45</b> , - <b>0.99</b> ]	
	م ا ما م م ا م		200			420	11.570	-1.72 [-2.45, -0.55]	<b>~</b>
Heterogeneity: Not ap									
Test for overall effect:	∠= 4.62	2 (P < L	.0000	1)					
1.5.3 Acute blood los	s/traum	ıa							
Blair 1986	2.6	1.34	5	4.6	1.47	24	7.7%	-2.00 [-3.31, -0.69]	
Topley 1956	7.2	7.13	8	11.34	6.87	10	0.7%	-4.14 [-10.66, 2.38]	<del></del>
Villanueva 2013A	1.5	2.3	444	3.7	3.8	445	13.1%	-2.20 [-2.61, -1.79]	÷
Subtotal (95% CI)			457			479	21.5%	-2.19 [-2.58, -1.80]	<b>•</b>
Heterogeneity: Tau² =	: 0.00; C	$hi^2 = 0$	.43, df=	= 2 (P =	0.81);	$I^2 = 0\%$	ı		
Test for overall effect:	Z = 10.9	91 (P <	0.0000	01)					
1.5.4 Acute coronary	svndro	me (A	CS)						
Carson 2013	-	1.03	55	1.59	1.13	55	13.1%	-1.09 [-1.49, -0.69]	•
Subtotal (95% CI)	0.43	1.03	<b>55</b>	1.30	1.13	<b>55</b>	13.1%		
Heterogeneity: Not as	plicable	)							
Test for overall effect:	Z = 5.29	9 (P < 0	0.00001	1)					
Total (95% CI)			964			1179	100.0%	-1.13 [-1.67, -0.59]	•
Heterogeneity: Tau <sup>2</sup> =	. n 52· C	hiz – 6		f = 0 /D :	~ 0 000			-1110 [-1101, -0100]	
- '				•	~ 0.000	001), 1	- 0470		-10 -5 0 5 10
		•			/D ~ 0	000041	. IZ = 02.2	004	Favours Restrictive Favours Liberal
Test for overall effect: Test for subgroup diff		•			(P < 0.	00001)	), I²= 92.2	!%	

Length of stay in hospital (adults) Figure 105: Restrictive Liberal Mean Difference Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI 2.2.1 Peri-operative surgical patients Bracey 1999 7.5 2.9 212 7.9 4.9 216 15.6% -0.40 [-1.16, 0.36] -1.00 [-4.02, 2.02] 0.10 [-1.35, 1.55] Bush 1997 9 10 6 50 11 49 3.2% Carson 1998 42 9.2% 6.4 3.4 42 6.3 3.4 4 Carson 2011 3.9 1009 3.7 3.4 1007 20.0% 0.30 [-0.02, 0.62] Fan 2014 8.7 2.7 94 9.3 3.9 92 13.5% -0.60 [-1.57, 0.37] Foss 2009 17 12.9 18.4 14.4 1.3% -1.40 [-6.29, 3.49] Johnson 1992 7.9 4.3 20 7.6 1.9 18 5.8% 0.30 [-1.78, 2.38] 2.00 [-2.96, 6.96] Shehata 2012 9 12 25 7 25 1.3% So-Osman 2010 Subtotal (95% CI) -0.60 [-1.61, 0.41] **0.01 [-0.30, 0.32]** 13.0% 9.6 5 299 10.2 7.4 304 1813 1811 83.0% Heterogeneity:  $Tau^2 = 0.02$ ;  $Chi^2 = 8.47$ , df = 8 (P = 0.39);  $I^2 = 6\%$ Test for overall effect: Z = 0.04 (P = 0.97) 2.2.2 Critical care Hebert 1999 34.8 19.5 418 35.5 19.4 420 4.0% -0.70 [-3.33, 1.93] Subtotal (95% CI) 4.0% -0.70 [-3.33, 1.93] 420 Heterogeneity: Not applicable Test for overall effect: Z = 0.52 (P = 0.60) 2.2.3 ACS (Acute MI) Cooper 2011 4.3 3.3 8.5 5.6 3.8% -4.20 [-6.93, -1.47] Subtotal (95% CI) -4.20 [-6.93, -1.47] 24 21 3.8% Heterogeneity: Not applicable Test for overall effect: Z = 3.01 (P = 0.003) 2.2.4 Acute blood loss/trauma Villanueva 2013A 9.6 8.7 444 11.5 12.8 445 -1.90 [-3.34, -0.46] Subtotal (95% CI) 444 445 9.3% -1.90 [-3.34, -0.46] Heterogeneity: Not applicable Test for overall effect: Z = 2.59 (P = 0.010) Total (95% CI) 2697 2699 100.0% -0.52 [-1.11, 0.06] <u>⊢</u> -10 Heterogeneity:  $Tau^2 = 0.42$ ;  $Chi^2 = 24.72$ , df = 11 (P = 0.01);  $I^2 = 55\%$ 10 Test for overall effect: Z = 1.75 (P = 0.08) Favours Restrictive Favours Liberal

Test for subgroup differences:  $Chi^2 = 15.25$ , df = 3 (P = 0.002),  $I^2 = 80.3\%$ 

Figure 106: All-cause mortality (30 days) Restrictive Liberal Risk Ratio Risk Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI 3.2.1 Perioperative surgical patients Bracey 1999 3 215 6 222 2.0% 0.52 [0.13, 2.04] Bush 1997 4 50 4 49 2.2% 0.98 [0.26, 3.70] Carson 1998 42 42 0.5% 1.00 [0.06, 15.47] Carson 2011 43 1009 52 1007 12.4% 0.83 [0.56, 1.22] 11.00 [0.62, 194.63] Foss 2009 5 60 0 60 0.5% Grover 2005 0 109 109 0.4% 0.33 [0.01, 8.09] Hajjar 2010 1.17 [0.57, 2.41] 249 253 15 13 6.0% Lotke 1999 0 62 Not estimable 0 65 0.5% Markatou 2012 0 25 2 27 0.22 [0.01, 4.28] Murphy 2015 26 1000 19 1003 8.0% 1.37 [0.76, 2.46] Shehata 2012 4 25 1 25 0.9% 4.00 [0.48, 33.33] So-Osman 2010 299 304 0.7% 0.51 [0.05, 5.58] Subtotal (95% CI) 3145 3166 34.1% 0.99 [0.75, 1.30] 102 101 Heterogeneity: Tau2 = 0.00; Chi2 = 9.23, df = 10 (P = 0.51); I2 = 0% Test for overall effect: Z = 0.09 (P = 0.93) 3.2.2 Critical care 0.97 [0.42, 2.22] Hebert 1995 8 33 9 36 4.8% Hebert 1999 78 418 98 420 16.6% 0.80 [0.61, 1.04] Holst 2014 168 502 175 496 19.8% 0.95 [0.80, 1.13] Pinheirodealmeida 2015 23 101 8 97 5.6% 2.76 [1.30, 5.87] Walsh 2013 12 51 49 7.1% 0.72 [0.38, 1.36] Subtotal (95% CI) 1105 1098 53.9% 0.98 [0.73, 1.31] 289 Total events Heterogeneity: Tau2 = 0.05; Chi2 = 9.93, df = 4 (P = 0.04); I2 = 60% Test for overall effect: Z = 0.16 (P = 0.87) 3.2.3 ACS (Acute MI) 7.13 [0.91, 56.02] Carson 2013 0.9% 54 55 1.75 [0.17, 17.95] 3.85 [0.82, 18.00] Cooper 2011 2 24 21 0.7% 76 78 Subtotal (95% CI) 1.7% Heterogeneity:  $Tau^2 = 0.00$ ;  $Chi^2 = 0.81$ , df = 1 (P = 0.37);  $I^2 = 0\%$ Test for overall effect: Z = 1.71 (P = 0.09) 3.2.4 Acute blood loss/trauma Blair 1986 0 0.5% 0.19 [0.01, 3.67] 26 24 445 Villanueva 2013A 9.8% 0.56 (0.34, 0.92) 23 444 41 Subtotal (95% CI) 0.55 [0.34, 0.89] 469 10.3% Total events 23 43 Heterogeneity: Tauz = 0.00; Chiz = 0.52, df = 1 (P = 0.47); Iz = 0% Test for overall effect: Z = 2.44 (P = 0.01) Total (95% CI) 4798 4809 100.0% 0.95 [0.77, 1.17] Total events 423 452 Heterogeneity: Tauz = 0.05; Chiz = 28.46, df = 19 (P = 0.07); Iz = 33% 0.005 0.1 10 200 Test for overall effect: Z = 0.50 (P = 0.62) Favours Restrictive Favours Liberal Test for subgroup differences: Chi<sup>2</sup> = 8.13, df = 3 (P = 0.04), I<sup>2</sup> = 63.1%

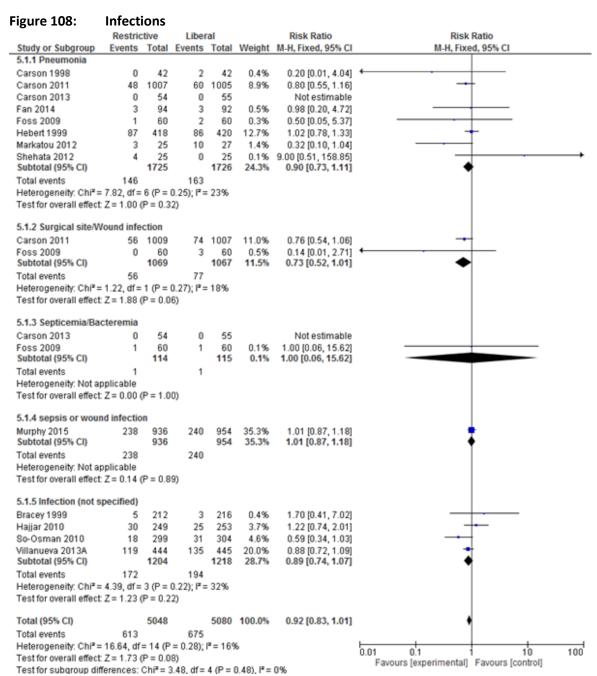
National Clinical Guideline Centre, 2015

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Figure 107: New cardiac events (MI,CHF) Restrictive Liberal Risk Ratio Risk Ratio Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI Study or Subgroup Events 4.1.1 Myocardial infarction Bracey 1999 212 0 216 1.2% 3.06 [0.13, 74.61] Bush 1997 50 2 49 2.2% 0.49 [0.05, 5.23] Carson 2011 38 1009 23 1007 34.1% 1.65 [0.99, 2.75] Carson 2013 54 5 10.0% 1.43 [0.48, 4.22] Fan 2014 1.3% 0.33 [0.01, 7.91] Foss 2009 3.00 [0.12, 72.20] 60 0 60 1.3% Grover 2005 0 109 109 1.3% 0.33 [0.01, 8.09] Hebert 1999 418 0.25 [0.07, 0.88] 3 12 420 7.6% Holst 2014 488 489 12.4% 2.17 [0.83, 5.67] 13 6 Johnson 1992 0.30 [0.01, 6.97] Ω 20 18 1.3% Lotke 1999 62 0 65 1.3% 3.14 [0.13, 75.72] Murphy 2015 3 987 981 5.5% 0.75 [0.17, 3.32] Pinheirodealmeida 2015 101 0 97 1.3% 2.88 [0.12, 69.91] Shehata 2012 25 0 25 1.3% 3.00 [0.13, 70.30] Villanueva 2013A 444 13 445 14.7% 0.62 [0.26, 1.47] Walsh 2013 51 49 3.4% 0.96 [0.14, 6.56] Subtotal (95% CI) 4184 4177 100.0% 1.13 [0.79, 1.61] 80 70 Total events Heterogeneity:  $Tau^2 = 0.03$ ;  $Chi^2 = 15.86$ , df = 15 (P = 0.39);  $I^2 = 5\%$ Test for overall effect: Z = 0.65 (P = 0.51) 4.1.2 Congestive heart failure Carson 2011 35 1009 27 1007 25.5% 1.29 [0.79, 2.12] Carson 2013 7 54 2 55 10.5% 3.56 [0.78, 16.40] Foss 2009 60 3.6% 5.00 [0.25, 102.00] 60 Hebert 1999 22 418 45 420 25.6% 0.49 [0.30, 0.80] Johnson 1992 0 20 18 3.3% 0.30 [0.01, 6.97] Pinheirodealmeida 2015 101 97 9.7% 2.40 [0.48, 12.08] 5 0.57 [0.29, 1.15] 1.00 [0.54, 1.83] Villanueva 2013A 12 444 21 445 21.9% Subtotal (95% CI) 2106 2102 100.0% 98 Total events 83 Heterogeneity:  $Tau^2 = 0.31$ ;  $Chi^2 = 15.50$ , df = 6 (P = 0.02);  $I^2 = 61\%$ Test for overall effect: Z = 0.01 (P = 0.99) 0.002 0.1 10 500 Favours Restrictive Favours Liberal

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Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.73), l² = 0%



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Figure 109: Adverse events (adults) Liberal Restrictive Risk Ratio Risk Ratio Study or Subgroup **Events** Total **Events** Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI Holst 2014 488 489 0.33 [0.01, 8.18] 0 1 0.7% Nielsen 2012A 0 0 25 23 Not estimable Villanueva 2013A 179 444 214 445 99.3% 0.84 [0.72, 0.97] Total (95% CI) 957 957 100.0% 0.83 [0.72, 0.97] Total events 179 215 Heterogeneity: Chi<sup>2</sup> = 0.32, df = 1 (P = 0.57);  $I^2 = 0\%$ 0.1 10 100 Test for overall effect: Z = 2.38 (P = 0.02)

Favours Restrictive Favours Liberal

Figure 110: Adverse events (adults)-TACO

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Holst 2014	0	488	0	489		Not estimable		
Villanueva 2013A	2	444	16	445	100.0%	0.13 [0.03, 0.54]		
Total (95% CI)		932		934	100.0%	0.13 [0.03, 0.54]		
Total events	2		16					
Heterogeneity: Not app		2 0 00	)E)				0.01 0.1 1 10 100	)
Test for overall effect: 2	Z = Z.70 (F	= 0.00	J5)				Favours Restrictive Favours Liberal	

Figure 111: Adverse events (adults)-TRALI

	Restric	tive	Liber	al		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-H, Fixe	ed, 95% CI	
Holst 2014	0	488	0	489		Not estimable				
Villanueva 2013A	0	444	0	445		Not estimable				
Total (95% CI)		932		934		Not estimable				
Total events	0		0							
Heterogeneity: Not ap	plicable						0.01 0	1	1 10	100
Test for overall effect:	Not applic	able						Restrictive	Favours Liberal	100

### K.3.2 RBC thresholds - children

Figure 112: Total RBC ml/patient (children)

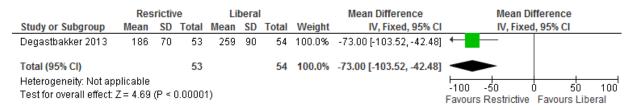


Figure 113: Number of units transfused-children

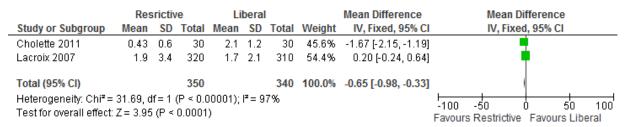


Figure 114: Number of patients needing transfusion -children

	Resric	tive	Liber	al		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI	
Cholette 2011	11	30	29	30	8.5%	0.38 [0.24, 0.61]	<u></u>		
Lacroix 2007	146	320	310	317	91.5%	0.47 [0.41, 0.53]			
Total (95% CI)		350		347	100.0%	0.46 [0.41, 0.52]	•		
Total events	157		339						
Heterogeneity: Chi²=	-			= 0%			0.01 0.1	1 10	100
Test for overall effect:	Z = 13.01	(P < U	.00001)				Favours Restrictive	Favours Libe	eral

Figure 115: Number of patients needing transfusion -children (sub-group analysis)

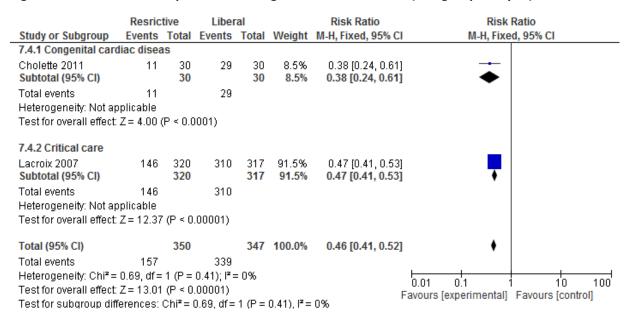


Figure 116: Mortality at 30 days (all-cause)- children

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Cholette 2011	0	30	1	30	9.6%	0.33 [0.01, 7.87]	<u> </u>
Lacroix 2007	14	320	14	317	90.4%	0.99 [0.48, 2.04]	-
Total (95% CI)		350		347	100.0%	0.93 [0.46, 1.87]	•
Total events	14		15				
Heterogeneity: Chi²=	-			: 0%			0.01 0.1 1 10 100
Test for overall effect:	Z = 0.21 (	P = 0.8	3)				Favours restrictive Favours liberal

Figure 117: ICU length of stay (children)

	Res	tricti	/e	Li	beral	l		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Lacroix 2007	9.5	7.9	320	9.9	7.4	317	100.0%	-0.40 [-1.59, 0.79]	
Total (95% CI)			320			317	100.0%	-0.40 [-1.59, 0.79]	ı
Heterogeneity: Not ap Test for overall effect:			0.51)						-100 -50 0 50 100 Favours Restrictive Favours Liberal

Figure 118: Pulmonary oedema (children)

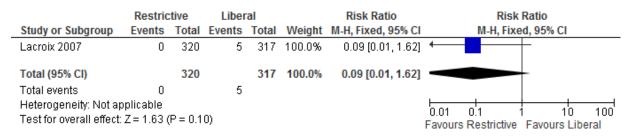


Figure 119: Infections (nosocomial infections) -children



# K.3.3 Target haemoglobin concentrations for blood transfusion

Figure 120: Number of patients needing transfusions-adults

	Restrictiv	e Libe	ral		Risk Ratio	Risk Ratio
Study or Subgroup	Events To	otal Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.2.4 Peri-operative s	urgical pati	ents				
Hajjar 2010	118	249 198	253	22.5%	0.61 [0.52, 0.70]	<b>+</b>
Markatou 2012	9	25 19	27	2.8%	0.51 [0.29, 0.91]	
Subtotal (95% CI)		274	280	25.3%	0.60 [0.52, 0.69]	•
Total events	127	217				
Heterogeneity: Tau² =	•		P = 0.5	B); I² = 0%	)	
Test for overall effect:	Z = 7.08 (P <	< 0.00001)				
1.2.6 Critical care						
Hebert 1995	18	33 35	36	8.1%	0.56 [0.41, 0.77]	<del></del>
Hebert 1999	280	418 420	420	36.5%	0.67 [0.63, 0.72]	•
Subtotal (95% CI)	4	451	456	44.6%	0.66 [0.59, 0.73]	<b>♦</b>
Total events	298	455				
Heterogeneity: Tau² =	0.00; Chi <sup>2</sup> =	1.18, df = 1	P = 0.23	8); I² = 15°	%	
Test for overall effect:	Z = 7.42 (P <	< 0.00001)				
1.2.9 Acute blood los	e/trauma					
Villanueva 2013A		444 384	445	30.1%	0.67 (0.60, 0.60)	_
Subtotal (95% CI)		444 384 <b>444</b>	445 445	30.1%	0.57 [0.52, 0.63] <b>0.57 [0.52, 0.63]</b>	
Total events	219	384	443	30.170	0.57 [0.52, 0.05]	•
Heterogeneity: Not ap		304				
Test for overall effect:	•	< 0.00001)				
TOOLIOI OVOIGII OIIOOL	2- 10.02 (1	0.000017				
1.2.10 Cancer						
Park 2008	0	0 0	0		Not estimable	
Subtotal (95% CI)		0	0		Not estimable	
Total events	0	0				
Heterogeneity: Not ap	•					
Test for overall effect:	Not applicat	ole				
Total (95% CI)	11	169	1181	100.0%	0.61 [0.55, 0.67]	•
Total events	644	1056				
Heterogeneity: Tau² =	0.01; Chi <sup>2</sup> =	8.92, df = 4 (	P = 0.0	8); I² = 55°	%	0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z = 9.71 (P <	< 0.00001)				Favours Restrictive Favours Liberal
Test for subgroup diffe	erences: Chi	i² = 3.33, df =	2 (P=	0.19), I²=	40.0%	

# K.4 Target haemoglobin concentrations for blood transfusion

Figure 121: Number of patients needing transfusions-adults

•		•			•		
	Restrict	tive	Liber	al		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.2.4 Peri-operative s	surgical pa	atients					
Hajjar 2010	118	249	198	253	23.5%	0.61 [0.52, 0.70]	<b>.</b>
Subtotal (95% CI)		249		253	23.5%	0.61 [0.52, 0.70]	<b>♦</b>
Total events	118		198				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 6.73 (F	o.00	0001)				
1.2.6 Critical care							
Hebert 1995	18	33	35	36	8.7%	0.56 [0.41, 0.77]	
Hebert 1999	280	418	420	420	36.9%	0.67 [0.63, 0.72]	<b>.</b>
Subtotal (95% CI)		451		456	45.6%	0.66 [0.59, 0.73]	♦
Total events	298		455				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 1.18,	df = 1 (P	= 0.28	); I <sup>2</sup> = 15%	, D	
Test for overall effect:	Z = 7.42 (F	o.00	0001)				
1.2.9 Acute blood los	ss/trauma						
Villanueva 2013A	219	444	384	445	30.9%	0.57 [0.52, 0.63]	<b>.</b>
Subtotal (95% CI)		444		445	30.9%	0.57 [0.52, 0.63]	•
Total events	219		384				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 10.82	(P < 0.0	00001)				
1.2.10 Cancer							
Park 2008	0	0	0	0		Not estimable	
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not applica	able					
							<b>.</b>
Total (95% CI)		1144		1154	100.0%	0.61 [0.55, 0.68]	▼
Total events	635		1037				
Heterogeneity: Tau <sup>2</sup> =	0.01; Chi <sup>2</sup>	= 8.31,	df = 3 (P	= 0.04	); I <sup>2</sup> = 64%	6	0.1 0.2 0.5 1 2 5 10

Figure 122: Number of units of blood transfused (in those who were transfused)-adults

-								=			-		
	Res	strictiv	/e	Li	bera	ı		Mean Difference		Mear	Differe	nce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% (	CI .	IV, Ra	ndom, 9	5% CI	
Cooper 2011	1.6	2	24	2.5	1.3	21	25.3%	-0.90 [-1.87, 0.07]	l		-		
Hebert 1999	3.88	4.49	280	5.6	5.3	420	32.2%	-1.72 [-2.45, -0.99]	l	4	-		
Villanueva 2013A	1.5	2.3	444	3.7	3.8	445	42.5%	-2.20 [-2.61, -1.79]	l	•			
Total (95% CI)			748			886	100.0%	-1.72 [-2.41, -1.02]		•	•		
Heterogeneity: Tau <sup>2</sup> =	0.25: CI	ni² = 6.	25. df =	= 2 (P =	0.04	): I <sup>2</sup> = 6	8%		-	-	-	-	$\overline{}$
Test for overall effect:	-			•		,, -			-10	-5	0	5	10
rest for overall effect.	4.02	. (, < (	3.0000	' /					Favour	s Restricti	ve Fav	ours Libe	ral

Figure 123: Length of hospital stay-adults

	Res	strictiv	/e	L	iberal			Mean Difference		Mea	n Differe	nce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	1	IV, Ra	andom, 9	5% CI	
Cooper 2011	4.3	3.3	24	8.5	5.6	21	24.9%	-4.20 [-6.93, -1.47]			-		
Hebert 1999	34.8	19.5	418	35.5	19.4	420	26.2%	-0.70 [-3.33, 1.93]		_	-		
Villanueva 2013A	9.6	8.7	444	11.5	12.8	445	48.9%	-1.90 [-3.34, -0.46]		_	_		
Total (95% CI)			886			886	100.0%	-2.16 [-3.81, -0.50]		<	<b>▶</b>		
Heterogeneity: Tau <sup>2</sup> =	0.92; Cł	ni² = 3.	42, df =	= 2 (P =	0.18);	$I^2 = 42$	%		<u> </u>	<u> </u>		<u> </u>	
Test for overall effect:	Z = 2.56	(P = 0	0.01)						-10	-5 s Restric	0 tive Favo	5 ours Libe	10 eral

Figure 124: Mortality at 30 days (all-cause)-adults

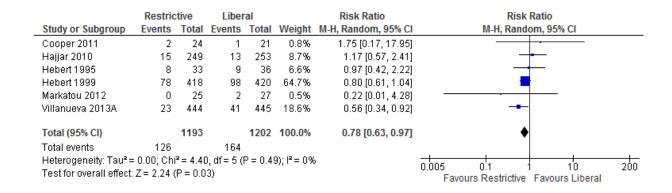


Figure 125: New cardiac events-adults

_										
	Restric	tive	Liber	al		Risk Ratio		Risk R	atio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rando	m, 95% CI	
4.1.1 Myocardial infa	rction									
Hebert 1999	3	418	12	420	100.0%	0.25 [0.07, 0.88]		_		
Subtotal (95% CI)		418		420	100.0%	0.25 [0.07, 0.88]				
Total events	3		12							
Heterogeneity: Not app	plicable									
Test for overall effect:	Z = 2.15 (I	P = 0.03	3)							
4.1.2 Congestive hea	rt failure									
Hebert 1999	22	418	45	420	97.4%	0.49 [0.30, 0.80]				
Park 2008	0	43	2	43	2.6%	0.20 [0.01, 4.05]		• .	_	
Subtotal (95% CI)		461		463	100.0%	0.48 [0.30, 0.78]		•		
Total events	22		47							
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 0.34,	df = 1 (P	= 0.56	); I <sup>2</sup> = 0%					
Test for overall effect:	Z = 2.97 (I	P = 0.00	03)							
							0.002	0.1 1	10	<del></del>
									TU Favours Lib	
Test for subgroup diffe	rences: C	$hi^2 = 0.8$	39, df = 1	(P = 0.	35), I <sup>2</sup> = 0		avouis	restrictive i	avours Lik	Jeral

Figure 126: Infection-adults

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
5.1.1 Pneumonia							
Hebert 1999	87	418	86	420	89.9%	1.02 [0.78, 1.33]	
Markatou 2012	3	25	10	27	10.1%	0.32 [0.10, 1.04]	
Subtotal (95% CI)		443		447	100.0%	0.95 [0.73, 1.22]	₹
Total events	90		96				
Heterogeneity: Chi²=	= 3.50, df=	1 (P = 1)	0.06); I <b>*</b> =	71%			
Test for overall effect	Z = 0.42 (	P = 0.6	8)				
5.1.5 Infection (not s	specified)						
Hajjar 2010	30	249	25	253	100.0%	1.22 [0.74, 2.01]	-
					400 00/		
Subtotal (95% CI)		249		253	100.0%	1.22 [0.74, 2.01]	<b>—</b>
	30	249	25	255	100.076	1.22 [0.74, 2.01]	
Total events		249	25	253	100.0%	1.22 [0.74, 2.01]	
Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect	pplicable			253	100.0%	1.22 [0.74, 2.01]	
Total events Heterogeneity: Not a	pplicable			253	100.0%	1.22 [0.74, 2.01]	
Total events Heterogeneity: Not a	pplicable			253	100.0%	1.22 [0.74, 2.01]	0.01 0.1 1 10 10

Test for subgroup differences:  $Chi^2 = 0.78$ , df = 1 (P = 0.38),  $I^2 = 0\%$ 

Figure 127: Adverse events (as defined by study)-adults

	Restric	tive	Liber	al		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	:1	M-H, Fix	ed, 95% C	I	
5.1.1 Pneumonia								_	<u>L</u>		
Hebert 1999	87	418	86	420	100.0%	1.02 [0.78, 1.33]					
Subtotal (95% CI)		418		420	100.0%	1.02 [0.78, 1.33]			•		
Total events	87		86								
Heterogeneity: Not app	olicable										
Test for overall effect: 2	Z = 0.12 (F	P = 0.90	O)								
5.1.5 Infection (not sp	ecified)										
Hajjar 2010	30	249	25	253	100.0%	1.22 [0.74, 2.01]		-			
Subtotal (95% CI)		249		253	100.0%	1.22 [0.74, 2.01]		•			
Total events	30		25								
Heterogeneity: Not app	olicable										
Test for overall effect: 2	Z = 0.78 (F	P = 0.44	4)								
							H		+ +		
							0.01	0.1	1 10		100
Test for subgroup diffe	rences: Cl	ni² = 0.4	10, df = 1	(P = 0.	53), I <sup>2</sup> = 0°		Favours	restrictive	Favours	libera	al .

Figure 128: Number of patients needing transfusion-children (critical care)

	Resrict	ive	Liber	al		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	1	M-H, Fixe	ed, 95% CI	
Lacroix 2007	146	320	310	317	100.0%	0.47 [0.41, 0.53]				
Total (95% CI)		320		317	100.0%	0.47 [0.41, 0.53]		<b>♦</b>		
Total events	146		310							
Heterogeneity: Not app	olicable						-	+	<del>                                     </del>	
Test for overall effect: 2	Z = 12.37	(P < 0.0	00001)				0.01 Favour	0.1 s Restrictive	1 10 Favours Lib	100 eral

Figure 129: Volume of RBC transfused in ml/patient- children (critical care)

	Res	rictiv	re	Li	bera	I		Mean Difference		Mea	n Differe	ence	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	ı	IV, F	Fixed, 95	% CI	
Lacroix 2007	1.9	3.4	146	1.7	2.1	310	100.0%	0.20 [-0.40, 0.80]					
Total (95% CI)			146			310	100.0%	0.20 [-0.40, 0.80]					
Heterogeneity: Not app	plicable								-100	<del></del>		<del></del>	100
Test for overall effect:	Z = 0.65	(P =	0.51)							s Restric	-	ours Libe	

Figure 130: Mortality at 30 days- children (critical care)



Figure 131: Length of ICU stay-children (critical care)

	Res	tricti	ve	Li	bera	I		Mean Difference		Mea	n Differe	nce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	1	IV, F	ixed, 95	% CI	
Lacroix 2007	9.5	7.9	320	9.9	7.4	317	100.0%	-0.40 [-1.59, 0.79]					
Total (95% CI)			320			317	100.0%	-0.40 [-1.59, 0.79]			1		
Heterogeneity: Not ap	plicable								-100	<del>-5</del> 0		<del></del>	100
Test for overall effect:	Z = 0.66	(P =	0.51)							rs Restric	tive Fav	ours Libe	

Figure 132: Pulmonary oedema- children (critical care)

	Restric	tive	Liber	al		Risk Ratio		R	isk Rat	io	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	:1	M-H, I	Fixed, 9	95% CI	
Lacroix 2007	0	320	5	317	100.0%	0.09 [0.01, 1.62]	<b>←</b>		+		
Total (95% CI)		320		317	100.0%	0.09 [0.01, 1.62]					
Total events	0		5								
Heterogeneity: Not app	olicable						-		+	10	100
Test for overall effect:	Z = 1.63 (I	P = 0.10	0)				0.01 Favours	0.1 s Restricti	ve Fa	10 vours Lib	100 eral

Figure 133: Nosocomial infections- children (critical care)

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% (	CI M-H, Fixed, 95% CI
Lacroix 2007	65	320	79	317	100.0%	0.82 [0.61, 1.09	1
Total (95% CI)		320		317	100.0%	0.82 [0.61, 1.09]	•
Total events	65		79				
Heterogeneity: Not app	olicable						
Test for overall effect:	Z = 1.39 (I	P = 0.17	7)				0.01 0.1 1 10 100 Favours Restrictive Favours Liberal

# **K.5** Platelets

### K.5.1 Low dose versus medium dose

Figure 134: Number of patients with bleeding (WHO grade 2 and above)



Figure 135: All-cause mortality at 30 days

	Low do	se	Medium	dose		Risk Ratio	Risk Ratio
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2009	1	58	1	61	19.7%	1.05 [0.07, 16.43]	
r 2010	9	417	4	423	80.3%	2.28 [0.71, 7.35]	<del>                                      </del>
uth 2004	0	56	0	55		Not estimable	
95% CI)		531		539	100.0%	2.04 [0.70, 5.93]	
vents	10		5				
geneity: Chi <sup>2</sup> = 0 r overall effect:	•	•	, .	0%			0.01 0.1 1 10 100  Favours low dose Favours medium dose

Figure 136: Infections

	Low do	ose	Medium	dose		Risk Ratio		Risk	Ratio	
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% CI	
r 2010	5	417	5	423	100.0%	1.01 [0.30, 3.48]				
95% CI)		417		423	100.0%	1.01 [0.30, 3.48]		<b>■</b>		
vents	5		5							
geneity: Not app r overall effect: 2		P = 0.9	8)				0.01 Fav	0.1 ours low dose	1 10 Favours m	

Figure 137: Serious adverse event (any)

	Low do	ose	Medium	dose		Risk Ratio		Ri	isk Ratio		
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, I	Fixed, 95	% CI	
r 2010	35	417	27	423	100.0%	1.31 [0.81, 2.13]					
95% CI)		417		423	100.0%	1.31 [0.81, 2.13]			•		
vents	35		27								
geneity: Not approverall effect:		P = 0.2	7)				0.01 Fave	0.1	1 se Favo	10 ours mediu	100 um dose

# K.5.2 High dose versus medium dose

Figure 138: Number of patients with bleeding (WHO grade 2 and above)



Figure 139: All-cause mortality at 30 days

	High d	ose	Medium	dose		Risk Ratio		1	Risk Ratio		
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	I	М-Н	, Fixed, 95	% CI	
pe 2004	0	0	0	0		Not estimable					
r 2010	7	432	4	423	100.0%	1.71 [0.51, 5.81]					
95% CI)		432		423	100.0%	1.71 [0.51, 5.81]				<b>-</b>	
vents	7		4								
geneity: Not app	olicable						0.04			10	400
r overall effect:	Z = 0.86 (	P = 0.39	9)				0.01	0.1	1_	10	100
	(-		-,				Favo	ours high d	ose Favo	urs mediu	ım dose

Figure 140: Infections

	High d	ose	Medium	dose		Risk Ratio		Ri	sk Ratio		
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	ı	M-H, F	ixed, 95%	6 CI	
r 2010	7	432	5	423	100.0%	1.37 [0.44, 4.29]		_		-	
95% CI)		432		423	100.0%	1.37 [0.44, 4.29]		-		-	
vents	7		5								
geneity: Not app	olicable						0.01	0.1	1	10	100
r overall effect: 2	Z = 0.54 (1	P = 0.5	9)					ours high dos	ι e Favoι	ırs medit	

Figure 141: Serious adverse events (any)

	High d	ose	Medium	dose		Risk Ratio		Risk	Ratio		
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	l	M-H, Fix	ed, 95% CI		
r 2010	36	432	27	423	100.0%	1.31 [0.81, 2.11]					
95% CI)		432		423	100.0%	1.31 [0.81, 2.11]			<b>•</b>		
vents	36		27								
geneity: Not approver overall effect: 2		P = 0.2	8)				0.01 Favo	0.1 ours high dose		<del> </del>  0 nediun	100 n dose

# K.5.3 Low dose versus high dose

Figure 142: Number of patients with bleeding (WHO grade 2 and above)

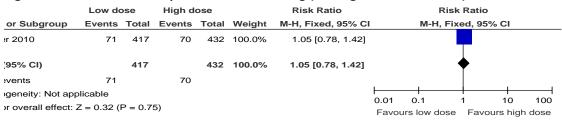


Figure 143: All-cause mortality at 30 days

	Low do	ose	High d	ose		Risk Ratio					
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	l	M-H, F	ixed, 95	% CI	
er 2010	9	417	7	432	100.0%	1.33 [0.50, 3.54]					
(95% CI)		417		432	100.0%	1.33 [0.50, 3.54]					
events	9		7								
ngeneity: Not apport overall effect:		P = 0.5	7)				0.01 Favor	0.1 urs low dos	1 se Favo	10 ours high	100 n dose

Figure 144: Infections

	Low do	ose	High d	ose		Risk Ratio		Ri	sk Ratio	,	
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, F	ixed, 95	% CI	
er 2010	5	417	7	432	100.0%	0.74 [0.24, 2.31]					
(95% CI)		417		432	100.0%	0.74 [0.24, 2.31]		<b>⋖</b>			
events	5		7								
geneity: Not app or overall effect: 2		P = 0.6	0)				0.01 Favou	0.1 Irs low dos	1 e Favo	10 ours high	100 n dose

Figure 145: Serious adverse events (any)

	Low do	ose	High d	ose		Risk Ratio		Risk Ratio			
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fix	(ed, 95%	CI	
r 2010	35	417	36	432	100.0%	1.01 [0.65, 1.57]		-	-		
(95% CI)		417		432	100.0%	1.01 [0.65, 1.57]		•	lack		
vents	35		36								
rigeneity: Not applicable or overall effect: Z = 0.03 (P = 0.97)							0.01 Favo	0.1 ours low dose	1 Favou	10 irs high	100 dose

# K.5.4 Platelet thresholds and Targets

Prophylactic transfusion versus no prophylactic transfusion - adults who are haematology patients (non-bleeding patients)

Figure 146: Number of patients with bleeding events (WHO grade 2 or higher)

	Prophylactic trans	sfusion	No prophylactic trans		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Stanworth 2013	128	299	151	301	54.4%	0.85 [0.72, 1.01]	
Wandt 2012	65	194	127	197	45.6%	0.52 [0.42, 0.65]	
Total (95% CI)		493		498	100.0%	0.70 [0.61, 0.80]	<b>•</b>
Total events	193		278				
Heterogeneity: Chi²=	11.85, $df = 1$ (P = $0.1$	0006); l²=	92%				0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z = 5.12 (P < 0.0000)	01)					Prophylactic transfusion No prophylactic transfusion

Figure 147: Number of patients with major bleeding events (WHO grade 3 or 4)

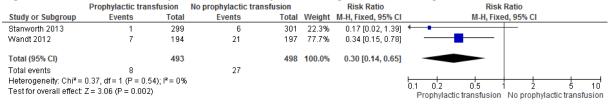


Figure 148: Serious adverse events (including sepsis and respiratory deterioration)

	Prophylactic trans	sfusion	No prophylactic tran	sfusion		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Stanworth 2013	20	298	18	300	100.0%	1.12 [0.60, 2.07]	
Total (95% CI)		298		300	100.0%	1.12 [0.60, 2.07]	
Total events	20		18				
Heterogeneity: Not ap Test for overall effect:							0.1 0.2 0.5 1 2 5 10 Prophylactic transfusion No prophylactic transfusion

Figure 149: Transfusion related serious adverse event (urticarial and angioedema)

	Prophylactic transfusion		No prophylactic trans	sfusion		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI	
Stanworth 2013	1	299	0	301	100.0%	3.02 [0.12, 73.84]			
Total (95% CI)		299		301	100.0%	3.02 [0.12, 73.84]			
Total events	1		0						
Heterogeneity: Not ap Test for overall effect:							0.01 0.1 Prophylactic transfusion	1 10 No prophylactic	100 transfusion

Figure 150: Number of patients needing platelet transfusion

0				0 1			
	Prophylactic tran	sfusion	No prophylactic tran	efusion		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Stanworth 2013	266	299	176	301	100.0%	1.52 [1.37, 1.69]	
Total (95% CI)		299		301	100.0%	1.52 [1.37, 1.69]	•
Total events	266		176				
Heterogeneity: Not ap	•	043					0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z= 1.91 (P < 0.000	01)					Prophylactic transfusion No prophylactic transfusion

Figure 151: Number of units (platelets) transfused per patient

	Prophylacti	ic transfu	ision				Mean Difference Mean Di			ifference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI		
Stanworth 2013	3.2	3.6	299	1.9	3.3	301	100.0%	1.30 [0.75, 1.85]					
Total (95% CI)			299			301	100.0%	1.30 [0.75, 1.85]			•		
Heterogeneity: Not ap Test for overall effect:		0.00001)							-10 Prophylad	-5 tic transfusion	0 No prophy	5 lactic trar	10 nsfusion

Figure 152: Mortality (all cause)

	Prophylactic trans	sfusion	No prophylactic trans	sfusion		Risk Ratio	Risl	( Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fix	ed, 95% CI		
Wandt 2012	5	194	7	197	100.0%	0.73 [0.23, 2.25]				
Total (95% CI)		194		197	100.0%	0.73 [0.23, 2.25]				
Total events	5		7							
Heterogeneity: Not ap Test for overall effect:	•						0.1 0.2 0.5 Prophylactic transfusion	1 2 No prophyla	5 actic trans	10 sfusion

Figure 153: Side effects of transfusion (not specified)

	Prophylactic trans	sfusion	No prophylactic trans	sfusion		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Wandt 2012	25	194	27	197	100.0%	0.94 [0.57, 1.56]	_ <del>-</del>
Total (95% CI)		194		197	100.0%	0.94 [0.57, 1.56]	-
Total events Heterogeneity: Not ap Test for overall effect:	•		27				0.1 0.2 0.5 1 2 5 10 Prophylactic transfusion No prophylactic transfusion

# K.5.5 Prophylactic transfusion versus no prophylactic transfusion - children who are haematology patients (non-bleeding patients)

Figure 154: Number of patients with major bleeding events (WHO grade 3 or 4)

	Prophyl	actic	No prophylactic tran	nsfusion		Risk Ratio		Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% Cl	1		
Murphy 1982	10	35	11	21	100.0%	0.55 [0.28, 1.06]			-			
Total (95% CI)		35		21	100.0%	0.55 [0.28, 1.06]			-			
Total events	10		11									
Heterogeneity: Not ap Test for overall effect:		P = 0.07	7)			F	.1 0.		Fougure	No prop	5 bulgatia	10
			*					avours Prophylactic	ravours	IND DEOD!	nviactic	transit

Figure 155: Mortality (all cause) 3 years

	Prophyl	actic	No prophylactic tran	sfusion		Risk Ratio		R	sk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		М-Н, Г	ixed, 95% CI		
Murphy 1982	12	35	7	21	100.0%	1.03 [0.48, 2.20]					
Total (95% CI)		35		21	100.0%	1.03 [0.48, 2.20]					
Total events	12		7								
Heterogeneity: Not ap	oplicable						0.1	0.2 0.5	+ +	<del></del>	10
Test for overall effect:	Z = 0.07 (	P = 0.94	4)				0.1	Favours Prophylad	tic Favours No	prophylactic	

Figure 156: Mortality from bleeding (3 years)

0		•••••	,				
	Prophyla	actic	No prophylactic trans	sfusion		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	I M-H, Fixed, 95% CI
Murphy 1982	1	35	2	21	100.0%	0.30 [0.03, 3.11]	1
Total (95% CI)		35		21	100.0%	0.30 [0.03, 3.11]	
Total events	1		2				
Heterogeneity: Not ap	plicable						01 02 05 1 2 5 10
Test for overall effect:	Z = 1.01 (	P = 0.31	)				Favours Prophylactic Favours No prophylactic transfu

# K.5.6 Low threshold versus high threshold - adults who are haematology patients (nonbleeding patients)

Figure 157: Mortality (all cause)

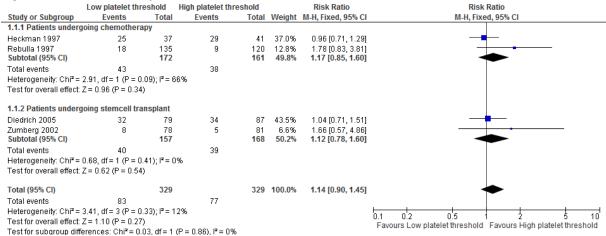
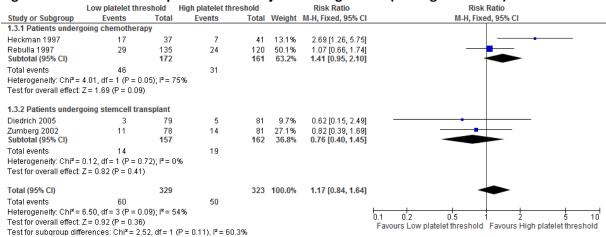


Figure 158: Number of patients with bleeding events (WHO grade 2 or higher)

	Low platelet thr	eshold	High platelet the	reshold		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI		
Diedrich 2005	14	79	13	0		Not estimable			_		
Zumberg 2002	74	78	79	81	100.0%	0.97 [0.91, 1.04]					
Total (95% CI)		157		81	100.0%	0.97 [0.91, 1.04]		•			
Total events	88		92								
Heterogeneity: Not ap	plicable						0.1 0.2	0.5 1	<del></del>	<u> </u>	10
Test for overall effect:	Z = 0.87 (P = 0.38)	)					Favours Low platele		Favours Hig	b platelet thr	

Figure 159: Number of patients with major bleeding events (WHO grade 3 or 4)





	Low platelet the	eshold	High platelet th	reshold		Risk Ratio		Risk	Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed	d, 95% CI			
Diedrich 2005	31	79	30	87	100.0%	1.14 [0.76, 1.70]		_				
Total (95% CI)		79		87	100.0%	1.14 [0.76, 1.70]			<b>-</b>			
Total events	31		30									
Heterogeneity: Not ap Test for overall effect:	•	3)					0.1 0.2 Favours Low plat	0.5 1 elet threshold	2 Favours H	ligh platelet	threst	10 hold

Figure 161: Adverse events

	Low platelet thre	eshold	High platelet th	reshold		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI	
Heckman 1997	0	37	8	41	100.0%	0.07 [0.00, 1.09]	+	†	
Total (95% CI)		37		41	100.0%	0.07 [0.00, 1.09]		-	
Total events	0		8						
Heterogeneity: Not ap Test for overall effect:	•	)					0.01 0.1 Favours Low platelet threshold	1 10 Favours High plat	100 elet threshold

Figure 162: Number of units (platelets) transfused per patient

•				•••		•			
	Low plate	elet thres	hold	High pla	telet thres	shold		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.6.1 Patients underg	oing chemo	otherapy							
Heckman 1997	8.4	5.3	37	11.4	7.1	41	15.0%	-3.00 [-5.76, -0.24]	<del></del>
Rebulla 1997	7.05	4.56	135	8.97	5.17	120	79.2%	-1.92 [-3.12, -0.72]	<b></b>
Subtotal (95% CI)			172			161	94.3%	-2.09 [-3.20, -0.99]	•
Heterogeneity: Chi <sup>2</sup> = I	0.49, df = 1	(P = 0.48)	$); I^2 = 0\%$	)					
Test for overall effect: 2	Z = 3.72 (P :	= 0.0002)	1						
1.6.2 Patients underg	oing stemo	ell trans	plant						
Zumberg 2002	10.4	17	78	10.2	11	81	5.7%	0.20 [-4.27, 4.67]	
Subtotal (95% CI)			78			81	5.7%	0.20 [-4.27, 4.67]	
Heterogeneity: Not app	plicable								
Test for overall effect:	Z= 0.09 (P:	= 0.93)							
Total (95% CI)			250			242	100.0%	-1.96 [-3.03, -0.89]	•
Heterogeneity: Chi <sup>2</sup> = 1	1.45, df = 2	(P = 0.49)	); I <sup>2</sup> = 0%	)					
Test for overall effect: 2	Z = 3.59 (P = 3.59)	0.0003)							-10 -5 0 5 10
Test for subgroup diffe	erences: Ch	i²= 0.95	df = 1 / E	= 0.33) 13	= 0%				Favours Low platelet threshold Favours High platelet threshold

# K.6 Fresh frozen plasma

# K.6.1 Therapeutic FFP transfusion versus no FFP transfusion

Figure 163: Mortality (all-cause)

	FFP transf	usion	No FFP trans	fusion		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% C	1	
Doussau 2014	88	562	21	405	100.0%	3.02 [1.91, 4.78]					
Total (95% CI)		562		405	100.0%	3.02 [1.91, 4.78]			•		
Total events	88		21								
Heterogeneity: Not ap Test for overall effect:	•	< 0.0000	01)				0.01	0.1 Favours FFP	1 Favours	10 no FFP	100

Figure 164: Adverse events

	FFP transf	usion	No FFP trans	fusion		Risk Ratio		Risk Ra	tio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed,	95% CI	
Doussau 2014	4	562	0	405	100.0%	6.49 [0.35, 120.21]		-		
Total (95% CI)		562		405	100.0%	6.49 [0.35, 120.21]				
Total events	4		0							
Heterogeneity: Not ap Test for overall effect	•	= 0.21)					0.01	0.1 1	10 avours No FFP	100

# **K.7** Prothrombin complex concentrates

# K.7.1 Low dose (25 IU/kg) versus high dose (40 IU/kg)

Figure 165: Mortality

	Low d	ose	High d	ose		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	d, 95%	CI	
Kerebel 2013	4	29	6	30	100.0%	0.69 [0.22, 2.19]			_		
Total (95% CI)		29		30	100.0%	0.69 [0.22, 2.19]		-	-		
Total events	4		6								
Heterogeneity: Not as	plicable						0.01	0.1	_	10	100
Test for overall effect	Z = 0.63	(P = 0.5)	53)				17.55.0	urs low dose	Favour	s high	

Figure 166: Patients with at least one adverse event

	Low do	ose	High de	ose		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Kerebel 2013	24	29	25	30	100.0%	0.99 [0.79, 1.25]	
Total (95% CI)		29		30	100.0%	0.99 [0.79, 1.25]	<b>+</b>
Total events	24		25				
Heterogeneity: Not ap Test for overall effect:	•	(P = 0.9	95)				0.01 0.1 1 10 100 Favours low dose Favours high dose

Figure 167: Patients with at least one serious adverse event

	Low d	ose	High de	ose		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Kerebel 2013	11	29	12	30	100.0%	0.95 [0.50, 1.80]	-
Total (95% CI)		29		30	100.0%	0.95 [0.50, 1.80]	<b>*</b>
Total events	11		12				
Heterogeneity: Not ap Test for overall effect:	•	(P = 0.8	37)				0.01 0.1 1 10 100 Favours low dose Favours high dose

Figure 168: Patients with at least one thrombotic event

	Low do	ose	High d	ose		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Kerebel 2013	2	29	2	29	100.0%	1.00 [0.15, 6.63]	
Total (95% CI)		29		29	100.0%	1.00 [0.15, 6.63]	
Total events	2		2				
Heterogeneity: Not ap Test for overall effect:	•	(P = 1.0	00)				0.01 0.1 1 10 100 Favours low dose Favours high dose

Figure 169: Target INR less than 1.2 achieved

	Low d	ose	High d	ose		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	d, 95% CI	
Kerebel 2013	13	29	23	30	100.0%	0.58 [0.37, 0.92]	-		
Total (95% CI)		29		30	100.0%	0.58 [0.37, 0.92]	•		
Total events	13		23						
Heterogeneity: Not ap Test for overall effect:	•	(P = 0.0	12)				0.01 0.1 1 Favours high dose	10 Favours low (	100 dose

# K.7.2 Low fixed dose (1040 IU FIX) versus variable dose

Figure 170: Target INR reached

0									
	fixed d	ose	variable	dose		Risk Ratio	Ris	k Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fi	xed, 95% CI	
Khorsand 2012	88	101	124	139	100.0%	0.98 [0.89, 1.07]			
Total (95% CI)		101		139	100.0%	0.98 [0.89, 1.07]		•	
Total events	88		124						
Heterogeneity: Not	applicable						0.01 0.1	1 10	100
Test for overall effe	ct: Z = 0.49 i	(P = 0.8)	i3)				Favours fixed dos	e Favours variab	

Figure 171: Deep Vein Thrombosis (DVT)

	fixed d	ose	variable	dose		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Khorsand 2012	0	101	1	139	100.0%	0.46 [0.02, 11.12]	
Total (95% CI)		101		139	100.0%	0.46 [0.02, 11.12]	
Total events	0		1				
Heterogeneity: Not ap Test for overall effect:	•	(P = 0.6	i3)				0.01 0.1 1 10 100 Favours fixed dose Favours variable dose

Figure 172: Mortality

	fixed d	ose	variable	dose		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI	
Khorsand 2012	14	101	36	139	100.0%	0.54 [0.31, 0.94]		-		
Total (95% CI)		101		139	100.0%	0.54 [0.31, 0.94]		•		
Total events	14		36							
Heterogeneity: Not ap Test for overall effect:	•	(P = 0.0	13)				0.01 Fav	0.1 vours fixed dose	1 10 Favours va	100 dose

# K.7.3 Standard dose (500 IU FIX/7 IU FIX/kg) versus individualised dosing regimen

Figure 173: Target INR at 15 minutes after the first dosage of PCC

	standard	dose	Individualised	d dose		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI	
Vannart 2006	20	47	41	46	100.0%	0.48 [0.34, 0.68]	-		
Total (95% CI)		47		46	100.0%	0.48 [0.34, 0.68]	•		
Total events	20		41						
Heterogeneity: Not ap Test for overall effect	•	< 0.000	1)				0.01 0.1 Favours individualised	1 10 Favours stand	100 dard dose

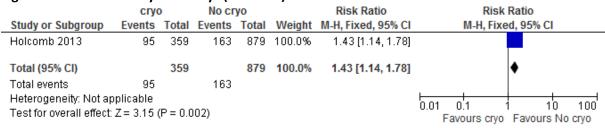
Figure 174: Serious adverse events

	standard	dose	Individualised	dose		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Vannart 2006	2	47	2	47	100.0%	1.00 [0.15, 6.81]	
Total (95% CI)		47		47	100.0%	1.00 [0.15, 6.81]	
Total events	2		2				
Heterogeneity: Not ap Test for overall effect:		= 1.00)					0.01 0.1 10 100 Favours standard dose Favours individualised

# K.8 Cryoprecipitate

# K.8.1 Cryoprecipitate versus no cryoprecipitate

Figure 175: Mortality at 30 days (all-cause)



# Appendix L: Network meta-analysis of alternatives to blood transfusion in surgical patients

# L.1 Introduction

The results of conventional meta-analyses of direct evidence alone (as presented in the GRADE profiles in chapter 6 and forest plots in appendix K.2) does not help inform which intervention is most effective as an alternative to blood transfusion in surgical patients. The challenge of interpretation has arisen for two reasons:

- In isolation, each pair-wise comparison does not inform the choice among the different treatments; in addition direct evidence is not available for some pair-wise comparisons in a randomised controlled trial (for example, ICS vs. PCS).
- There are frequently multiple overlapping comparisons (for example, ICS+TXA vs. TXA, ICS+PCS+TXA vs. TXA and ICS+PCS+TXA vs. ICS+PCS), that could potentially give inconsistent estimates of effect.

To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was performed. This type of analysis allows for the synthesis of data from direct and indirect comparisons without breaking randomisation and allows for the ranking of different interventions. In this case, in order of efficacy, the outcomes were defined as:

- the number of people who are transfused with allogeneic blood
- · the units of allogeneic blood transfused
- length of stay in hospital

The analysis also provided estimates of effect (with 95% credible intervals) for each intervention compared to one another and compared to a single baseline risk (in this case the baseline treatment was standard treatment). These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. Furthermore, these estimates were used to parameterise treatment effectiveness in the de novo cost-effectiveness modelling presented in appendix M.

Conventional fixed effects meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same effect on people in trials of intervention A compared to intervention B as it does for people in trials of intervention A versus intervention C, and so on. Thus, in a random effects network meta-analysis, the assumption is that intervention A has the same effect distribution across trials of A versus B, A versus C and so on.

This specific method is usually referred to as mixed-treatment comparisons analysis but the term network meta-analysis will be used to refer generically to this kind of analysis. It was agreed that

this would be best since the term "network" better describes the data structure, whereas "mixed treatments" could easily be misinterpreted as referring to combinations of treatments.

# L.2 Methods

# L.2.1 Study selection and data collection

To estimate the relative risks, an NMA was performed that simultaneously used all the relevant RCT evidence from the clinical evidence review. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence, nor does it make any assumptions about adding the effects of different interventions. The effectiveness of a particular treatment strategy combination will be derived only from randomised controlled trials that had that particular combination in a trial arm.

From the outset, efforts were made to minimise any clinical or methodological heterogeneity by focusing the analysis on RCTs with comparable routes of administration of treatments, identifying equivalent outcomes and including only RCTs on cell salvage that were conducted after 2003 as this was defining watershed in transfusion practice (also see rationale in section 6.2.3, chapter 6). All of the dosages of drugs in the included RCTs were within the therapeutic range as indicated by the BNF. In consultation with the GDG, it was agreed that an NMA would be performed for alternatives to blood transfusion including combinations of different types of cell salvage and/or tranexamic acid. The evidence on these interventions included multiple comparisons and an NMA would allow the synthesis of the evidence in a more comprehensive way.

As such, five networks of evidence were identified, defined by outcome measure. Three networks were in the high risk group and two were in the moderate risk group (For definitions of risk groups see section 6, Chapter 6.4.2). The networks were as follows:

# High risk group:

Network 1: Number of people receiving allogeneic transfusions

Network 2: Units of allogeneic blood transfused

Network 3: Length of stay in hospital

## Moderate risk group:

Network 4: Number of people receiving allogeneic transfusions

Network 5: Units of allogeneic blood transfused

### L.2.2 Outcome measures

The NMA evidence reviews for interventions considered three clinical efficacy outcomes identified from the clinical evidence review; number of people receiving allogeneic transfusions, units of allogeneic blood transfused and length of stay in hospital. Other outcomes were not considered for the NMA as they were infrequently reported across the studies. The GDG considered the number of people receiving allogeneic transfusions and units of allogeneic blood transfused to be the most important clinical outcomes for testing effectiveness of alternatives to reduce blood transfusion requirements.

# L.2.3 Comparability of interventions

The interventions compared in the model were those found in the randomised controlled trials and included in the clinical evidence review already presented in chapter 6 of the full guideline. If an intervention was evaluated in a study that met the inclusion criteria for the network (that is if it reported at least one of the outcomes of interest and matched the inclusion criteria for the meta-analysis) then it was included in the network meta-analysis, otherwise it was excluded.

The treatments included in each network are shown in **Table 1**.

Table 1: Treatments included in network meta-analysis

High risk group			Moderate risk group	
Network 1: Number of people receiving allogeneic transfusions	Network 2: Units of allogeneic blood transfused	Network 3: Length of stay in hospital	Network 4: Number of people receiving allogeneic transfusions	Network 5: Units of allogeneic blood transfused
Standard treatment	Standard treatment	Standard treatment	Standard treatment	Standard treatment
TXA	ICS	TXA	TXA	TXA
PCS	TXA	ICS	PCS	PCS
ICS	PCS	PCS	ICS	ICS+PCS
ICS+PCS	ICS+TXA	ICS+PCS	ICS+PCS	
ICS+TXA	-	ICS+TXA	ICS+PCS+TXA	
ICS+PCS+TXA	-	-	PCS+TXA	
-	_	-	ICS+TXA	

Abbreviations: TXA-Tranexamic acid, PCS-Post-operative cell salvage, ICS-Intra-operative cell salvage

The details of these interventions can be found in the clinical evidence review in chapter 6 of the full guideline and evidence tables in section H.2, appendix H.

# L.2.4 Baseline risk

The baseline risk is defined here as the risk of achieving the outcome of interest in the standard treatment group. This figure is useful because it allows the conversion of the results of the NMA from odds ratios to relative risks.

Baseline odds were derived by the logistic regression in WinBUGS. This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale, and also ensures that the uncertainty in the estimation of baseline and relative effects is accounted for in the model. This method produced baseline odds [mean (SD)] as follows:

- -0.06809 (1.188) for number of patients receiving allogeneic transfusions in the high risk group
- -0.5185 (1.444) for number of patients receiving allogeneic transfusions in the moderate risk group

A baseline risk model of mortality was conducted in both risk groups to estimate baseline mortality for the economic model. The method produced baseline relative risk [mean (SD)] of

0.0343 (0.01135) in the high risk group. In the moderate risk group, this was 0.00162 (0.002384). For details of data informing these models, please refer to the full cost- effectiveness analysis (section M.2.3.3, Appendix M).

# L.2.5 Statistical analysis

A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS. We adapted a three-arm random effects model template for the networks, from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). This model accounts for the correlation between study level effects induced by multi-arm trials.

In order to be included in the analysis, a fundamental requirement is that each treatment is connected directly or indirectly to every other intervention in the network. For each outcome subgroup, a diagram of the evidence network is presented in section L.3.

The model used was a random effects logistic regression model, with parameters estimated by Markov chain Monte Carlo simulation. As it was a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. These were estimated from the baseline models for the dichotomous outcomes using the following equations.

- Predictive probability of response (MeanA) = mean of mu.new
- Precision (PrecA)=1/(standard deviation of mu.new)<sup>2</sup>

A non-informative prior distribution was used to maximise the weighting given to the data for continuous outcomes. These priors were normally distributed with a mean of 0 and standard deviation of 10,000.

For the analyses, a series of 100,000 burn-in simulations were run to allow convergence and then a further 100,000 simulations were run to produce the outputs. For the baseline analyses, a series of 50,000 burn-in simulations were run to allow convergence and then a further 50,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

The goodness of fit of the model was tested by calculating the residual deviance. If the residual deviance is close to the number of unconstrained data points (the number of trial arms in the analysis) then the model is explaining the data well.

The results, in terms of relative risk, of pair-wise meta-analyses are presented in the clinical evidence review (Chapter 6).

The aim of the NMA was to calculate treatment specific log odds ratios and relative risks for response to be consistent with the comparative effectiveness results presented elsewhere in the clinical evidence review and for ease of interpretation. Let BO,  $\widetilde{\theta}$ ,  $\widetilde{OR}$  and p denote the baseline odds, treatment specific odds, treatment specific log odds ratio and absolute probability respectively. Then:

$$\widetilde{\boldsymbol{\theta}} = Ln(\widetilde{\boldsymbol{OR}}) + Ln(\boldsymbol{BO})$$

And:

$$p = \frac{e^{\widetilde{\theta}}}{1 + e^{\widetilde{\theta}}}$$

Once the treatment specific probabilities for response were calculated, these were divided by the baseline probability  $(p_h)$  to get treatment specific relative risks  $(rr_h)$ :

$$p_b = rac{e^{BO}}{1 + e^{BO}}$$
  $rr_b = rac{p}{p_b}$ 

This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale, and also ensures that the uncertainty in the estimation of both baseline and relative effects is accounted for in the model.

The overall ranking of interventions according to their relative risk compared to control group and counting the proportion of simulations of the Markov chain in which each intervention had the highest relative risk.

Due to the skewness of the data, the NMA relative risks and rank results are reported as medians rather than means (as in the direct comparisons) to give a more accurate representation of the 'most likely' value.

A key assumption behind NMA is that the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another. Discrepancies between direct and indirect estimates of effect may result from several possible causes. First, there is chance and if this is the case then the network meta-analysis results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. Second, there could be differences between the trials included in terms of their clinical or methodological characteristics. Differences that could lead to inconsistency include:

- Different populations
- Different interventions
- Different routes of administration

This heterogeneity is a problem for network meta-analysis but may be dealt with by subgroup analysis, meta-regression or by carefully defining inclusion criteria. In this analysis, sub-group analyses based on various factors such as haemoglobin status at baseline, different haemoglobin thresholds for blood transfusion and different routes of administration was undertaken to account for heterogeneity in the pair wise meta-analyses. Inconsistency in the network, caused by heterogeneity, was assessed subjectively by comparing the odds ratios for binary outcomes and mean differences for continuous outcomes from the direct evidence (from pair-wise meta-analysis) with the corresponding effects estimated from the combined direct and indirect evidence (from NMA). We assumed the evidence to be inconsistent where the odds ratio or mean difference from the NMA did not fit within the confidence interval of the odds ratio or mean difference from the direct comparison. We further tested for inconsistency by developing inconsistency models for networks of binary outcomes (number of patients transfused). We assumed the evidence to be consistent when the difference in deviance information criterion

(DiC) values between the consistency and the inconsistency models was less then 3-5. No inconsistency was identified.

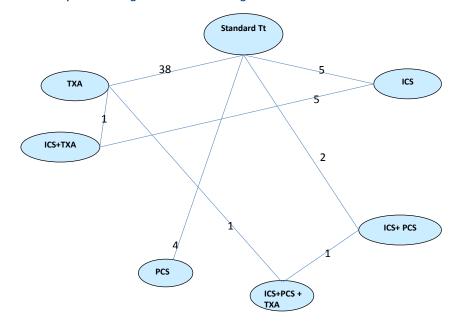
# L.3 Results

A total of 129 studies from the original evidence review met the inclusion criteria for at least one network. Figure 1 – Figure 4 show the four networks created by eligible comparisons for each NMA. The number on the line linking two treatments indicates the number of studies included that assessed that direct comparison.

## L.3.1 NMA models

Figure 176: Adults-High risk group: Network for number of patients receiving allogeneic transfusions

Number exposed to allogeneic transfusions-High risk



TXA

16

ICS+TXA

2

PCS

Figure 177: Adults-High risk group: Network for units of allogeneic blood transfused
Units of allogeneic blood transfused- High risk

Figure 178: Adults-High risk group: Length of stay in hospital

Length of stay in hospital-High risk

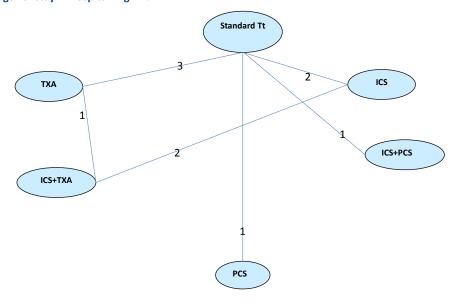


Figure 179: Adults-Moderate risk group: Network for number of patients receiving allogeneic transfusions

Number exposed to allogeneic transfusions-Moderate risk

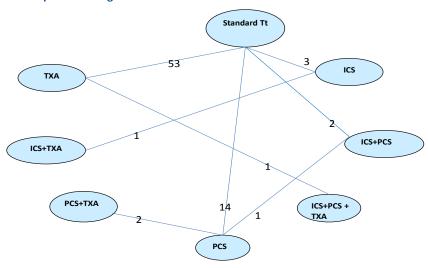
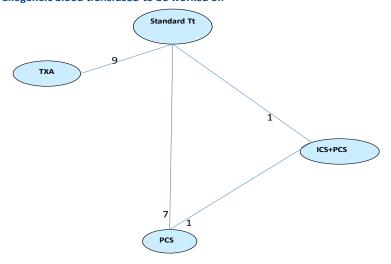


Figure 180: Adults-Moderate risk group: Network for units of allogeneic blood transfused
Units of allogeneic blood transfused-to be worked on



## L.3.2 Trial data

# L.3.2.1 High risk group

Trial data from the 56 studies included in the NMA for number of adult patients receiving allogeneic transfusions are shown in Table 2. The trial data from the 23 studies included in the NMA for number of units of allogeneic blood transfused are shown in Table 3. The trial data from the 10 studies included in the NMA for length of stay in hospital are shown in Table 4.

Table 2: Study data for number of patients receiving allogeneic transfusions

Study	Treatment	Comparator	Treatme	nt	Compara	or
			Events	N	Events	N
Mercer2004 <sup>85</sup>	Standard treatment	ICS	31	41	21	40
Murphy2005 <sup>88</sup>	Standard treatment	ICS	7	31	4	30
Damgard2006 <sup>35</sup>	Standard treatment	ICS	21	29	17	30
Aghdaii 2012 <sup>2</sup>	Standard treatment	ICS	8	25	7	25
Naumenko2003 <sup>90</sup>	Standard treatment	PCS	1	33	2	32
Zhao2003 <sup>137</sup>	Standard treatment	PCS	30	30	19	30
Pleym2005 <sup>96</sup>	Standard treatment	PCS	3	24	1	23
Sirvinkas2007 <sup>110</sup>	Standard treatment	PCS	19	49	6	41
Murphy2004 <sup>87</sup>	Standard treatment	ICS+PCS	64	102	41	98
Wiefferink2007 <sup>127</sup>	Standard treatment	ICS+PCS	10	15	8	15
Casati2004 <sup>24</sup>	ICS	ICS+TXA	13	50	9	52
Diprose2005 <sup>38</sup>	ICS	ICS+TXA	27	60	20	60
Jiminez2007 <sup>64</sup>	ICS	ICS+TXA	19	26	9	24
Kuitunen2005 <sup>75</sup>	ICS	ICS+TXA	12	20	5	20
Later2009 <sup>76</sup>	ICS	ICS+TXA	73	103	57	99
Reyes2011 <sup>100</sup>	TXA	ICS+TXA	13	29	12	24
Murphy2006 <sup>89</sup>	ICS+PCS	ICS+PCS+TXA	14	50	13	50
Klein2008 <sup>73</sup>	TXA	ICS+PCS+TXA	33	111	31	102
Ahn2012 <sup>4</sup>	Standard treatment	TXA	27	38	20	38
Andreasen2004 <sup>10</sup>	Standard treatment	TXA	5	17	6	20
Baric2007 <sup>14</sup>	Standard	TXA	51	96	51	97

Study	Treatment	Comparator	Treatmen	nt	Comparato	r
	treatment					
Dellamore2012 <sup>37</sup>	Standard treatment	TXA	10	43	8	44
Ghaffari2012 <sup>47</sup>	Standard treatment	TXA	23	50	15	50
Jares2003 <sup>63</sup>	Standard treatment	TXA	7	25	2	22
Karski2005 <sup>67</sup>	Standard treatment	TXA	41	165	24	147
Mansour2004 <sup>82</sup>	Standard treatment	TXA	12	20	7	20
Mehraein2007 <sup>83</sup>	Standard treatment	TXA	8	33	5	33
Nouraei2013 <sup>93</sup>	Standard treatment	TXA	21	40	15	40
Pleym2003 <sup>97</sup>	Standard treatment	TXA	8	39	7	40
Santos2006 <sup>105</sup>	Standard treatment	TXA	12	31	7	29
Shi2013 <sup>108</sup>	Standard treatment	TXA	221	278	166	274
Shi2013a <sup>109</sup>	Standard treatment	TXA	54	59	42	58
Taghaddomi2009 <sup>116</sup>	Standard treatment	TXA	27	50	8	50
Vanek2005 <sup>122</sup>	Standard treatment	TXA	6	30	3	32
Wang2012 <sup>125</sup>	Standard treatment	TXA	54	115	37	116
Wei2006 <sup>126</sup>	Standard treatment	TXA	8	40	3	36
Wu2006 <sup>130</sup>	Standard treatment	TXA	17	108	0	106
Armellin2001 <sup>12</sup>	Standard treatment	TXA	63	140	35	143
Blauhut1994 <sup>19</sup>	Standard treatment	TXA	9	14	7	15
Casati2001 <sup>23</sup>	Standard treatment	TXA	4	20	2	20
Coffey1995 <sup>30</sup>	Standard treatment	TXA	8	14	9	16
Corbeau1995 <sup>31</sup>	Standard treatment	TXA	12	20	15	41
Dalmau2000 <sup>34</sup>	Standard treatment	TXA	37	40	29	42

Study	Treatment	Comparator	Treatme	nt	Comparato	r
Debonis2000 <sup>36</sup>	Standard treatment	TXA	4	20	3	20
Fawzy2009 <sup>44</sup>	Standard treatment	TXA	13	19	14	19
Hardy1998 <sup>52</sup>	Standard treatment	TXA	27	44	28	42
Horrow1991 <sup>56</sup>	Standard treatment	TXA	16	44	12	37
Katoh1997 <sup>68</sup>	Standard treatment	TXA	10	31	7	62
Katsaros1996 <sup>69</sup>	Standard treatment	TXA	27	106	11	104
Krohn2003 <sup>74</sup>	Standard treatment	TXA	9	14	2	16
Menichetti1996 <sup>84</sup>	Standard treatment	TXA	18	24	12	24
Speekenbrink1995 <sup>115</sup>	Standard treatment	TXA	11	15	13	15
Esfandiari2013 <sup>42</sup>	Standard treatment	TXA	43	75	22	75
Lundin2014 <sup>79</sup>	Standard treatment	TXA	22	50	15	50
Ghavidel 2014 <sup>5</sup>	Standard treatment	TXA	74	100	60	100
Vermeijden2015 <sup>123</sup>	Standard treatment	ICS	108	177	98	189

Table 3: Study data for units of allogeneic blood transfused

Study	Treatment	Comparator	Treatment		Comparato	or
			Mean	Standard error	Mean	Standard error
Bowley2006 <sup>20</sup>	Standard treatment	ICS	11.17	1.2635973	6.47	1.12164
Niranjan2006 <sup>91</sup>	Standard treatment	ICS	1.38	0.2071292	0.53	0.102774
Goel2007 <sup>49</sup>	Standard treatment	ICS	2.4	0.258	1.54	0.224537
Aghdaii2012 <sup>2</sup>	Standard treatment	ICS	0.7	0.2	0.4	0.16
Zhao2003 <sup>137</sup>	Standard treatment	PCS	2.22	0.0730297	1.2	0.049295
Diprose2005 <sup>38</sup>	ICS	ICS+TXA	1.68	0.4531391	0.87	0.196231

Study	Treatment	Comparator	Treatment		Comparate	or
Jiminez2007 <sup>64</sup>	ICS	ICS+TXA	3.21	0.1078639	1.58	0.100021
Armellin2001 <sup>12</sup>	Standard treatment	TXA	1.93	0.16	1.68	0.208
Blauhut1994 <sup>19</sup>	Standard treatment	TXA	2.44	0.38	1.71	0.3591
Corbeau1995 <sup>31</sup>	Standard treatment	TXA	2.83	0.42	2.19	0.1188
Dalmau2000 <sup>34</sup>	Standard treatment	TXA	8.38	1.01	7.72	1.0102
Horrow1990 <sup>55</sup>	Standard treatment	TXA	0.76	0.24	0.92	0.188562
Katoh1997 <sup>68</sup>	Standard treatment	TXA	3.03	0.82	1.42	0.34798
Speekenbrink1995 <sup>115</sup>	Standard treatment	TXA	4.27	0.95	3.37	0.44
Uozaki2001 <sup>121</sup>	Standard treatment	TXA	9.16	2.69	4.1	0.910394
Yassen1993 <sup>132</sup>	Standard treatment	TXA	12.4	2.53	7.9	1.043552
Zabeeda2002 <sup>134</sup>	Standard treatment	TXA	1.68	0.20	0.52	0.18
Ahn2012 <sup>4</sup>	Standard treatment	TXA	1.4	0.19	0.8	0.129777
Maddali2007 <sup>81</sup>	Standard treatment	TXA	3.17	0.09	2.03	0.074034
Shi2013 <sup>108</sup>	Standard treatment	TXA	6.51	0.44	3.93	0.281521
Shi2013a <sup>108</sup>	Standard treatment	TXA	9.36	1.49	4.84	0.768143
Wang2012 <sup>125</sup>	Standard treatment	TXA	1.62	0.24	0.91	0.147628
Ghavidel2014 <sup>5</sup>	Standard treatment	TXA	1.65	0.053	1.25	0.055

Table 4: Study data for length of stay

Study	Treatment	Comparator	Treatment		Comparator		
			Mean	Standard error	Mean	Standard error	
Niranjan2006 <sup>91</sup>	Standard treatment	ICS	7.85	0.419	7.65	0.341526	
Sirvinskas2007 <sup>110</sup>	Standard treatment	PCS	16.45	0.931	9.32	0.398243	

Study	Treatment	Comparator	Treatment		Comparato	or
Murphy2004 <sup>87</sup>	Standard	ICS+PCS	6.8	0.406	9.6	2.472393
	treatment	103+703		0.406	9.0	2.472595
Jimenez2007 <sup>64</sup>	ICS	ICS+TXA	4	0.728	4.5	0.724641
Later2009 <sup>76</sup>	ICS	ICS+TXA	8.5	0.729	9.4	0.864333
Reyes2011 <sup>100</sup>	TXA	ICS+TXA	12.1	1.356	14.2	2.43528
Mansour2004 <sup>82</sup>	Standard treatment	TXA	6.4	0.671	5.8	0.491935
Mehraein2007 <sup>83</sup>	Standard treatment	TXA	4.8	0.157	4.8	0.069631
Wei2006 <sup>126</sup>	Standard treatment	TXA	7.3	0.190	7.1	0.133333
Vermeijden2015 <sup>123</sup>	Standard treatment	ICS	11.8	0.72158	11.5	0.763763

# L.3.2.2 Moderate risk group

The trial data from the 73 studies included in the NMA for number of patients receiving allogeneic transfusions are shown in Table 5. The trial data from the 16 studies included in the NMA for number of units of allogeneic transfusions received are shown in Table 42.

Table 5: Study data for number of patients receiving allogeneic transfusions

Study	Treatment	Compara tor 1	Compa rator 2	Treatme	reatment Comparator 1		Comparator 2		
				Events	N	Events	N	Events	N
Zhang2008 <sup>136</sup>	Standard treatment	ICS		16	20	10	20	NA	NA
Cip2013 <sup>28</sup>	Standard treatment	ICS		23	70	23	70	NA	NA
Horstmann2013 <sup>57</sup>	Standard treatment	ICS		9	102	8	102	NA	NA
Atay2010i <sup>13</sup>	Standard treatment	PCS		15	19	9	17	NA	NA
Atay2010ii <sup>13</sup>	Standard treatment	PCS		8	21	1	20	NA	NA
Cheng2005 <sup>27</sup>	Standard treatment	PCS		13	34	4	26	NA	NA
Dramis2006 <sup>39</sup>	Standard treatment	PCS		10	17	3	32	NA	NA
Soosman2006 <sup>112</sup>	Standard treatment	PCS		10	22	22	47	NA	NA
Zacharopoulos2007	Standard treatment	PCS		10	30	5	30	NA	NA

Study	Treatment	Compara tor 1	Compa rator 2	Treatme	nt	Compara	itor 1	Compara	tor 2
- Cana,	Standard	00. 2	1000			oopuno			
Abuzakuk2007 <sup>1</sup>	treatment	PCS		12	52	13	52	NA	NA
s acc=111	Standard	200		4=	00	-	=6		
Smith2007 <sup>111</sup>	treatment	PCS		17	82	6	76	NA	NA
Moonen2007 <sup>86</sup>	Standard treatment	PCS		15	80	5	80	NA	NA
	Standard								
Tripkovic2008 <sup>120</sup>	treatment	PCS		24	30	4	30	NA	NA
0	Standard								
Amin2008 <sup>9</sup>	treatment	PCS		13	86	12	92	NA	NA
Thomassen2014 <sup>118</sup>	Standard treatment	PCS		12	190	29	382	NA	NA
11101110330112014	Standard	1 03		12	150	23	302	IVA	IVA
Horstmann2014 <sup>58</sup>	treatment	PCS		11	56	6	59	NA	NA
	Standard		ICS+PC						
Soosman2014 <sup>113</sup>	treatment	PCS	S	54	658	33	321	23	321
Horstmann2014a <sup>59</sup>	Standard	ICC + DCC		4	62	2	r.c	NA	NIA
Wong2008 <sup>129</sup>	treatment	ICS+PCS ICS+TXA		30	74	23	56 73	NA NA	NA NA
Alvarez2008 <sup>8</sup>	PCS	PCS+TXA		6	49	1	46	NA	NA
Oremus2014 <sup>94</sup>	PCS	PCS+TXA		5	49	3	49	NA	NA
Oremus2014	PC3	ICS+PCS+		3	43	3	43	IVA	IVA
Thomassen2012 <sup>119</sup>	TXA	TXA		13	101	9	96	NA	NA
	Standard								
Aguilera2013 <sup>3</sup>	treatment	TXA		12	42	2	41	NA	NA
Benoni1996 <sup>15</sup>	Standard	TVA		2.4	42	0	42		
Benoni1996	treatment	TXA		24	43	8	43	NA	NA
Benoni2000 <sup>17</sup>	Standard treatment	TXA		15	19	9	20	NA	NA
	Standard								
Benoni2001 <sup>16</sup>	treatment	TXA		8	20	4	18	NA	NA
10	Standard								
Bidolegui2014 <sup>18</sup>	treatment	TXA		8	25	0	25	NA	NA
Dakir2014 <sup>33</sup>	Standard treatment	TXA		2	6	0	6	NA	NA
Dakii 2014	Standard	IAA		2	U	U	U	INA	IVA
Ellis2001 <sup>40</sup>	treatment	TXA		7	10	1	10	NA	NA
	Standard								
Engel2001 <sup>41</sup>	treatment	TXA		3	12	0	12	NA	NA
11:: l- 4005 <sup>53</sup>	Standard	TVA		42	42	10	4.5	NIA	A
Hiipala1995 <sup>53</sup>	treatment	TXA		12	13	10	15	NA	NA
Hiipala1997 <sup>54</sup>	Standard treatment	TXA		34	38	17	39	NA	NA
				-					

		C	<b>C</b>					<b>C</b>	
Study	Treatment	Compara tor 1	Compa rator 2	Treatme	nt	Compara	tor 1	Compara	itor 2
Jansen1999 <sup>62</sup>	Standard treatment	TXA		13	21	2	21	NA	NA
Sorin1999 <sup>114</sup>	Standard treatment	TXA		13	21	2	21	NA	NA
Tanaka2001 <sup>117</sup>	Standard treatment	TXA		26	26	47	73	NA	NA
Alshryda2013 <sup>6</sup>	Standard treatment	TXA		13	78	1	79	NA	NA
Bradshaw2012 <sup>21</sup>	Standard treatment	TXA		1	20	0	26	NA	NA
Caglar2008 <sup>22</sup>	Standard treatment	TXA		10	50	15	50	NA	NA
Charoeanch2012 <sup>25</sup>	Standard treatment	TXA		102	120	57	120	NA	NA
Charoeanch2011 <sup>26</sup>	Standard treatment	TXA		45	50	28	50	NA	NA
Claeys2007 <sup>29</sup>	Standard treatment	TXA		6	20	1	20	NA	NA
Crescenti2011 <sup>32</sup>	Standard treatment	TXA		55	100	34	100	NA	NA
Farrokhi2011 <sup>43</sup>	Standard treatment	TXA		15	38	10	38	NA	NA
Garneti2004 <sup>45</sup>	Standard treatment	TXA		14	25	16	25	NA	NA
Georgiadis2013 <sup>46</sup>	Standard treatment	TXA		4	51	0	50	NA	NA
Gill2009 <sup>48</sup>	Standard treatment	TXA		4	5	1	5	NA	NA
Good2003 <sup>50</sup>	Standard treatment	TXA		14	24	3	27	NA	NA
Gungorduk2011 <sup>51</sup>	Standard treatment	TXA		7	330	2	330	NA	NA
Husted2003 <sup>60</sup>	Standard treatment	TXA		7	20	2	20	NA	NA
Ishida2011 <sup>61</sup>	Standard treatment	TXA		1	50	0	50	NA	NA
Johansson2005 <sup>65</sup>	Standard treatment	TXA		23	53	8	47	NA	NA
Karimi2012 <sup>66</sup>	Standard treatment	TXA		1	16	0	16	NA	NA
Kazemi2010 <sup>70</sup>	Standard treatment	TXA		11	32	4	32	NA	NA
Kim2014i <sup>71</sup>	Standard	TXA		6	90	1	90	NA	NA

		Compara	Compa					Compara	itor 2
Study	Treatment	tor 1	rator 2	Treatme	nt	Compara	tor 1		
	treatment								
Kim 2014ii <sup>71</sup>	Standard treatment	TXA		20	73	5	73	NA	NA
Lee2013 <sup>77</sup>	Standard treatment	TXA		20	34	9	34	NA	NA
Lemay2004 <sup>78</sup>	Standard treatment	TXA		8	19	0	20	NA	NA
Macgillvray2010 <sup>80</sup>	Standard treatment	TXA		10	20	13	40	NA	NA
Niskanen2005 <sup>92</sup>	Standard treatment	TXA		8	20	5	19	NA	NA
Orpen2006 <sup>95</sup>	Standard treatment	TXA		3	14	1	15	NA	NA
Rajesparan2009 <sup>98</sup>	Standard treatment	TXA		10	37	3	36	NA	NA
Raviraj2012 <sup>99</sup>	Standard treatment	TXA		18	88	7	88	NA	NA
Roy2012 <sup>101</sup>	Standard treatment	TXA		7	25	2	25	NA	NA
Sa- ngasoongsong2011	Standard treatment	TXA		8	24	1	24	NA	NA
Sa- ngasoongsong2013	Standard treatment	TXA		10	45	6	90	NA	NA
Sadeghi2007 <sup>104</sup>	Standard treatment	TXA		20	35	12	32	NA	NA
Seo2013 <sup>106</sup>	Standard treatment	TXA		47	50	10	50	NA	NA
Shahid2013 <sup>107</sup>	Standard treatment	TXA		12	36	3	38	NA	NA
Vijay2013 <sup>124</sup>	Standard treatment	TXA		18	45	7	45	NA	NA
Wong2010 <sup>128</sup>	Standard treatment	TXA		9	35	5	64	NA	NA
Zohar2004 <sup>138</sup>	Standard treatment	TXA		12	20	3	20	NA	NA
Yang2014 <sup>131</sup>	Standard treatment	TXA		19	40	10	40	NA	NA
Yue2015 <sup>133</sup>	Standard treatment	TXA		11	49	3	52	NA	NA

Table 6: Study data for units of allogeneic blood transfused

•	ata ioi units	Comp								
Study	Treatment	arato r 1	Compara tor 2	Treatm	Treatment		Comparator 1		Comparator 2	
				Mean	SE	Mean	SE	Mean	SE	
Altinel 2007 <sup>7</sup>	Standard treatment	PCS	NA	2.29	0.31	1.02	0.28	NA	NA	
Antinolfi2014 <sup>11</sup>	Standard treatment	TXA	NA	2.2	0.22	0.8	0.18	NA	NA	
Atay2010i <sup>13</sup>	Standard treatment	PCS	NA	1.68	0.33	0.82	0.26	NA	NA	
Atay2010ii <sup>13</sup>	Standard treatment	PCS	NA	0.71	0.21	0.05	0.05	NA	NA	
Calgar2008 <sup>22</sup>	Standard treatment	TXA	NA	1.6	0.21	1.8	0.14	NA	NA	
Charoench2011 <sup>26</sup>	Standard treatment	TXA	NA	1.89	0.12	0.71	0.11	NA	NA	
Charoench2012 <sup>25</sup>	Standard treatment	TXA	NA	1.55	0.09	0.55	0.06	NA	NA	
Hiipala1995 <sup>53</sup>	Standard treatment	TXA	NA	3.58	0.45	2.25	0.28	NA	NA	
Hiipala1997 <sup>54</sup>	Standard treatment	TXA	NA	3.46	0.21	2.29	0.13	NA	NA	
Jansen1999 <sup>62</sup>	Standard treatment	TXA	NA	2.5	0.54	0.46	0.32	NA	NA	
Kazemi2010 <sup>70</sup>	Standard treatment	TXA	NA	0.84	0.16	0.31	0.11	NA	NA	
Kirkos2006 <sup>72</sup>	Standard treatment	PCS	NA	1.06	0.13	0.54	0.10	NA	NA	
Macgillivray2010 <sup>8</sup>	Standard treatment	TXA	NA	1.11	0.22	0.76	0.12	NA	NA	
So-osman2006 <sup>112</sup>	Standard treatment	PCS	NA	1.9	0.22	2.36	0.19	NA	NA	
Soosmonan2014ii	Standard treatment	PCS	ICS+PCS	2.68	0.12	1.26	0.12	3.49	0.10	
Tripkovic2008 <sup>120</sup>	Standard treatment	PCS	NA	1.74	0.21	0.22	0.18	NA	NA	

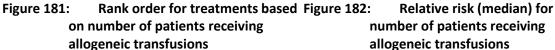
# L.3.3 Network 1: Number of patients receiving allogeneic transfusions (Adults-high risk group)

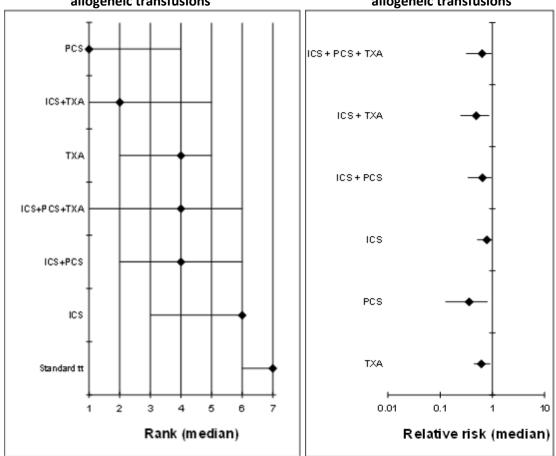
Table 7 summarises the results of the conventional meta-analyses in terms of odds ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of odds ratios for every possible treatment comparison.

Table 7: Odds ratios for number of patients receiving allogeneic transfusions (Adults- high risk group)

Comparison		Odds ratio		
			NMA (median)	
Versus	TXA vs. standard treatment	0.48(0.41, 0.57)	0.4523 (0.3797, 0.5359)	
standard	PCS vs. standard treatment	0.29(0.08, 1.14)	0.2092 (0.08271, 0.4785)	
treatment	ICS vs. standard treatment	0.61(0.44, 0.86)	0.6287 (0.412, 0.9501)	
	ICS+PCS vs. standard treatment	0.44(0.26, 0.75)	0.4591 (0.2529, 0.8438)	
	ICS+TXA vs. standard treatment	-	0.317 (0.1785, 0.5555)	
	ICS+PCS+TXA vs. standard treatment	-	0.4486 (0.2293, 0.863)	
Versus	PCS vs. TXA	-	0.4625 (0.1807, 1.079)	
TXA	ICS vs. TXA	-	1.39 (0.8904, 2.164)	
	ICS+PCS vs. TXA	-	1.013 (0.5527, 1.895)	
	ICS+TXA vs. TXA	0.67(0.24, 1.85)	0.6996 (0.3905, 1.24)	
	ICS+PCS+TXA vs. TXA	1.03(0.57, 1.85)	0.9899 (0.5123, 1.897)	
Versus	ICS vs. PCS	-	3.003 (1.191, 8.247)	
PCS	ICS+PCS vs. PCS	-	2.198 (0.7904, 6.539)	
	ICS+TXA vs. PCS	-	1.517 (0.5531, 4.423)	
	ICS+PCS+TXA vs. PCS	-	2.146 (0.7407, 6.562)	
Versus	ICS+PCS vs. ICS	-	0.728 (0.3492, 1.535)	
ICS	ICS+TXA vs. ICS	0.49(0.34, 0.71)	0.5045 (0.3257, 0.765)	
	ICS+PCS+TXA vs. ICS	-	0.7125 (0.3249, 1.556)	
Versus	ICS+TXA vs. ICS+PCS	-	0.6896 (0.2966, 1.577)	
ICS+PCS	ICS+PCS+TXA vs. ICS+PCS	0.9(0.37, 2.17)	0.9746 (0.4659, 2.011)	
Versus ICS+TXA	ICS+PCS+TXA vs. ICS+TXA	-	1.409 (0.5999, 3.368)	

Figure 181 shows the rank of each intervention compared to the others. Figure 182 shows the median relative risk of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 7 different interventions being evaluated.





Based on the relative risks from the direct comparisons, efficacy as assessed by number of patients receiving allogeneic transfusions favours tranexamic acid, post-operative cell salvage, intra-operative cell salvage and the combination of intra-operative and post-operative cell salvage over standard treatment and the combination of intra-operative cell salvage and tranexamic acid over intra-operative cell salvage. No other treatment effects reached statistical significance.

The random effects model used for the NMA is a relatively good fit, with a residual deviance of 125.8 reported. This corresponds fairly well to the total number of trial arms, 112. The between study variance was 0.2149 (0.01189, 0.4721). No inconsistency was identified between the direct and NMA results for any comparison. All the median odds ratios from the NMA lie within the 95% confidence interval from the direct comparison of the same comparisons (see Table 42). The DiC value from the network was 624.777 and the DiC value from the inconsistency model was 626.856.

#### **Evidence statement:**

A network meta-analysis of 56 studies comparing seven treatments suggested that PCS is ranked as the best treatment, ICS+TXA is ranked second, TXA, ICS+PCS+TXA and ICS+PCS are jointly ranked fourth and standard treatment ranked least effective at reducing the number of adult patients receiving allogeneic transfusions in the high risk group, but there was considerable uncertainty.

# L.3.4 Network 2: Units of allogeneic blood transfused (Adults- high risk group)

Table 8 summarises the results of the conventional meta-analyses in terms of mean differences generated from studies directly comparing different interventions, together with the results of the NMA in terms of mean differences for every possible treatment comparison.

Table 8: Mean differences for units of allogeneic blood transfused (Adults- high risk group)

		Mean difference			
Comparison		Direct (mean)	NMA (median)		
Versus	ICS vs. standard treatment	-0.78 (-1.37, -0.19)	-0.818 (-1.671, -0.1148)		
standard	TXA vs. standard treatment	-0.83 (-1.17, -0.50)	-0.8536 (-1.343, -0.4843)		
treatment	PCS vs. standard treatment	-1.02 (-1.19, -0.86)	-1.021 (-2.29, 0.2511)		
	ICS+TXA vs. standard treatment	-	-2.16 (-3.444, -0.9444)		
Versus	TXA vs. ICS	-	-0.03479 ( -0.8862, 0.8435)		
ICS	PCS vs. ICS	-	-0.2067 (-1.609, 1.375)		
	ICS+TXA vs. ICS	-1.56 (-1.84, -1.29)	-1.346 (-2.291, -0.3032)		
Versus	PCS vs. TXA	-	-0.1725 (-1.438, 1.243)		
TXA	ICS+TXA vs. TXA	-	-1.309 (-2.589, 0.03418)		
Versus PCS	ICS+TXA vs. PCS	-	-1.141 (-2.965, 0.6136)		

Abbreviations: TXA-Tranexamic acid, PCS-Post-operative cell salvage, ICS-Intra-operative cell salvage

Figure 183 shows the rank of each intervention compared to the others. Figure 184 shows the median of the mean differences of each intervention compared to the others. The rank is based on the mean difference compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 5 interventions being evaluated.

Figure 183: Rank order for treatments based on units of allogeneic blood transfused

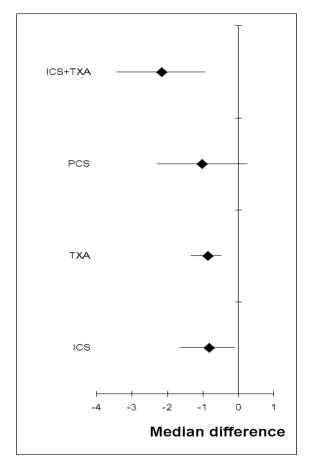
PCS
TXA

2

Rank (median)

Standard tt

Figure 184: Mean differences (median) for units of allogeneic blood transfused



Based on the direct comparisons (first results column Table 8), efficacy as assessed by reduced number of units of allogeneic transfusions received favours intra-operative cell salvage, post-operative cell salvage, tranexamic acid over standard treatment, and the combination of intra-operative cell salvage and tranexamic acid over intra-operative cell salvage. No other treatment effects reached statistical significance.

The random effects model used for the NMA is a relatively good fit, with a residual deviance of 54.55 reported. This corresponds fairly well to the total number of trial arms, 46. The between study variance was 0.5521 (0.2752, 1.078). The DiC value for the network was 61.454. No inconsistency was identified between the direct and NMA results for any comparison. All the mean differences from the NMA lie within the 95% confidence interval from the direct comparison of the same comparisons.

#### **Evidence statement:**

A network meta-analysis of 23 studies comparing five treatments suggested that ICS+TXA is ranked as the best treatment, PCS is ranked second, TXA and ICS are jointly ranked third, and standard treatment ranked least effective at reducing the number of units of allogeneic blood transfusions in adult patients in the high risk group, but there was considerable uncertainty.

# L.3.5 Network 3: Length of stay in hospital (Adults- high risk group)

Table 9 summarises the results of the conventional meta-analyses in terms of mean differences generated from studies directly comparing different interventions, together with the results of the NMA in terms of mean differences for every possible treatment comparison.

Table 9: Mean differences for length of stay in hospital (Adults- high risk group)

	,	, ,	<b>U</b> 17		
		Mean difference			
Comparison		Direct (mean)	NMA (median)		
Versus	TXA vs. standard treatment	-0.08 (-0.35, 0.18)	-0.1266 (-0.9664, 0.4938)		
standard	ICS vs. standard treatment	-0.22 (-1.16, 0.72)	-0.1668 (-1.346 , 1.041)		
treatment	PCS vs. standard treatment	-7.13 (-9.12, -5.14)	-7.123 (-9.394, -4.869)		
	ICS+PCS vs. standard treatment	2.80 (-2.11, 7.71)	2.83 (-2.182, 7.842)		
	ICS+TXA vs. standard treatment	-	0.6375 (-1.306, 2.607)		
Versus	ICS vs. TXA	-	-0.03038 (-1.315, 1.428)		
TXA	PCS vs. TXA	-	-6.987 (-9.315, -4.577)		
	ICS+PCS vs. TXA	-	2.977 (-2.077, 8.056)		
	ICS+TXA vs. TXA	2.10 (-3.36, 7.56)	0.7759 (-1.204, 2.864)		
Versus	PCS vs. ICS	-	-6.962 (-9.537, -4.427)		
ICS	ICS+PCS vs. ICS	-	2.994 (-2.137, 8.15)		
	ICS+TXA vs. ICS	0.68 (-0.81, 2.17)	0.8029 (-0.8243, 2.432)		
Versus PCS	ICS+PCS vs. PCS	-	9.961 (4.498, 15.46)		
	ICS+TXA vs. PCS	-	7.748 (4.834, 10.78)		
Versus ICS+PCS	ICS+TXA vs. ICS+PCS	-	-2.196 (-7.537, 3.248)		

Abbreviations: TXA-Tranexamic acid, PCS-Post-operative cell salvage, ICS-Intra-operative cell salvage

Figure 185 shows the rank of each intervention compared to the others. Figure 186 shows the median of the mean differences of each intervention compared to the others. The rank is based on the mean difference compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 6 different interventions being evaluated.

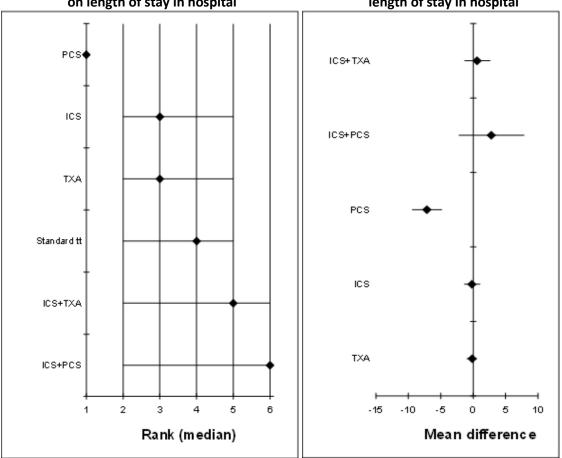


Figure 185: Rank order for treatments based Figure 186: Mean differences (median) for on length of stay in hospital length of stay in hospital

Based on the direct comparisons (first results column Table 9), efficacy as assessed by reduced length of stay in hospital favours post-operative cell salvage over standard treatment. No other treatment effects reached statistical significance.

The random effects model used for the NMA is a relatively good fit, with a residual deviance of 16.82 reported. This corresponds fairly well to the total number of trial arms, 20. The between study variance was 0.261 (0.01098, 1.459). The DiC value for this network was 44.320. No inconsistency was identified between the direct and NMA results for any comparison. All the mean differences from the NMA lie within the 95% confidence interval from the direct comparison of the same comparisons.

### **Evidence statement:**

A network meta-analysis of 10 studies comparing six treatments suggested that PCS is ranked as the best treatment, ICs and TXA are jointly ranked third, standard treatment is ranked fourth,

ICS+TXA is ranked fifth and ICS+PCS is ranked least effective at reducing length of stay in hospital in adult patients in the high risk group, but there was considerable uncertainty.

# L.3.6 Network 4: Number of patients receiving allogeneic blood (Adults- moderate risk group)

Table 10 summarises the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of risk ratios for every possible treatment comparison.

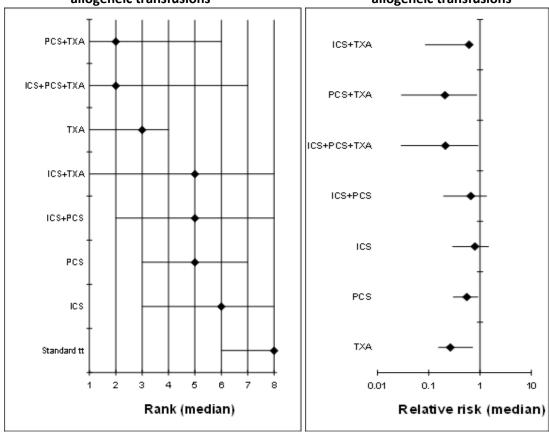
Table 10: Risk ratios for number of patients receiving allogeneic transfusions (Adults-moderate risk group)

	iciate risk group)	Odds ratio			
Comparison		Direct (mean)	NMA (median)		
Versus	TXA vs. standard treatment	0.23(0.18, 0.3)	0.1790 (0.1285, 0.2428)		
standard	PCS vs. standard treatment	0.43(0.25, 0.73)	0.4111 (0.2421, 0.6789)		
treatment	ICS vs. standard treatment	0.56(0.24, 1.3)	0.655 (0.2171, 1.925)		
	ICS+PCS vs. standard treatment	0.83(0.51, 1.35)	0.4954 (0.1385, 1.713)		
	ICS+PCS+TXA vs. standard treatment	-	0.1239 (0.01897, 0.7784)		
	PCS+TXA vs. standard treatment	-	0.1223 (0.01919, 0.6719)		
	ICS+TXA vs. standard treatment	-	0.4382 (0.0562, 3.374)		
Versus	PCS vs. TXA	-	2.293 (1.264, 4.181)		
TXA	ICS vs. TXA	-	3.654 (1.18, 11.39)		
	ICS+PCS vs. TXA	-	2.766 (0.7558, 10.05)		
	ICS+PCS+TXA vs. TXA	0.7(0.28, 1.72)	0.6914 (0.1102, 4.311)		
	PCS+TXA vs. TXA	-	0.6822 (0.1059, 3.903)		
	ICS+TXA vs. TXA	-	2.442 (0.311, 19.47)		
Versus	ICS vs. PCS	-	1.591 (0.4809, 5.349)		
PCS	ICS+PCS vs. PCS	0.67 (0.39, 1.2)	1.207 (0.3335, 4.359)		
	ICS+PCS+TXA vs. PCS	-	0.3014 (0.04394, 2.061)		
	PCS+TXA vs. PCS	0.35(0.11, 1.13)	0.2981 (0.05066, 1.535)		
	ICS+TXA vs. PCS	-	1.064 (0.1306, 8.837)		
Versus	ICS+PCS vs. ICS	-	0.7563 (0.1434, 3.972)		
ICS	ICS+PCS+TXA vs. ICS	-	0.1895 (0.02182, 1.628)		
	PCS+TXA vs. ICS	-	0.1869 (0.02193, 1.426)		
	ICS+TXA vs. ICS	0.67 (0.34, 1.33)	0.6697 (0.1192, 3.782)		
Versus	ICS+PCS+TXA vs. ICS+PCS	-	0.2497 (0.02635, 2.353)		
ICS+PCS	PCS+TXA vs. ICS+PCS	-	0.2465 (0.02783, 1.981)		
	ICS+TXA vs. ICS+PCS	-	0.8879 (0.08067, 9.756)		
Versus	PCS+TXA vs. ICS+PCS+TXA	-	0.9818 (0.07212, 12.35)		
ICS+PCS+TXA	ICS+TXA vs. ICS+PCS +TXA	-	3.536 (0.2247, 56.38)		

Versus	ICS+TXA vs. PCS +TXA	-	
PCS+TXA			3.62 (0.2495, 56.34)

Figure 187 shows the rank of each intervention compared to the others. Figure 188 shows the median relative risk of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 8 different interventions being evaluated.

Figure 187: Rank order for treatments based Figure 188: Relative risk (median) for on number of patients receiving allogeneic transfusions allogeneic transfusions



Based on the direct comparisons (first results column Table 10), efficacy as assessed by number of patients receiving allogeneic transfusions favours the use of post-operative cell salvage or tranexamic acid over standard treatment. No other treatment effects reached statistical significance.

The random effects model used for the NMA is a relatively good fit, with a residual deviance of 145.2 reported. This corresponds fairly well to the total number of trial arms, 147. The between

study variance was 0.7827 (0.5682, 1.057). On evaluating inconsistency by comparing the odds ratios, the NMA estimated odds ratio for ICS+PCS vs. standard treatment (0.4954 [0.1385, 1.713]) lay outside of the confidence interval of the odds ratio estimated from the direct comparison (0.83[0.51, 1.35]). However, the DiC values generated from the network and the inconsistency models were similar highlighting that there was no inconsistency. The DiC value from the network was 745. 119 and the DiC value from the inconsistency model was 745.202.

#### **Evidence statement:**

A network meta-analysis of 73 studies comparing eight treatments suggested that PCS+TXA is ranked as the best treatment, ICS +TXA is ranked second, TXA is ranked fourth, ICS+TXA, ICS+PCS and PCS are jointly ranked fifth, ICS is ranked sixth and standard treatment is ranked least effective at reducing the number of adult patients receiving allogeneic transfusions in the moderate risk group, but there was considerable uncertainty.

# L.3.7 Network 5: Units of allogeneic blood transfused (Adults- moderate risk group)

Table summarises the results of the conventional meta-analyses in terms of mean differences generated from studies directly comparing different interventions, together with the results of the NMA in terms of mean differences for every possible treatment comparison.

Table 11: Mean differences for units of allogeneic blood transfused (Adults- Moderate risk group)

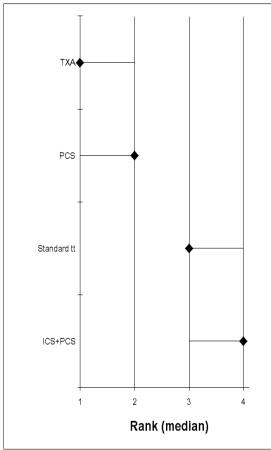
		Mean difference		
Comparison		Direct (mean)	NMA (median)	
Versus	TXA vs. standard treatment	-0.88 (-1.22, -0.54)	-0.9028 (-1.397, -0.4369)	
Standard	PCS vs. standard treatment	-0.82 (-1.31, -0.33)	-0.8217 (-1.364, -0.2834)	
treatment	ICS+PCS vs. standard treatment	0.81 (0.49, 1.13)	1.11(-0.1026, 2.313)	
Versus	PCS vs. TXA	-	0.0816(-0.6285, 0.8177)	
TXA	ICS+PCS vs. TXA	-	2.013(0.7254, 3.317)	
Versus PCS	ICS+PCS vs. PCS	2.23 (1.92, 2.54)	1.932(0.7209, 3.136)	

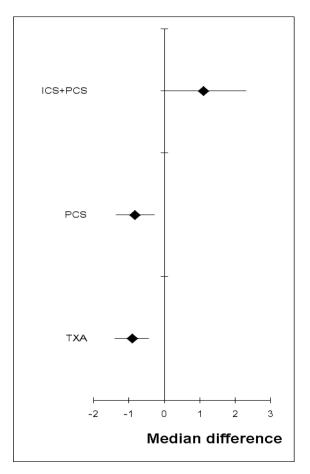
(a) Abbreviations: TXA-Tranexamic acid, PCS-Post-operative cell salvage, ICS-Intra-operative cell salvage

Figure 205 shows the rank of each intervention compared to the others. Figure 206 shows the median of the mean differences of each intervention compared to the others. The rank is based on the mean difference compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 4 interventions being evaluated.

Figure 189: Rank order for treatments based on units of allogeneic blood transfused

Figure 190: Mean differences (median) for units of allogeneic blood transfused





Based on the direct comparisons (first results column Table 46), efficacy as assessed by reduced number of units of allogeneic transfusions received favours tranexamic acid and post-operative cell salvage over standard treatment, and standard treatment over the combination of intra-operative cell salvage and post-operative cell salvage. No other treatment effects reached statistical significance.

The random effects model used for the NMA is a relatively good fit, with a residual deviance of 33.45 reported. This corresponds fairly well to the total number of trial arms, 33. The DiC value of the network was 8.237. No inconsistency was identified between the direct and NMA results for any comparison. All the mean differences from the NMA lie within the 95% confidence interval from the direct comparison of the same comparisons.

### Evidence statement:

A network meta-analysis of 16 studies comparing four treatments suggested that PCS and TXA are jointly ranked as the best treatment, standard treatment is ranked third and the combination of ICS+PCS is ranked least effective at reducing the number of units of allogeneic blood transfusions in adult patients in the moderate risk group, but there was some uncertainty.

# L.4 Discussion

Based on the results of conventional meta-analyses of direct evidence, as has been previously presented in chapter 6 and appendix 6.5.2, deciding upon the most effective intervention as an alternative to blood transfusion in surgical patients is challenging. In order to overcome the difficulty of interpreting the conclusions from numerous separate comparisons, network meta-analysis of the direct evidence were performed.

Our analyses were divided into two risk groups- high and moderate risk groups (For details of stratification, please refer section 6.2.2, chapter 6). 73 studies formed 3 networks, each for a different outcome, in the high risk group; 56 studies were included in a network for one outcome in the moderate risk group. Four treatment interventions were evaluated alone or in combination with one another in these analyses.

The findings from the NMA were used to facilitate the GDG in decision making when developing recommendations for alternatives to blood transfusion in surgical patients.

In the first network of number of adult patients receiving allogeneic transfusions in the high risk group, all treatments were found to be superior to standard treatment; ICS+TXA was found to be superior to TXA, ICS, ICS+PCS+TXA, ICS+PCS; TXA alone was found to be superior to ICS, ICS+PCS; ICS+PCS+TXA was found to be superior to ICS, ICS+PCS; ICS+PCS was found to be superior to ICS alone.

In the ranking of treatments PCS was ranked as the best treatment although there is considerable uncertainty about this estimate as the credible intervals are quite wide; the GDG also discussed concerns regarding the applicability of this evidence and highlighted that it may not be an appropriate intervention in all high risk surgeries (for details, please refer the full cost-effectiveness analysis in Appendix M and the LETR). ICS+TXA was ranked second and the GDG noted that in surgical patients who were expected to have very high blood loss, this may well be the most appropriate blood saving intervention. TXA was ranked third, with much smaller credible intervals only spanning three ranking positions.

In the second network of number of units of allogeneic transfusions received in the high risk group, all treatments were found to be superior to standard treatment; ICS+TXA was found to be superior to PCS, TXA, ICS; PCS was found to be superior to TXA,ICS; TXA and ICS were found to be superior to standard treatment.

In the ranking of treatments ICS +TXA was ranked as the best treatment with very precise credible intervals spanning only two ranking interventions; the GDG agreed that ICS+TXA was the most blood saving intervention in the high risk group in terms of number of units transfused. PCS was ranked second ICS+TXA was ranked second, but with very wide credible intervals; TXA and ICs were jointly ranked third.

In the third network of length of stay in hospital in the high risk group, all treatments were found to be superior to ICS+PCS; PCS was found to be superior to ICS, TXA, Standard treatment, ICS+TXA; ICS was found to be superior to TXA, Standard treatment, ICS+TXA; Standard treatment was found to be superior to ICS+TXA.

In the ranking of treatments PCS was ranked as the best treatment with very precise credible intervals. However, the GDG noted that this was based on data from one study where the baseline group had a very high length of stay. ICS and TXA were jointly ranked as the second best interventions having reduced length of stay, with identical credible intervals. Standard treatment was ranked as the third best intervention over ICS+TXA and ICS+PCS, but all three had very wide credible intervals spanning greater than three ranking interventions.

In the fourth network of number of adult patients receiving allogeneic transfusions in the moderate risk group, all treatments were found to be superior to standard treatment; PCS+TXA was found to be superior to ICS+PCS+TXA, TXA, ICS+TXA, ICS+PCS, PCS, ICS; ICS+PCS+TXA was found to be superior to TXA, ICS+TXA, ICS+PCS, PCS; TXA alone was found to be superior to ICS+TXA, ICS+PCS, PCS, ICS; ICS+TXA was found to be superior to ICS+PCS, PCS, ICS; ICS+PCS was found to be superior to PCS, ICS; PCS was found to be superior to ICS.

In the ranking of treatments PCS+TXA was ranked first and ICS+PCS+TXA was ranked second, although both rankings had very wide credible intervals spanning greater than five treatment ranking interventions. TXA was ranked third, but with much smaller credible intervals only spanning three ranking positions. ICS +TXA and ICS+PCS were jointly ranked fifth with very wide credible intervals spanning greater than six treatment ranking interventions. PCS was also ranked fifth, but had smaller credible intervals spanning four treatment ranking interventions. ICs was ranked sixth but again, had very wide credible intervals.

All four networks seem to fit well, as demonstrated by residual deviance and no inconsistencies in the networks were found.

In summary, the three outcomes chosen for this analysis were considered to be among the most important for assessing efficacy of alternatives to blood transfusion in adult surgical patients in the high and moderate risk groups. All of these outcomes contributed to the cost effectiveness analysis (see Appendix M).

# L.5 Conclusion

This analysis allowed us to combine findings from many different comparisons presented in the reviews for alternatives to blood transfusion even when direct comparative data was lacking.

Overall, the GDG agreed that results of the four networks in the high and moderate risk groups were not conclusive. It was acknowledged that the combination of intra-operative cell salvage and tranexamic acid and, tranexamic acid alone were likely to be the most effective blood saving interventions and therefore appropriate as alternatives to blood transfusion in adult surgical patients.

It should be noted that this analysis does not take into account the adverse effect profile of these treatments, but known profiles have been taken into account in the development of the associated recommendations. For details of the rationale and discussion around the discussion leading to recommendations, please refer the section linking the evidence to the recommendations (section 4.5, chapter 4).

## L.6 WinBUGS codes

# L.6.1 WinBUGS code for assessment of baseline risk of receiving allogeneic transfusions (High risk group)

```
# Baseline random effects model
                    # *** PROGRAM STARTS
model{
for (i in 1:ns){ # LOOP THROUGH STUDIES
  r[i] \sim dbin(p[i],n[i])
                               # Likelihood
  logit(p[i]) <- mu[i]
                                      # Log-odds of response
  mu[i] ~ dnorm(m,tau.m) # Random effects model
mu.new ~ dnorm(m,tau.m)
                                 # predictive dist. (log-odds)
m \sim dnorm(0,.0001) # vague prior for mean
var.m <- 1/tau.m
                 # between-trial variance
tau.m <- pow(sd.m,-2) # between-trial precision = (1/between-trial variance)
sd.m \sim dunif(0,5)
                      # vague prior for between-trial SD
#tau.m ~ dgamma(0.001,0.001)
#sd.m <- sqrt(var.m)
logit(R) <- m
                     # posterior probability of response
logit(R.new) <- mu.new
                          # predictive probability of response
}
Data
list(ns=48) # ns=number of studies
r[]
       n[]
31
       41
7
       31
21
       29
```

- 8 251 33
- 30 30
- 3 24
- 19 49
- 64 102
- 10 15
- 27 38
- 5 17
- 51 96
- 10 43
- 23 50
- 7 25
- 41 165
- 12 20
- 8 33
- 21 40
- 8 39
- 12 31
- 221 278
- 54 59
- 27 50
- 6 30
- 54 115
- 8 40
- 17 108
- 63 140
- 9 14
- 4 20

- 8 14
- 12 20
- 37 40
- 4 20
- 13 19
- 27 44
- 16 44
- 10 31
- 27 106
- 9 14
- 18 24
- 11 15
- 43 75
- 22 50
- 74 100
- 108 177

Inits

# L.6.2 WinBUGS code for number of adult patients receiving allogeneic transfusions (High risk group)

NUMBER TRANSFUSED HIGH RISK

# Binomial likelihood, logit link

```
# Random effects model for multi-arm trials
model{
                         # *** PROGRAM STARTS
for(i in 1:ns){
                          # LOOP THROUGH STUDIES
  w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
  delta[i,1] <- 0
                        # treatment effect is zero for control arm
  mu[i] \sim dnorm(0,.0001)
                                 # vague priors for all trial baselines
  for (k in 1:na[i]) {
                           # LOOP THROUGH ARMS
    r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
    logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
    rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k]) - log(rhat[i,k]))
       + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
                                                                     }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {
                          # LOOP THROUGH ARMS
# trial-specific LOR distributions
    delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
    md[i,k] \leftarrow d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
    taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
    w[i,k] \leftarrow (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
    sw[i,k] <- sum(w[i,1:k-1])/(k-1)
   }
 }
totresdev <- sum(resdev[]) # Total Residual Deviance
```

```
d[1]<-0
            # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k \text{ in 2:nt}) \{ d[k] \sim dnorm(0,.0001) \}
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
# Provide estimates of treatment effects T[k] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k \text{ in 1:nt}) \{ logit(T[k]) <- A + d[k] \}
rr [1] < -1
for (k \text{ in } 2:nt) \{rr[k] < -T[k]/T[1] \}
for (c in 1:(nt-1))
{ for (k in (c+1):nt)
\{ lor[c,k] <- d[k] - d[c] \}
log(or[c,k]) \leftarrow lor[c,k]
Irr[c,k] \leftarrow log(rr[k]) - log(rr[c])
log(rrisk[c,k]) <- lrr[c,k] }}</pre>
for (k in 1:nt) {
rk[k]<-rank(rr[],k)
best[k]<-equals(rank(rr[],k),1)}
}
                      # *** PROGRAM ENDS
Data
# ns= number of studies; nt=number of treatments
list(ns=56, nt=7, meanA=-0.07213, precA=0.708544479588251)
r[,1]
         r[,2]
                 n[,1]
                          n[,2]
                                   t[,1]
                                            t[,2]
                                                     na[]
```

31	21	41	40	1	4	2
7	4	31	30	1	4	2
21	17	29	30	1	4	2
8	7	25	25	1	4	2
1	2	33	32	1	3	2
30	19	30	30	1	3	2
3	1	24	23	1	3	2
19	6	49	41	1	3	2
64	41	102	98	1	5	2
10	8	15	15	1	5	2
13	9	50	52	4	6	2
27	20	60	60	4	6	2
19	9	26	24	4	6	2
12	5	20	20	4	6	2
73	57	103	99	4	6	2
13	12	29	24	2	6	2
14	13	50	50	5	7	2
33	31	111	102	2	7	2
27	20	38	38	1	2	2
5	6	17	20	1	2	2
51	51	96	97	1	2	2
10	8	43	44	1	2	2
23	15	50	50	1	2	2
7	2	25	22	1	2	2
41	24	165	147	1	2	2
12	7	20	20	1	2	2
8	5	33	33	1	2	2
21	15	40	40	1	2	2
8	7	39	40	1	2	2

12	7	31	29	1	2	2
221	166	278	274	1	2	2
54	42	59	58	1	2	2
27	8	50	50	1	2	2
6	3	30	32	1	2	2
54	37	115	116	1	2	2
8	3	40	36	1	2	2
17	0	108	106	1	2	2
63	35	140	143	1	2	2
9	7	14	15	1	2	2
4	2	20	20	1	2	2
8	9	14	16	1	2	2
12	15	20	41	1	2	2
37	29	40	42	1	2	2
4	3	20	20	1	2	2
13	14	19	19	1	2	2
27	28	44	42	1	2	2
16	12	44	37	1	2	2
10	7	31	62	1	2	2
27	11	106	104	1	2	2
9	2	14	16	1	2	2
18	12	24	24	1	2	2
11	13	15	15	1	2	2
43	22	75	75	1	2	2
22	15	50	50	1	2	2
74	60	100	100	1	2	2
108	98	177	189	1	4	2

L.6.3

```
Initial Values
list(
d=c(NA,0,0,0,0,0,0),
sd=.2,
2,2,2,0,1,2,0,0,-2,1,-2,-2,-3,-2,1,2,1,2))
list(
d=c(NA,1,1,1,1,1,1),
sd=.1,
mu=c(2,1,3,1,2,0,2,0,-1,3,2,0,1,3,1,1,2,-3,2,0,0,1,1,-3,3,1,-3,0,-3,0,3,-3,1,-1,-
3,2,1,3,0,2,2,1,1,2,1,1,0,1,0,0,-3,0,1,2,1,2))
list(
d=c(NA,0.5,0.5,0.5,0.5,0.5,0.5),
sd=.15,
3,2,1,3,1,2,2,0.5,1,2,0.5,0.5,1,1,1,1,-3,-2,1,2,1,2))
WinBUGS code for inconsistency model for number of adult patients receiving
allogeneic transfusions (High risk group)
High risk number transfused
56 trials
7 treatments
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{
                #*** PROGRAM STARTS
for(i in 1:ns){
            # LOOP THROUGH STUDIES
 delta[i,1]<-0
                 # treatment effect is zero in control arm
 mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines
  for (k in 1:na[i]) { # LOOP THROUGH ARMS
   r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
```

```
logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
#Deviance contribution
    rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
     + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
   }
# summed residual deviance contribution for this trial
 resdev[i] <- sum(dev[i,1:na[i]])
 for (k in 2:na[i]) { # LOOP THROUGH ARMS
# trial-specific LOR distributions
    delta[i,k] ~ dnorm(d[t[i,1],t[i,k]],tau)
   }
 }
totresdev <- sum(resdev[]) # Total Residual Deviance
for (c in 1:(nt-1)) { # priors for all mean treatment effects
  for (k \text{ in } (c+1):nt) \{ d[c,k] \sim dnorm(0,.0001) \}
}
sd ~ dunif(0,5) # vague prior for between-trial standard deviation
var <- pow(sd,2) # between-trial variance</pre>
tau <- 1/var # between-trial precision
} # *** PROGRAM ENDS
Data
# High risk number transfused
# nt=no. treatments, ns=no. studies
list(nt=7,ns=56)
r[,1]
        r[,2]
                n[,1]
                         n[,2] t[,1]
                                          t[,2]
                                                   na[]
```

31	21	41	40	1	4	2
7	4	31	30	1	4	2
21	17	29	30	1	4	2
8	7	25	25	1	4	2
1	2	33	32	1	3	2
30	19	30	30	1	3	2
3	1	24	23	1	3	2
19	6	49	41	1	3	2
64	41	102	98	1	5	2
10	8	15	15	1	5	2
13	9	50	52	4	6	2
27	20	60	60	4	6	2
19	9	26	24	4	6	2
12	5	20	20	4	6	2
73	57	103	99	4	6	2
13	12	29	24	2	6	2
14	13	50	50	5	7	2
33	31	111	102	2	7	2
27	20	38	38	1	2	2
5	6	17	20	1	2	2
51	51	96	97	1	2	2
10	8	43	44	1	2	2
23	15	50	50	1	2	2
7	2	25	22	1	2	2
41	24	165	147	1	2	2
12	7	20	20	1	2	2
8	5	33	33	1	2	2
21	15	40	40	1	2	2
8	7	39	40	1	2	2

12	7	31	29	1	2	2
221	166	278	274	1	2	2
54	42	59	58	1	2	2
27	8	50	50	1	2	2
6	3	30	32	1	2	2
54	37	115	116	1	2	2
8	3	40	36	1	2	2
17	0	108	106	1	2	2
63	35	140	143	1	2	2
9	7	14	15	1	2	2
4	2	20	20	1	2	2
8	9	14	16	1	2	2
12	15	20	41	1	2	2
37	29	40	42	1	2	2
4	3	20	20	1	2	2
13	14	19	19	1	2	2
27	28	44	42	1	2	2
16	12	44	37	1	2	2
10	7	31	62	1	2	2
27	11	106	104	1	2	2
9	2	14	16	1	2	2
18	12	24	24	1	2	2
11	13	15	15	1	2	2
43	22	75	75	1	2	2
22	15	50	50	1	2	2
74	60	100	100	1	2	2
108	98	177	189	1	4	2

#### **INITS**

## # chain 1

list(sd=1, mu=c(2,0,3,0,2, -2,2,-2,-1,3, 2,-2,1,3,1, 1,2,-3,2,-2, -2,1,0,-3,3, 0,-3,-2,-3,-2, 3,-3,0,-1,-3, 2,1,3,-2,2, 2,0,1,2,0, 0,-2,1,-2,-2, 2,1,1, 2,2,3),

d=structure(.Data=c(NA,0,1,0,0,-2,0, NA,NA,0,0,2,0,0, NA,NA,NA,0,0,0,0, NA,NA,NA,NA,NA,0,0,0,0,

NA,NA,NA,NA,NA,O,O,NA,NA,NA,NA,NA,NA,NA,O),.Dim = c(6,7)))

#### # chain 2

list(sd=1.5, mu=c(2,1,3,1,2, 0,2,0,-1,3, 2,0,1,3,1, 1,2,-3,2,0, 0,1,1,-3,3, 1,-3,0,-3,0, 3,-3,1,-1,-3, 2,1,3,0,2, 2,1,1,2,1, 1,0,1,0,0, 2,3,1, -2,1,2),

d = structure(.Data = c(NA,0,1,0,0,-1,2, NA,NA,1,0.5,2,0,0, NA,NA,NA,2,1,1,0,NA,NA,NA,NA,NA,0.5,2,0,

NA,NA,NA,NA,NA,2,0, NA,NA,NA,NA,NA,NA,1), .Dim = c(6,7))

#### # chain 3

list(sd=3, mu=c(2,0.5,3,0.5,2, -2,2,1,-1,3, 2,1,1,3,1, 1,2,-3,2,1, 1,1,0.5,-3,3, 0.5,-3,1,-3,1, 3,-3,0.5,-1,-3, 2,1,3,1,2, 2,0.5,1,2,0.5, 0.5,1,1,1,1, 2,1,0,-1,0,1),

d = structure(.Data =c(NA,0,1,0,0,-2,0, NA,NA,0,1,-2,0,-1, NA,NA,NA,2,0,1,0, NA,NA,NA,NA,0,1,2,

NA, NA, NA, NA, NA, 1, 1, NA, NA, NA, NA, NA, NA, -1, .Dim = c(6,7))

# L.6.4 WinBUGS code for number of units of receiving allogeneic blood transfusions (High risk group)

UNITS TRANSFUSED - HIGH RISK

# Normal likelihood, identity link

# Random effects model for multi-arm trials

```
model{
                         # *** PROGRAM STARTS
for(i in 1:ns){
                          # LOOP THROUGH STUDIES
  w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
  delta[i,1] <- 0
                        # treatment effect is zero for control arm
  mu[i] \sim dnorm(0,.0001)
                                 # vague priors for all trial baselines
  for (k in 1:na[i]) {
                           # LOOP THROUGH ARMS
    var[i,k] <- pow(se[i,k],2) # calculate variances</pre>
    prec[i,k] <- 1/var[i,k] # set precisions</pre>
    y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
    theta[i,k] <- mu[i] + delta[i,k] # model for linear predictor
#Deviance contribution
    dev[i,k] \leftarrow (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
   }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {
                          # LOOP THROUGH ARMS
# trial-specific LOR distributions
    delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
    md[i,k] \leftarrow d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
    taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
    w[i,k] \leftarrow (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
    sw[i,k] <- sum(w[i,1:k-1])/(k-1)
   }
 }
totresdev <- sum(resdev[]) #Total Residual Deviance
```

```
d[1]<-0
           # treatment effect is zero for control arm
# vague priors for treatment effects
for (k \text{ in 2:nt}) \{ d[k] \sim dnorm(0,.0001) \}
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k \text{ in 1:nt}) \{ T[k] <- A + d[k] \}
for (k in 1:nt) {
rk[k]<-rank(d[],k)
best[k]<-equals(rank(d[],k),1)}
for (c in 1:(nt-1))
{ for (k in (c+1):nt)
\{ D[c,k] \leftarrow d[k] - d[c] \} \}
}
                     # *** PROGRAM ENDS
Data
# ns= number of studies; nt=number of treatments
list(ns=23, nt=5, meanA=-1, precA=1)
t[,1]
        t[,2]
                y[,1]
                        y[,2]
                                se[,1] se[,2] na[]
1
        2
                11.17
                        6.47
                                 1.263597349 1.121639956 2
        2
                        0.53
                                0.207129187  0.102774024  2
1
                1.38
        2
                        1.54
                                                         2
1
                2.4
                                0.258 0.22453656
1
        2
                0.7
                        0.4
                                0.2
                                         0.16
                                                 2
```

2.22

1.68

1.2

0.87

1

2

4

5

0.073029674 0.04929503

2

2	5	3.21	1.58	0.107863874	0.100020831	2
1	3	0.87	0.41	0.109870053	0.077770507	2
1	3	1.57	0.8	0.400891863	0.278854801	2
1	3	1.7	0.8	0.402492236	0.171791138	2
1	3	7.75	5.33	0.996117463	0.890330329	2
1	3	0.76	0.92	0.241495342	0.188561808	2
1	3	3.03	1.42	0.82079623	0.347980348	2
1	3	3.13	2.87	0.852056336	0.490577891	2
1	3	9.16	4.1	2.694438717	0.910393688	2
1	3	12.4	7.9	2.529822128	1.043551628	2
1	3	1.68	0.52	0.2 0.18	2	
1	3	1.4	0.8	0.194665705	0.129777137	2
1	3	3.17	2.03	0.092068326	0.074034324	2
1	3	6.51	3.93	0.439624185	0.281520895	2
1	3	9.36	4.84	1.485455474	0.768142632	2
1	3	1.62	0.91	0.239653736	0.147627794	2
1	3	1.65	1.25	0.053 0.055	2	
END						
Initial	Values					
#chain	1					
list(d=	c( NA, 0,	0,0,0), s	d=1, mu	=c(0,0,0,0,0,0,0,0,	0,0,0,0,1,1,1,0,	0, 0, 0, 0, 1,1,1,0))
#chain	2					

list(d=c( NA, -1,-3,1,-1), sd=4, mu=c(0,3,0,-1,0,2,1,0,-3,0,-2,1,1,1, 2, 0, 0, 1, 1,1,1,2,0))

list(d=c( NA, 2,2,2,2), sd=2, mu=c(2,3,1,-1,1,2,0,0,-3,0,2,1,-1,1,-2, 0, 0,-1,-1,1,1,-1,0))

## L.6.5 WinBUGS code for length of stay in hospital (High risk group)

LENGTH OF STAY - HIGH RISK

#chain 3

```
# Normal likelihood, identity link
# Random effects model for multi-arm trials
model{
                         # *** PROGRAM STARTS
for(i in 1:ns){
                          # LOOP THROUGH STUDIES
  w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
  delta[i,1] <- 0
                        # treatment effect is zero for control arm
  mu[i] \sim dnorm(0,.0001)
                                 # vague priors for all trial baselines
  for (k in 1:na[i]) {
                           # LOOP THROUGH ARMS
    var[i,k] <- pow(se[i,k],2) # calculate variances</pre>
    prec[i,k] <- 1/var[i,k] # set precisions</pre>
    y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
    theta[i,k] <- mu[i] + delta[i,k] # model for linear predictor
#Deviance contribution
    dev[i,k] \leftarrow (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
   }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {
                           # LOOP THROUGH ARMS
# trial-specific LOR distributions
    delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
    md[i,k] \leftarrow d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
    taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
    w[i,k] < -(delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
    sw[i,k] <- sum(w[i,1:k-1])/(k-1)
   }
```

```
}
totresdev <- sum(resdev[])
                                 #Total Residual Deviance
d[1]<-0
           # treatment effect is zero for control arm
# vague priors for treatment effects
for (k \text{ in } 2:nt) \{ d[k] \sim dnorm(0,.0001) \}
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k \text{ in 1:nt}) \{ T[k] <- A + d[k] \}
for (k in 1:nt) {
rk[k]<-rank(d[],k)
best[k]<-equals(rank(d[],k),1)}
for (c in 1:(nt-1))
{ for (k in (c+1):nt)
\{ D[c,k] \leftarrow d[k] - d[c] \} \}
                     # *** PROGRAM ENDS
}
Data
# ns= number of studies; nt=number of treatments
list(ns=10, nt=6, meanA=-1, precA=1)
t[,1]
                                se[,1] se[,2] na[]
        t[,2]
                y[,1]
                        y[,2]
1
        3
                7.85
                        7.65
                                0.41900179
                                                 0.341525987
                                                                 2
1
        4
                        9.32
                                0.931428571  0.398243093  2
                16.45
1
        5
                6.8
                        9.6
                                0.406138466 2.472393026 2
3
        6
                4
                        4.5
                                0.727590861  0.724640716  2
```

3	6	8.5	9.4	0.729143666	0.864332521	2
2	6	12.1	14.2	1.355575969	2.435279909	2
1	2	6.4	5.8	0.670820393	0.491934955	2
1	2	4.8	4.8	0.15666989	0.069631062	2
1	2	7.3	7.1	0.18973666	0.133333333	2
1	3	11.8	11.5	0.721580187	0.763762616	2

```
END
Initial Values
#chain 1
list(d=c( NA, 0,0,0,0,0), sd=1, mu=c(1,0, 0, 0, 0, 0, 1,1,0,2))
#chain 2
list(d=c( NA, -3,1,-1,-3,-1), sd=4, mu=c(1, 2, 0, 0, 1, 1,1,1,0,1))
#chain 3
list(d=c( NA, 2,2,2,2,2), sd=2, mu=c(-2, 1, 0, 0,-1,-1,1,1,0,1))
```

# L.6.6 WinBUGS code for assessment of baseline risk of receiving allogeneic transfusions (Moderate risk group)

```
# Binomial likelihood, logit link
# Baseline random effects model
                    # *** PROGRAM STARTS
model{
for (i in 1:ns){
                   # LOOP THROUGH STUDIES
  r[i] ~ dbin(p[i],n[i])
                               # Likelihood
  logit(p[i]) <- mu[i]
                                       # Log-odds of response
  mu[i] ~ dnorm(m,tau.m) # Random effects model
}
mu.new ~ dnorm(m,tau.m)
                                  # predictive dist. (log-odds)
m \sim dnorm(0,.0001)
                          # vague prior for mean
```

```
var.m <- 1/tau.m
                        # between-trial variance
tau.m <- pow(sd.m,-2) # between-trial precision = (1/between-trial variance)
sd.m ~ dunif(0,5)
                       # vague prior for between-trial SD
#tau.m ~ dgamma(0.001,0.001)
#sd.m <- sqrt(var.m)
logit(R) <- m
                     # posterior probability of response
logit(R.new) <- mu.new # predictive probability of response</pre>
}
Data
list(ns=69) # ns=number of studies
r[]
       n[]
16
       20
23
       70
9
       102
15
       19
8
       21
13
       34
10
       17
10
       22
10
       30
12
       52
17
       82
15
       80
24
       30
13
       86
12
       190
       56
11
```

- 54 658
- 4 62
- 12 42
- 24 43
- 15 19
- 8 20
- 8 25
- 2 6
- 7 10
- 3 12
- 12 13
- 34 38
- 13 21
- 13 21
- 26 26
- 13 78
- 1 20
- 10 50
- 102 120
- 45 50
- 6 20
- 55 100
- 15 38
- 14 25
- 4 51
- 4 5
- 14 24
- 7 330
- 7 20

## **END**

## Inits

# L.6.7 WinBUGS code for number of adult patients receiving allogeneic transfusions (Moderate risk group)

```
NUMBER TRANSFUSED MODERATE RISK
# Binomial likelihood, logit link
# Random effects model for multi-arm trials
model{
                        # *** PROGRAM STARTS
for(i in 1:ns){
                         # LOOP THROUGH STUDIES
  w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
  delta[i,1] <- 0
                       # treatment effect is zero for control arm
  mu[i] \sim dnorm(0,.0001)
                                # vague priors for all trial baselines
  for (k in 1:na[i]) {
                          # LOOP THROUGH ARMS
    r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
    logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
    rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
      + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
                                                                   }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {
                          # LOOP THROUGH ARMS
# trial-specific LOR distributions
    delta[i,k] ~ dnorm(md[i,k],taud[i,k])
```

```
# mean of LOR distributions (with multi-arm trial correction)
     md[i,k] \leftarrow d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
     taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
     w[i,k] \leftarrow (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
     sw[i,k] <- sum(w[i,1:k-1])/(k-1)
   }
 }
totresdev <- sum(resdev[])
                                    # Total Residual Deviance
            # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k \text{ in 2:nt}) \{ d[k] \sim dnorm(0,.0001) \}
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
# Provide estimates of treatment effects T[k] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k \text{ in 1:nt}) \{ logit(T[k]) <- A + d[k] \}
rr [1] < -1
for (k \text{ in } 2:nt) \{rr[k] < -T[k]/T[1] \}
for (c in 1:(nt-1))
{ for (k in (c+1):nt)
\{ lor[c,k] <- d[k] - d[c] \}
log(or[c,k]) \leftarrow lor[c,k]
Irr[c,k] \leftarrow log(rr[k]) - log(rr[c])
log(rrisk[c,k]) <- lrr[c,k] }}</pre>
```

```
for (k in 1:nt) {
rk[k]<-rank(rr[],k)
best[k]<-equals(rank(rr[],k),1)}
}
                  # *** PROGRAM ENDS
Data
# ns= number of studies; nt=number of treatments
list(ns=73, nt=8, meanA=-0.5185, precA=0.479585024669854)
r[,1]
                                                  t[,2]
       r[,2]
              r[,3]
                     n[,1]
                            n[,2]
                                   n[,3]
                                          t[,1]
                                                         t[,3]
                                                                na[]
                                                                2
16
       10
                     20
                            20
                                           1
                                                  4
                                                         NA
              NA
                                   NA
                     70
                                                                2
23
       23
                            70
                                   NA
                                           1
              NA
                                                  4
                                                         NA
9
                                                                2
       8
                     102
                            102
              NA
                                   NA
                                           1
                                                  4
                                                         NA
                                                                2
       9
                     19
                            17
                                                  3
15
              NA
                                   NA
                                           1
                                                         NA
8
                                                                2
       1
                            20
                                           1
                                                  3
              NA
                     21
                                   NA
                                                         NA
                                                                2
13
       4
                     34
                            26
                                   NA
                                           1
                                                  3
              NA
                                                         NA
                                                                2
10
       3
                     17
                            32
                                   NA
                                           1
                                                  3
              NA
                                                         NA
                                                                2
10
       22
                     22
                            47
                                           1
                                                  3
              NA
                                   NA
                                                         NA
                                                                2
10
       5
                     30
                            30
                                           1
                                                  3
              NA
                                   NA
                                                         NA
                                                                2
12
       13
                     52
                            52
                                                  3
              NA
                                   NA
                                           1
                                                         NA
                                                                2
17
       6
                     82
                            76
                                                  3
              NA
                                   NA
                                           1
                                                         NA
                     80
                                                                2
15
       5
              NA
                            80
                                   NA
                                           1
                                                  3
                                                         NA
                     30
                                                                2
24
       4
              NA
                            30
                                   NA
                                           1
                                                  3
                                                         NA
                                                                2
13
       12
              NA
                     86
                            92
                                   NA
                                           1
                                                  3
                                                         NA
                                                                2
12
       29
              NA
                     190
                            382
                                   NA
                                           1
                                                  3
                                                         NA
       6
                     56
                            59
                                   NA
                                           1
                                                  3
                                                                2
11
              NA
                                                         NA
54
       33
                     658
                            321
                                           1
                                                  3
                                                         5
                                                                3
              23
                                   321
4
       2
                                                  5
                                                                2
              NA
                     62
                            56
                                   NA
                                           1
                                                         NA
       23
                     74
                                           4
                                                                2
30
              NA
                            73
                                   NA
                                                  8
                                                         NA
```

NA

NA

NA

5	3	NA	49	49	NA	3	7	NA	2
13	9	NA	101	96	NA	2	6	NA	2
12	2	NA	42	41	NA	1	2	NA	2
24	8	NA	43	43	NA	1	2	NA	2
15	9	NA	19	20	NA	1	2	NA	2
8	4	NA	20	18	NA	1	2	NA	2
8	0	NA	25	25	NA	1	2	NA	2
2	0	NA	6	6	NA	1	2	NA	2
7	1	NA	10	10	NA	1	2	NA	2
3	0	NA	12	12	NA	1	2	NA	2
12	10	NA	13	15	NA	1	2	NA	2
34	17	NA	38	39	NA	1	2	NA	2
13	2	NA	21	21	NA	1	2	NA	2
13	2	NA	21	21	NA	1	2	NA	2
26	47	NA	26	73	NA	1	2	NA	2
13	1	NA	78	79	NA	1	2	NA	2
1	0	NA	20	26	NA	1	2	NA	2
10	15	NA	50	50	NA	1	2	NA	2
102	57	NA	120	120	NA	1	2	NA	2
45	28	NA	50	50	NA	1	2	NA	2
6	1	NA	20	20	NA	1	2	NA	2
55	34	NA	100	100	NA	1	2	NA	2
15	10	NA	38	38	NA	1	2	NA	2
14	16	NA	25	25	NA	1	2	NA	2
4	0	NA	51	50	NA	1	2	NA	2
4	1	NA	5	5	NA	1	2	NA	2
14	3	NA	24	27	NA	1	2	NA	2
7	2	NA	330	330	NA	1	2	NA	2
7	2	NA	20	20	NA	1	2	NA	2

1	0	NA	50	50	NA	1	2	NA	2
23	8	NA	53	47	NA	1	2	NA	2
1	0	NA	16	16	NA	1	2	NA	2
11	4	NA	32	32	NA	1	2	NA	2
6	1	NA	90	90	NA	1	2	NA	2
20	5	NA	73	73	NA	1	2	NA	2
20	9	NA	34	34	NA	1	2	NA	2
8	0	NA	19	20	NA	1	2	NA	2
10	13	NA	20	40	NA	1	2	NA	2
8	5	NA	20	19	NA	1	2	NA	2
3	1	NA	14	15	NA	1	2	NA	2
10	3	NA	37	36	NA	1	2	NA	2
18	7	NA	88	88	NA	1	2	NA	2
7	2	NA	25	25	NA	1	2	NA	2
8	1	NA	24	24	NA	1	2	NA	2
10	6	NA	45	90	NA	1	2	NA	2
20	12	NA	35	32	NA	1	2	NA	2
47	10	NA	50	50	NA	1	2	NA	2
12	3	NA	36	38	NA	1	2	NA	2
18	7	NA	45	45	NA	1	2	NA	2
9	5	NA	35	64	NA	1	2	NA	2
12	3	NA	20	20	NA	1	2	NA	2
19	10	NA	40	40	NA	1	2	NA	2
11	3	NA	49	52	NA	1	2	NA	2

**Initial Values** 

list(

# L.6.8 WinBUGS code for inconsistency model for number of adult patients receiving allogeneic transfusions (Moderate risk group)

Moderate risk number transfused

73 trials (including one 3-arm-trial),

8 treatments

```
# Binomial likelihood, logit link, inconsistency model
```

# Random effects model

model{ # \*\*\* PROGRAM STARTS

for(i in 1:ns){ # LOOP THROUGH STUDIES

delta[i,1]<-0 # treatment effect is zero in control arm

mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines

for (k in 1:na[i]) { # LOOP THROUGH ARMS

```
r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
    logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor</pre>
#Deviance contribution
    rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
     + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
   }
# summed residual deviance contribution for this trial
 resdev[i] <- sum(dev[i,1:na[i]])
 for (k in 2:na[i]) { # LOOP THROUGH ARMS
# trial-specific LOR distributions
    delta[i,k] ~ dnorm(d[t[i,1],t[i,k]],tau)
   }
 }
totresdev <- sum(resdev[]) # Total Residual Deviance
for (c in 1:(nt-1)) { # priors for all mean treatment effects
  for (k \text{ in } (c+1):nt) \{ d[c,k] \sim dnorm(0,.0001) \}
}
sd ~ dunif(0,5) # vague prior for between-trial standard deviation
var <- pow(sd,2) # between-trial variance</pre>
tau <- 1/var # between-trial precision
} # *** PROGRAM ENDS
Data
# Moderate risk number transfused
# nt=no. treatments, ns=no. studies
list(nt=8,ns=73)
```

r[,1]	r[,2]	r[,3]	n[,1]	n[,2]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
16	10	NA	20	20	NA	1	4	NA	2
23	23	NA	70	70	NA	1	4	NA	2
9	8	NA	102	102	NA	1	4	NA	2
15	9	NA	19	17	NA	1	3	NA	2
8	1	NA	21	20	NA	1	3	NA	2
13	4	NA	34	26	NA	1	3	NA	2
10	3	NA	17	32	NA	1	3	NA	2
10	22	NA	22	47	NA	1	3	NA	2
10	5	NA	30	30	NA	1	3	NA	2
12	13	NA	52	52	NA	1	3	NA	2
17	6	NA	82	76	NA	1	3	NA	2
15	5	NA	80	80	NA	1	3	NA	2
24	4	NA	30	30	NA	1	3	NA	2
13	12	NA	86	92	NA	1	3	NA	2
12	29	NA	190	382	NA	1	3	NA	2
11	6	NA	56	59	NA	1	3	NA	2
54	33	23	658	321	321	1	3	5	3
4	2	NA	62	56	NA	1	5	NA	2
30	23	NA	74	73	NA	4	8	NA	2
6	1	NA	49	46	NA	3	7	NA	2
5	3	NA	49	49	NA	3	7	NA	2
13	9	NA	101	96	NA	2	6	NA	2
12	2	NA	42	41	NA	1	2	NA	2
24	8	NA	43	43	NA	1	2	NA	2
15	9	NA	19	20	NA	1	2	NA	2
8	4	NA	20	18	NA	1	2	NA	2
8	0	NA	25	25	NA	1	2	NA	2
2	0	NA	6	6	NA	1	2	NA	2

7	1	NA	10	10	NA	1	2	NA	2
3	0	NA	12	12	NA	1	2	NA	2
12	10	NA	13	15	NA	1	2	NA	2
34	17	NA	38	39	NA	1	2	NA	2
13	2	NA	21	21	NA	1	2	NA	2
13	2	NA	21	21	NA	1	2	NA	2
26	47	NA	26	73	NA	1	2	NA	2
13	1	NA	78	79	NA	1	2	NA	2
1	0	NA	20	26	NA	1	2	NA	2
10	15	NA	50	50	NA	1	2	NA	2
102	57	NA	120	120	NA	1	2	NA	2
45	28	NA	50	50	NA	1	2	NA	2
6	1	NA	20	20	NA	1	2	NA	2
55	34	NA	100	100	NA	1	2	NA	2
15	10	NA	38	38	NA	1	2	NA	2
14	16	NA	25	25	NA	1	2	NA	2
4	0	NA	51	50	NA	1	2	NA	2
4	1	NA	5	5	NA	1	2	NA	2
14	3	NA	24	27	NA	1	2	NA	2
7	2	NA	330	330	NA	1	2	NA	2
7	2	NA	20	20	NA	1	2	NA	2
1	0	NA	50	50	NA	1	2	NA	2
23	8	NA	53	47	NA	1	2	NA	2
1	0	NA	16	16	NA	1	2	NA	2
11	4	NA	32	32	NA	1	2	NA	2
6	1	NA	90	90	NA	1	2	NA	2
20	5	NA	73	73	NA	1	2	NA	2
20	9	NA	34	34	NA	1	2	NA	2
8	0	NA	19	20	NA	1	2	NA	2

10	13	NA	20	40	NA	1	2	NA	2
8	5	NA	20	19	NA	1	2	NA	2
3	1	NA	14	15	NA	1	2	NA	2
10	3	NA	37	36	NA	1	2	NA	2
18	7	NA	88	88	NA	1	2	NA	2
7	2	NA	25	25	NA	1	2	NA	2
8	1	NA	24	24	NA	1	2	NA	2
10	6	NA	45	90	NA	1	2	NA	2
20	12	NA	35	32	NA	1	2	NA	2
47	10	NA	50	50	NA	1	2	NA	2
12	3	NA	36	38	NA	1	2	NA	2
18	7	NA	45	45	NA	1	2	NA	2
9	5	NA	35	64	NA	1	2	NA	2
12	3	NA	20	20	NA	1	2	NA	2
19	10	NA	40	40	NA	1	2	NA	2
11	3	NA	49	52	NA	1	2	NA	2

**INITS** 

### # chain 1

d=structure(.Data=c(NA,0,1,0,0,-2,0,0, NA,NA,0,0,2,0,0,-2, NA,NA,NA,NA,0,0,0,0,0,0, NA,NA,NA,NA,NA,0,0,0,0,0,

#### # chain 2

list(sd=1.5, mu=c(2,1,3,1,2, 0,2,0,-1,3, 2,0,1,3,1, 1,2,-3,2,0, 0,1,1,-3,3, 1,-3,0,-3,0, 3,-3,1,-1,-3, 2,1,3,0,2, 2,1,1,2,1, 1,0,1,0,0, -3,0,1,2,0, 2,0,3,0,2, -2,2,-2,-1,3, 2,0,3,0,2, -2,1,2),

```
d = structure(.Data =c(NA,0,1,0,0,-1,2,0, NA,NA,1,0.5,2,0,0,-2, NA,NA,NA,NA,2,1,1,0,0, NA,NA,NA,NA,0.5,2,0,1,
```

#### # chain 3

list(sd=3, mu=c(2,0.5,3,0.5,2, -2,2,1,-1,3, 2,1,1,3,1, 1,2,-3,2,1, 1,1,0.5,-3,3, 0.5,-3,1,-3,1, 3,-3,0.5,-1,-3, 2,1,3,1,2, 2,0.5,1,2,0.5, 0.5,1,1,1,1, -3,-2,1,2,0, 2,0,3,0,2, -2,2,-2,-1,3, 2,0,3,0,2, -1,0,1),

d = structure(.Data =c(NA,0,1,0,0,-2,0,0, NA,NA,0,1,-2,0,-1,0, NA,NA,NA,NA,2,0,1,0,2, NA,NA,NA,NA,NA,0,1,2,0,

# L.6.9 WinBUGS code for number of units of receiving allogeneic blood transfusions (Moderate risk group)

Units Transfused - Moderate risk

# Normal likelihood, identity link

# Random effects model for multi-arm trials

model{ # \*\*\* PROGRAM STARTS

for(i in 1:ns){ # LOOP THROUGH STUDIES

w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm

delta[i,1] <- 0 # treatment effect is zero for control arm

mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines

for (k in 1:na[i]) { # LOOP THROUGH ARMS

var[i,k] <- pow(se[i,k],2) # calculate variances</pre>

prec[i,k] <- 1/var[i,k] # set precisions</pre>

y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood

theta[i,k] <- mu[i] + delta[i,k] # model for linear predictor

#Deviance contribution

 $dev[i,k] \leftarrow (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]$ 

```
}
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {
                           # LOOP THROUGH ARMS
# trial-specific LOR distributions
    delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
    md[i,k] \leftarrow d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
    taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
    w[i,k] < -(delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
    sw[i,k] <- sum(w[i,1:k-1])/(k-1)
   }
 }
totresdev <- sum(resdev[])
                                   #Total Residual Deviance
d[1]<-0
           # treatment effect is zero for control arm
# vague priors for treatment effects
for (k \text{ in } 2:nt) \{ d[k] \sim dnorm(0,.0001) \}
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k \text{ in 1:nt}) \{ T[k] <- A + d[k] \}
for (k in 1:nt) {
rk[k]<-rank(d[],k)
```

## Data

# ns= number of studies; nt=number of treatments

list(ns=16, nt=4, meanA=-1, precA=1)

t[,1]	t[,2]	t[,3]	y[,1]	y[,2]	y[,3]	se[,1] se[,2]	se[,3] na[]		
1	3	NA	1.68	0.82	NA	0.330358657	0.259513119	NA 2	
1	3	NA	0.71	0.05	NA	0.209489175	0.049193496	NA 2	
1	3	NA	1.9	2.36	NA	0.221359436	0.189748638	NA 2	
1	3	NA	1.06	0.54	NA	0.133789717	0.097375825	NA 2	
1	3	NA	2.29	1.02	NA	0.305 0.28	NA 2		
1	3	NA	1.74	0.22	NA	0.209960314	0.178922702	NA 2	
1	3	4	2.68	1.26	3.49	0.122474487	0.121854359	0.1042572	07 3
1	2	NA	3.58	2.25	NA	0.453219961	0.275118156	NA 2	
1	2	NA	3.46	2.29	NA	0.214373231	0.126118525	NA 2	
1	2	NA	2.5	0.46	NA	0.538998189	0.316415941	NA 2	
1	2	NA	1.6	1.8	NA	0.208710326	0.1394274	NA 2	
1	2	NA	1.89	0.71	NA	0.12303658	0.110308658	NA 2	
1	2	NA	1.55	0.55	NA	0.089461351	0.056597998	NA 2	
1	2	NA	0.84	0.31	NA	0.159099026	0.113137085	NA 2	
1	2	NA	1.11	0.76	NA	0.216898594	0.118585412	NA 2	
1	2	NA	2.2	0.8	NA	0.223606798	0.178885438	NA 2	

```
Initial Values

#chain 1

list(d=c( NA, 0,0,0), sd=1, mu=c(0,0,0,0,0, 0,0,0,0, 0,1,1,1, 0, 0))

#chain 2

list(d=c( NA, -1,-3,1), sd=4, mu=c(0,3,0,-1,0, 2,1,0,-3,0, -2,1,1,1, 2, 0))

#chain 3

list(d=c( NA, 2,2,2), sd=2, mu=c(2,3,1,-1,1, 2,0,0,-3,0, 2,1,-1,1,-2, 0))
```

## L.6.10 WinBUGS code for assessment of baseline risk of mortality (High risk group)- for use in economic model

```
# Binomial likelihood, logit link
# Baseline random effects model
                    # *** PROGRAM STARTS
model{
for (i in 1:ns){
                   # LOOP THROUGH STUDIES
  r[i] \sim dbin(p[i],n[i])
                               # Likelihood
  logit(p[i]) <- mu[i]
                                       # Log-odds of response
  mu[i] ~ dnorm(m,tau.m) # Random effects model
}
mu.new ~ dnorm(m,tau.m)
                                  # predictive dist. (log-odds)
m \sim dnorm(0,.0001)
                          # vague prior for mean
var.m <- 1/tau.m
                        # between-trial variance
tau.m <- pow(sd.m,-2) # between-trial precision = (1/between-trial variance)
```

```
sd.m \sim dunif(0,5)
                        # vague prior for between-trial SD
#tau.m ~ dgamma(0.001,0.001)
#sd.m <- sqrt(var.m)
logit(R) <- m
                     # posterior probability of response
logit(R.new) <- mu.new # predictive probability of response
}
Data
list(ns=24) # ns=number of studies
r[]
       n[]
1
       41
15
       23
1
       40
2
       29
0
       25
3
       97
       50
4
0
       23
3
       96
1
       165
2
       31
3
       278
1
       59
3
       150
3
       20
1
       14
4
       40
4
       19
0
       16
```

## L.6.11 WinBUGS code for assessment of baseline risk of mortality (Moderate risk group)for use in economic model

```
# Binomial likelihood, logit link
# Baseline random effects model
                    # *** PROGRAM STARTS
model{
for (i in 1:ns){
                   # LOOP THROUGH STUDIES
  r[i] ~ dbin(p[i],n[i])
                               # Likelihood
  logit(p[i]) <- mu[i]
                                       # Log-odds of response
  mu[i] ~ dnorm(m,tau.m) # Random effects model
}
mu.new ~ dnorm(m,tau.m)
                                  # predictive dist. (log-odds)
m \sim dnorm(0,.0001)
                          # vague prior for mean
var.m <- 1/tau.m
                        # between-trial variance
tau.m <- pow(sd.m,-2) # between-trial precision = (1/between-trial variance)
sd.m \sim dunif(0,5)
                       # vague prior for between-trial SD
#tau.m ~ dgamma(0.001,0.001)
#sd.m <- sqrt(var.m)
```

```
logit(R) <- m
                   # posterior probability of response
                        # predictive probability of response
logit(R.new) <- mu.new
}
Data
list(ns=10) # ns=number of studies
r[]
      n[]
0
      62
1
      38
0
      78
0
      100
0
      42
1
      35
0
      50
0
      35
0
      86
0
      57
END
Inits
list(mu=c( 0,0,0,0,0, 0,0,0,0,0), sd.m=1, m=0)
list(mu = c(1,-1,-1,-1, -1,-1,-1,-1), sd.m=2, m= -1)
```

## References

- 1 Abuzakuk T, Senthil K, V, Shenava Y, Bulstrode C, Skinner JA, Cannon SR et al. Autotransfusion drains in total knee replacement. Are they alternatives to homologous transfusion? International Orthopaedics. 2007; 31(2):235-239
- 2 Aghdaii N, Kabiri M, Yazdanian F, Ghaffarinejad MH. Effect of retransfusion of heparin remaining in the salvaged blood on postoperative blood loss in coronary artery bypass grafting: Comparison with homologous blood transfusion (running title: Postoperative blood loss in CABG). Iranian Heart Journal. 2012; 13(2):24-34
- 3 Aguilera X, Martinez-Zapata MJ, Bosch A, Urrutia G, Gonzalez JC, Jordan M et al. Efficacy and safety of fibrin glue and tranexamic acid to prevent postoperative blood loss in total knee arthroplasty: a randomized controlled clinical trial. Journal of Bone and Joint Surgery American Volume. 2013; 95(22):2001-2007
- 4 Ahn SW, Shim JK, Youn YN, Song JW, Yang SY, Chung SC et al. Effect of tranexamic acid on transfusion requirement in dual antiplatelet-treated anemic patients undergoing off-pump coronary artery bypass graft surgery. Circulation Journal. 2012; 76(1):96-101
- 5 Alizadeh Ghavidel A, Totonchi Z, Chitsazan M, Gholampour Dehaki M, Jalili F, Farsad F et al. Safety and efficacy of caproamin fides and tranexamic Acid versus placebo in patients undergoing coronary artery revascularization. Journal of Cardiovascular and Thoracic Research. 2014; 6(3):197-202
- 6 Alshryda S, Mason J, Vaghela M, Sarda P, Nargol A, Maheswaran S et al. Topical (intraarticular) tranexamic acid reduces blood loss and transfusion rates following total knee replacement: a randomized controlled trial (TRANX-K). Journal of Bone and Joint Surgery American Volume. 2013; 95(21):1961-1968
- 7 Altinel L, Kaya E, Kose KC, Fidan F, Ergan V, Fidan H. Effect of shed blood retransfusion on pulmonary perfusion after total knee arthroplasty: a prospective controlled study. International Orthopaedics. 2007; 31(6):837-844
- 8 Alvarez JC, Santiveri FX, Ramos I, Vela E, Puig L, Escolano F. Tranexamic acid reduces blood transfusion in total knee arthroplasty even when a blood conservation program is applied. Transfusion. 2008; 48(3):519-525
- 9 Amin A, Watson A, Mangwani J, Nawabi D, Ahluwalia R, Loeffler M. A prospective randomised controlled trial of autologous retransfusion in total knee replacement. Journal of Bone and Joint Surgery British Volume. 2008; 90(4):451-454
- 10 Andreasen JJ, Nielsen C. Prophylactic tranexamic acid in elective, primary coronary artery bypass surgery using cardiopulmonary bypass. European Journal of Cardio-Thoracic Surgery. 2004; 26(2):311-317
- 11 Antinolfi P, Innocenti B, Caraffa A, Peretti G, Cerulli G. Post-operative blood loss in total knee arthroplasty: knee flexion versus pharmacological techniques. Knee Surgery, Sports Traumatology, Arthroscopy. 2014; 22(11):2756-2762
- 12 Armellin G, Casella S, Guzzinati S, Pasini L, Marcassa A, Giron G. Tranexamic acid in aortic valve replacement. Journal of Cardiothoracic and Vascular Anesthesia. 2001; 15(3):331-335

- 13 Atay EF, Guven M, Altintas F, Kadioglu B, Ceviz E, Ipek S. Allogeneic blood transfusion decreases with postoperative autotransfusion in hip and knee arthroplasty. Acta Orthopaedica Et Traumatologica Turcica. 2010; 44(4):306-312
- 14 Baric D, Biocina B, Unic D, Sutlic Z, Rudez I, Vrca VB et al. Topical use of antifibrinolytic agents reduces postoperative bleeding: a double-blind, prospective, randomized study. European Journal of Cardio-Thoracic Surgery. 2007; 31(3):366-371
- 15 Benoni G, Fredin H. Fibrinolytic inhibition with tranexamic acid reduces blood loss and blood transfusion after knee arthroplasty: a prospective, randomised, double-blind study of 86 patients. Journal of Bone and Joint Surgery British Volume. 1996; 78(3):434-440
- 16 Benoni G, Fredin H, Knebel R, Nilsson P. Blood conservation with tranexamic acid in total hip arthroplasty: a randomized, double-blind study in 40 primary operations. Acta Orthopaedica Scandinavica. 2001; 72(5):442-448
- 17 Benoni G, Lethagen S, Nilsson P, Fredin H. Tranexamic acid, given at the end of the operation, does not reduce postoperative blood loss in hip arthroplasty. Acta Orthopaedica Scandinavica. 2000; 71(3):250-254
- 18 Bidolegui F, Arce G, Lugones A, Pereira S, Vindver G. Tranexamic acid reduces blood loss and transfusion in patients undergoing total knee arthroplasty without tourniquet: a prospective randomized controlled trial. Open Orthopaedics Journal. 2014; 8:250-254
- 19 Blauhut B, Harringer W, Bettelheim P, Doran JE, Spath P, Lundsgaard-Hansen P. Comparison of the effects of aprotinin and tranexamic acid on blood loss and related variables after cardiopulmonary bypass. Journal of Thoracic and Cardiovascular Surgery. 1994; 108(6):1083-1091
- 20 Bowley DM, Barker P, Boffard KD. Intraoperative blood salvage in penetrating abdominal trauma: a randomised, controlled trial. World Journal of Surgery. 2006; 30(6):1074-1080
- 21 Bradshaw AR, Monoghan J, Campbell D. Oral tranexamic acid reduces blood loss in total knee replacement arthroplasty. Current Orthopaedic Practice. 2012; 23(3):209-212
- 22 Caglar GS, Tasci Y, Kayikcioglu F, Haberal A. Intravenous tranexamic acid use in myomectomy: a prospective randomized double-blind placebo controlled study. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2008; 137(2):227-231
- 23 Casati V, Bellotti F, Gerli C, Franco A, Oppizzi M, Cossolini M et al. Tranexamic acid administration after cardiac surgery: a prospective, randomized, double-blind, placebocontrolled study. Anesthesiology. 2001; 94(1):8-14
- 24 Casati V, Della Valle P, Benussi S, Franco A, Gerli C, Baili P et al. Effects of tranexamic acid on postoperative bleeding and related hematochemical variables in coronary surgery: Comparison between on-pump and off-pump techniques. Journal of Thoracic and Cardiovascular Surgery. 2004; 128(1):83-91
- 25 Chareancholvanich K, Siriwattanasakul P, Narkbunnam R, Pornrattanamaneewong C. Temporary clamping of drain combined with tranexamic acid reduce blood loss after total knee arthroplasty: a prospective randomized controlled trial. BMC Musculoskeletal Disorders. 2012; 13:124

- 26 Charoencholvanich K, Siriwattanasakul P. Tranexamic acid reduces blood loss and blood transfusion after TKA: a prospective randomized controlled trial. Clinical Orthopaedics and Related Research. 2011; 469(10):2874-2880
- 27 Cheng SC, Hung TS, Tse PY. Investigation of the use of drained blood reinfusion after total knee arthroplasty: a prospective randomised controlled study. Journal of Orthopaedic Surgery. 2005; 13(2):120-124
- 28 Cip J, Widemschek M, Benesch T, Waibel R, Martin A. Does single use of an autologous transfusion system in TKA reduce the need for allogenic blood?: a prospective randomized trial. Clinical Orthopaedics and Related Research. 2013; 471(4):1319-1325
- 29 Claeys MA, Vermeersch N, Haentjens P. Reduction of blood loss with tranexamic acid in primary total hip replacement surgery. Acta Chirurgica Belgica. 2007; 107(4):397-401
- 30 Coffey A, Pittmam J, Halbrook H, Fehrenbacher J, Beckman D, Hormuth D. The use of tranexamic acid to reduce postoperative bleeding following cardiac surgery: a double-blind randomized trial. American Surgeon. 1995; 61(7):566-568
- 31 Corbeau JJ, Monrigal JP, Jacob JP, Cottineau C, Moreau X, Bukowski JG et al. Comparison of effects of aprotinin and tranexamic acid on blood loss in heart surgery. Annales Francaises D'Anesthesie Et De Reanimation. 1995; 14(2):154-161
- 32 Crescenti A, Borghi G, Bignami E, Bertarelli G, Landoni G, Casiraghi GM et al. Intraoperative use of tranexamic acid to reduce transfusion rate in patients undergoing radical retropubic prostatectomy: double blind, randomised, placebo controlled trial. BMJ. 2011; 343:d5701
- 33 Dakir A, Ramalingam B, Ebenezer V, Dhanavelu P. Efficacy of tranexamic acid in reducing blood loss during maxillofacial trauma surgery-a pilot study. Journal of Clinical and Diagnostic Research. 2014; 8(5):ZC06-ZC08
- 34 Dalmau A, Sabate A, Acosta F, Garcia-Huete L, Koo M, Sansano T et al. Tranexamic acid reduces red cell transfusion better than epsilon-aminocaproic acid or placebo in liver transplantation. Anesthesia and Analgesia. 2000; 91(1):29-34
- Damgaard S, Steinbruchel DA. Autotransfusion with cell saver for off-pump coronary artery bypass surgery: a randomized trial. Scandinavian Cardiovascular Journal. 2006; 40(3):194-198
- 36 De Bonis M, Cavaliere F, Alessandrini F, Lapenna E, Santarelli F, Moscato U et al. Topical use of tranexamic acid in coronary artery bypass operations: a double-blind, prospective, randomized, placebo-controlled study. Journal of Thoracic and Cardiovascular Surgery. 2000; 119(3):575-580
- 37 Dell'Amore A, Caroli G, Nizar A, Cassanelli N, Luciano G, Greco D et al. Can topical application of tranexamic acid reduce blood loss in thoracic surgery? A prospective randomised double blind investigation. Heart, Lung and Circulation. 2012; 21(11):706-710
- 38 Diprose P, Herbertson MJ, O'Shaughnessy D, Deakin CD, Gill RS. Reducing allogeneic transfusion in cardiac surgery: a randomized double-blind placebo-controlled trial of antifibrinolytic therapies used in addition to intra-operative cell salvage. British Journal of Anaesthesia. 2005; 94(3):271-278
- 39 Dramis A, Plewes J. Autologous blood transfusion after primary unilateral total knee replacement surgery. Acta Orthopaedica Belgica. 2006; 72(1):15-17

- 40 Ellis MH, Fredman B, Zohar E, Ifrach N, Jedeikin R. The effect of tourniquet application, tranexamic acid, and desmopressin on the procoagulant and fibrinolytic systems during total knee replacement. Journal of Clinical Anesthesia. 2001; 13(7):509-513
- 41 Engel JM, Hohaus T, Ruwoldt R, Menges T, Jurgensen I, Hempelmann G. Regional hemostatic status and blood requirements after total knee arthroplasty with and without tranexamic acid or aprotinin. Anesthesia and Analgesia. 2001; 92(3):775-780
- 42 Esfandiari BR, Bistgani MM, Kabiri M. Low dose tranexamic acid effect on post-coronary artery bypass grafting bleeding. Asian Cardiovascular and Thoracic Annals. 2013; 21(6):669-674
- 43 Farrokhi MR, Kazemi AP, Eftekharian HR, Akbari K. Efficacy of prophylactic low dose of tranexamic acid in spinal fixation surgery: a randomized clinical trial. Journal of Neurosurgical Anesthesiology. 2011; 23(4):290-296
- 44 Fawzy H, Elmistekawy E, Bonneau D, Latter D, Errett L. Can local application of tranexamic acid reduce post-coronary bypass surgery blood loss? A randomized controlled trial. Journal of Cardiothoracic Surgery. 2009; 4:25
- 45 Garneti N, Field J. Bone bleeding during total hip arthroplasty after administration of tranexamic acid. Journal of Arthroplasty. 2004; 19(4):488-492
- 46 Georgiadis AG, Muh SJ, Silverton CD, Weir RM, Laker MW. A prospective double-blind placebo controlled trial of topical tranexamic acid in total knee arthroplasty. Journal of Arthroplasty. 2013; 28(8 Suppl):78-82
- 47 Ghaffari Nejad MH, Baharestani B, Esfandiari R, Hashemi J, Panahipoor A. Evaluation and comparison of using low-dose aprotinin and tranexamic acid in CABG: a double blind randomized clinical trial. Journal of Tehran Heart Center. 2012; 7(1):15-18
- 48 Gill JB, Chase E, Rosenstein AD. The use of tranexamic acid in revision total hip arthroplasty: a pilot study. Current Orthopaedic Practice. United States 2009; 20(2):152-156
- 49 Goel P, Pannu H, Mohan D, Arora R. Efficacy of cell saver in reducing homologous blood transfusions during OPCAB surgery: a prospective randomized trial. Transfusion Medicine. 2007; 17(4):285-289
- 50 Good L, Peterson E, Lisander B. Tranexamic acid decreases external blood loss but not hidden blood loss in total knee replacement. British Journal of Anaesthesia. 2003; 90(5):596-599
- 51 Gungorduk K, Yildirim G, Asicioglu O, Gungorduk OC, Sudolmus S, Ark C. Efficacy of intravenous tranexamic acid in reducing blood loss after elective cesarean section: a prospective, randomized, double-blind, placebo-controlled study. American Journal of Perinatology. 2011; 28(3):233-240
- 52 Hardy JF, Belisle S, Dupont C, Harel F, Robitaille D, Roy M et al. Prophylactic tranexamic acid and epsilon-aminocaproic acid for primary myocardial revascularization. Annals of Thoracic Surgery. 1998; 65(2):371-376
- 53 Hiippala S, Strid L, Wennerstrand M, Arvela V, Mantyla S, Ylinen J et al. Tranexamic acid (Cyklokapron) reduces perioperative blood loss associated with total knee arthroplasty. British Journal of Anaesthesia. 1995; 74(5):534-537

- 54 Hiippala ST, Strid LJ, Wennerstrand MI, Arvela JV, Niemela HM, Mantyla SK et al. Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. Anesthesia and Analgesia. 1997; 84(4):839-844
- 55 Horrow JC, Hlavacek J, Strong MD, Collier W, Brodsky I, Goldman SM et al. Prophylactic tranexamic acid decreases bleeding after cardiac operations. Journal of Thoracic and Cardiovascular Surgery. 1990; 99(1):70-74
- 56 Horrow JC, Van Riper DF, Strong MD, Brodsky I, Parmet JL. Hemostatic effects of tranexamic acid and desmopressin during cardiac surgery. Circulation. 1991; 84(5):2063-2070
- 57 Horstmann WG, Swierstra MJ, Ohanis D, Castelein RM, Kollen BJ, Verheyen CCPM. Reduction of blood loss with the use of a new combined intra-operative and post-operative autologous blood transfusion system compared with no drainage in primary total hip replacement. Bone and Joint Journal. 2013; 95-B(5):616-622
- 58 Horstmann W, Kuipers B, Ohanis D, Slappendel R, Kollen B, Verheyen C. Autologous retransfusion drain compared with no drain in total knee arthroplasty: a randomised controlled trial. Blood Transfusion. 2014; 12 Suppl 1:s176-s181
- 59 Horstmann WG, Swierstra MJ, Ohanis D, Rolink R, Kollen BJ, Verheyen CCPM. Favourable results of a new intraoperative and postoperative filtered autologous blood re-transfusion system in total hip arthroplasty: a randomised controlled trial. International Orthopaedics. 2014; 38(1):13-18
- 60 Husted H, Blond L, Sonne-Holm S, Holm G, Jacobsen TW, Gebuhr P. Tranexamic acid reduces blood loss and blood transfusions in primary total hip arthroplasty: a prospective randomized double-blind study in 40 patients. Acta Orthopaedica Scandinavica. 2003; 74(6):665-669
- 61 Ishida K, Tsumura N, Kitagawa A, Hamamura S, Fukuda K, Dogaki Y et al. Intra-articular injection of tranexamic acid reduces not only blood loss but also knee joint swelling after total knee arthroplasty. International Orthopaedics. 2011; 35(11):1639-1645
- 62 Jansen AJ, Andreica S, Claeys M, D'Haese J, Camu F, Jochmans K. Use of tranexamic acid for an effective blood conservation strategy after total knee arthroplasty. British Journal of Anaesthesia. 1999; 83(4):596-601
- 63 Jares M, Vanek T, Straka Z, Brucek P. Tranexamic acid reduces bleeding after off-pump coronary artery bypass grafting. Journal of Cardiovascular Surgery. 2003; 44(2):205-208
- 64 Jimenez JJ, Iribarren JL, Lorente L, Rodriguez JM, Hernandez D, Nassar I et al. Tranexamic acid attenuates inflammatory response in cardiopulmonary bypass surgery through blockade of fibrinolysis: a case control study followed by a randomized double-blind controlled trial. Critical Care. 2007; 11(6):R117
- 65 Johansson T, Pettersson LG, Lisander B. Tranexamic acid in total hip arthroplasty saves blood and money: a randomized, double-blind study in 100 patients. Acta Orthopaedica. 2005; 76(3):314-319
- 66 Karimi A, Mohammadi SS, Hasheminasab M. Efficacy of tranexamic acid on blood loss during bimaxilary osteotomy: A randomized double blind clinical trial. Saudi Journal of Anaesthesia. 2012; 6(1):41-45

- 67 Karski J, Djaiani G, Carroll J, Iwanochko M, Seneviratne P, Liu P et al. Tranexamic acid and early saphenous vein graft patency in conventional coronary artery bypass graft surgery: a prospective randomized controlled clinical trial. Journal of Thoracic and Cardiovascular Surgery. 2005; 130(2):309-314
- 68 Katoh J, Tsuchiya K, Sato W, Nakajima M, Iida Y. Additional postbypass administration of tranexamic acid reduces blood loss after cardiac operations. Journal of Thoracic and Cardiovascular Surgery. 1997; 113(4):802-804
- 69 Katsaros D, Petricevic M, Snow NJ, Woodhall DD, Van Bergen R. Tranexamic acid reduces postbypass blood use: a double-blinded, prospective, randomized study of 210 patients. Annals of Thoracic Surgery. 1996; 61(4):1131-1135
- 70 Kazemi SM, Mosaffa F, Eajazi A, Kaffashi M, Besheli LD, Bigdeli MR et al. The effect of tranexamic acid on reducing blood loss in cementless total hip arthroplasty under epidural anesthesia. Orthopedics. 2010; 33(1):17
- 71 Kim TK, Chang CB, Kang YG, Seo ES, Lee JH, Yun JH et al. Clinical value of tranexamic acid in unilateral and simultaneous bilateral TKAs under a contemporary blood-saving protocol: a randomized controlled trial. Knee Surgery, Sports Traumatology, Arthroscopy. 2014; 22(8):1870-1878
- 72 Kirkos JM, Krystallis CT, Konstantinidis PA, Papavasiliou KA, Kyrkos MJ, Ikonomidis LG. Postoperative re-perfusion of drained blood in patients undergoing total knee arthroplasty: is it effective and cost-efficient? Acta Orthopaedica Belgica. 2006; 72(1):18-23
- 73 Klein AA, Nashef SAM, Sharples L, Bottrill F, Dyer M, Armstrong J et al. A randomized controlled trial of cell salvage in routine cardiac surgery. Anesthesia and Analgesia. 2008; 107(5):1487-1495
- 74 Krohn CD, Sorensen R, Lange JE, Riise R, Bjornsen S, Brosstad F. Tranexamic acid given into the wound reduces postoperative blood loss by half in major orthopaedic surgery. European Journal of Surgery Supplement. 2003;(588):57-61
- 75 Kuitunen A, Hiippala S, Vahtera E, Rasi V, Salmenpera M. The effects of aprotinin and tranexamic acid on thrombin generation and fibrinolytic response after cardiac surgery. Acta Anaesthesiologica Scandinavica. 2005; 49(9):1272-1279
- 76 Later AFL, Maas JJ, Engbers FHM, Versteegh MIM, Bruggemans EF, Dion RAE et al. Tranexamic acid and aprotinin in low- and intermediate-risk cardiac surgery: a non-sponsored, double-blind, randomised, placebo-controlled trial. European Journal of Cardio-Thoracic Surgery. 2009; 36(2):322-329
- 77 Lee YC, Park SJ, Kim JS, Cho CH. Effect of tranexamic acid on reducing postoperative blood loss in combined hypotensive epidural anesthesia and general anesthesia for total hip replacement. Journal of Clinical Anesthesia. 2013; 25(5):393-398
- 78 Lemay E, Guay J, Cote C, Roy A. Tranexamic acid reduces the need for allogenic red blood cell transfusions in patients undergoing total hip replacement. Canadian Journal of Anaesthesia. 2004; 51(1):31-37
- 79 Lundin ES, Johansson T, Zachrisson H, Leandersson U, Backman F, Falknas L et al. Single-dose tranexamic acid in advanced ovarian cancer surgery reduces blood loss and transfusions:

- double-blind placebo-controlled randomized multicenter study. Acta Obstetricia Et Gynecologica Scandinavica. 2014; 93(4):335-344
- 80 MacGillivray RG, Tarabichi SB, Hawari MF, Raoof NT. Tranexamic acid to reduce blood loss after bilateral total knee arthroplasty: a prospective, randomized double blind study. Journal of Arthroplasty. 2011; 26(1):24-28
- 81 Maddali MM, Rajakumar MC. Tranexamic acid and primary coronary artery bypass surgery: a prospective study. Asian Cardiovascular and Thoracic Annals. 2007; 15(4):313-319
- 82 Mansour EE, Mustafa B. Aprotinin versus tranexamic acid in patients receiving aspirin and undergoing off-pump coronary artery bypass. Egyptian Journal of Anaesthesia. 2004; 20(3):229-236
- 83 Mehr-Aein A, Davoodi S, Madani-Civi M. Effects of tranexamic acid and autotransfusion in coronary artery bypass. Asian Cardiovascular and Thoracic Annals. 2007; 15(1):49-53
- 84 Menichetti A, Tritapepe L, Ruvolo G, Speziale G, Cogliati A, Di Giovanni C et al. Changes in coagulation patterns, blood loss and blood use after cardiopulmonary bypass: aprotinin vs tranexamic acid vs epsilon aminocaproic acid. Journal of Cardiovascular Surgery. 1996; 37(4):401-407
- 85 Mercer KG, Spark JI, Berridge DC, Kent PJ, Scott DJ. Randomized clinical trial of intraoperative autotransfusion in surgery for abdominal aortic aneurysm. British Journal of Surgery. 2004; 91(11):1443-1448
- 86 Moonen AF, Knoors NT, van Os JJ, Verburg AD, Pilot P. Retransfusion of filtered shed blood in primary total hip and knee arthroplasty: a prospective randomized clinical trial. Transfusion. 2007; 47(3):379-384
- 87 Murphy GJ, Allen SM, Unsworth-White J, Lewis CT, Dalrymple-Hay MJ. Safety and efficacy of perioperative cell salvage and autotransfusion after coronary artery bypass grafting: a randomized trial. Annals of Thoracic Surgery. 2004; 77(5):1553-1559
- 88 Murphy GJ, Rogers CS, Lansdowne WB, Channon I, Alwair H, Cohen A et al. Safety, efficacy, and cost of intraoperative cell salvage and autotransfusion after off-pump coronary artery bypass surgery: a randomized trial. Journal of Thoracic and Cardiovascular Surgery. 2005; 130(1):20-28
- 89 Murphy GJ, Mango E, Lucchetti V, Battaglia F, Catapano D, Rogers CA et al. A randomized trial of tranexamic acid in combination with cell salvage plus a meta-analysis of randomized trials evaluating tranexamic acid in off-pump coronary artery bypass grafting. Journal of Thoracic and Cardiovascular Surgery. 2006; 132(3):475-478
- 90 Naumenko SE, Pokrovskii MG, Belavin AS, Kim SF. Blood-saving effectiveness of preoperative reservation of autoblood for surgical treatment of ischemic heart disease. Vestnik Khirurgii Imeni I I Grekova. 2003; 162(2):59-64
- 91 Niranjan G, Asimakopoulos G, Karagounis A, Cockerill G, Thompson M, Chandrasekaran V. Effects of cell saver autologous blood transfusion on blood loss and homologous blood transfusion requirements in patients undergoing cardiac surgery on- versus off-cardiopulmonary bypass: a randomised trial. European Journal of Cardio-Thoracic Surgery. 2006; 30(2):271-277

- 92 Niskanen RO, Korkala OL. Tranexamic acid reduces blood loss in cemented hip arthroplasty: a randomized, double-blind study of 39 patients with osteoarthritis. Acta Orthopaedica. 2005; 76(6):829-832
- 93 Nouraei M, Gholipour BA, Ghafari R, Habibi MR, Emami ZA, Sharifi N. Decreasing blood loss and the need for transfusion after CABG surgery: A double-blind randomized clinical trial of topical tranexamic acid. Turkish Journal of Medical Sciences. 2013; 43(2):273-278
- 94 Oremus K, Sostaric S, Trkulja V, Haspl M. Influence of tranexamic acid on postoperative autologous blood retransfusion in primary total hip and knee arthroplasty: a randomized controlled trial. Transfusion. 2014; 54(1):31-41
- 95 Orpen NM, Little C, Walker G, Crawfurd EJP. Tranexamic acid reduces early post-operative blood loss after total knee arthroplasty: a prospective randomised controlled trial of 29 patients. Knee. 2006; 13(2):106-110
- 96 Pleym H, Tjomsland O, Asberg A, Lydersen S, Wahba A, Bjella L et al. Effects of autotransfusion of mediastinal shed blood on biochemical markers of myocardial damage in coronary surgery. Acta Anaesthesiologica Scandinavica. 2005; 49(9):1248-1254
- 97 Pleym H, Stenseth R, Wahba A, Bjella L, Karevold A, Dale O. Single-dose tranexamic acid reduces postoperative bleeding after coronary surgery in patients treated with aspirin until surgery. Anesthesia and Analgesia. 2003; 96(4):923-928
- 98 Rajesparan K, Biant LC, Ahmad M, Field RE. The effect of an intravenous bolus of tranexamic acid on blood loss in total hip replacement. Journal of Bone and Joint Surgery British Volume. 2009; 91(6):776-783
- 99 Raviraj A, Anand A, Chakravarthy M, Kumarswamy S, Prabhu A, Pai S. Tranexamic acid reduces blood loss in simultaneous bilateral total knee arthroplasty: a randomized control trial. European Journal of Orthopaedic Surgery and Traumatology. 2012; 22(5):381-386
- 100 Reyes G, Prieto M, Alvarez P, Orts M, Bustamante J, Santos G et al. Cell saving systems do not reduce the need of transfusion in low-risk patients undergoing cardiac surgery. Interactive Cardiovascular and Thoracic Surgery. 2011; 12(2):189-193
- 101 Roy SP, Tanki UF, Dutta A, Jain SK, Nagi ON. Efficacy of intra-articular tranexamic acid in blood loss reduction following primary unilateral total knee arthroplasty. Knee Surgery, Sports Traumatology, Arthroscopy. 2012; 20(12):2494-2501
- 102 Sa-Ngasoongsong P, Channoom T, Kawinwonggowit V, Woratanarat P, Chanplakorn P, Wibulpolprasert B et al. Postoperative blood loss reduction in computer-assisted surgery total knee replacement by low dose intra-articular tranexamic acid injection together with 2-hour clamp drain: a prospective triple-blinded randomized controlled trial. Orthopedic Reviews. 2011; 3(2):e12
- 103 Sa-Ngasoongsong P, Wongsak S, Chanplakorn P, Woratanarat P, Wechmongkolgorn S, Wibulpolprasert B et al. Efficacy of low-dose intra-articular tranexamic acid in total knee replacement; a prospective triple-blinded randomized controlled trial. BMC Musculoskeletal Disorders. 2013; 14:340
- 104 Sadeghi M, Mehr-Aein A. Does a single bolus dose of tranexamic acid reduce blood loss and transfusion requirements during hip fracture surgery? A prospective randomized double blind study in 67 patients. Acta Medica Iranica. 2007; 45(6):437-442

- 105 Santos ATL, Kalil RAK, Bauemann C, Pereira JB, Nesralla IA. A randomized, double-blind, and placebo-controlled study with tranexamic acid of bleeding and fibrinolytic activity after primary coronary artery bypass grafting. Brazilian Journal of Medical and Biological Research. 2006; 39(1):63-69
- 106 Seo JG, Moon YW, Park SH, Kim SM, Ko KR. The comparative efficacies of intra-articular and IV tranexamic acid for reducing blood loss during total knee arthroplasty. Knee Surgery, Sports Traumatology, Arthroscopy. 2013; 21(8):1869-1874
- 107 Shahid A, Khan A. Tranexamic acid in decreasing blood loss during and after caesarean section. Journal of the College of Physicians and Surgeons--Pakistan. 2013; 23(7):459-462
- 108 Shi J, Ji H, Ren F, Wang G, Xu M, Xue Y et al. Protective effects of tranexamic acid on clopidogrel before coronary artery bypass grafting: a multicenter randomized trial. JAMA Surgery. 2013; 148(6):538-547
- 109 Shi J, Wang G, Lv H, Yuan S, Wang Y, Ji H et al. Tranexamic acid in on-pump coronary artery bypass grafting without clopidogrel and aspirin cessation: randomized trial and 1-year follow-up. Annals of Thoracic Surgery. 2013; 95(3):795-802
- 110 Sirvinskas E, Veikutiene A, Benetis R, Grybauskas P, Andrejaitiene J, Veikutis V et al. Influence of early re-infusion of autologous shed mediastinal blood on clinical outcome after cardiac surgery. Perfusion. 2007; 22(5):345-352
- 111 Smith LK, Williams DH, Langkamer VG. Post-operative blood salvage with autologous retransfusion in primary total hip replacement. Journal of Bone and Joint Surgery British Volume. 2007; 89(8):1092-1097
- 112 So-Osman C, Nelissen RG, Eikenboom HC, Brand A. Efficacy, safety and user-friendliness of two devices for postoperative autologous shed red blood cell re-infusion in elective orthopaedic surgery patients: A randomized pilot study. Transfusion Medicine. 2006; 16(5):321-328
- 113 So-Osman C, Nelissen RGHH, Koopman-van Gemert AWMM, Kluyver E, Poll RG, Onstenk R et al. Patient blood management in elective total hip- and knee-replacement surgery (part 2): a randomized controlled trial on blood salvage as transfusion alternative using a restrictive transfusion policy in patients with a preoperative hemoglobin above 13 g/dl. Anesthesiology. 2014; 120(4):852-860
- 114 Sorin A, Claeys MA, Jansen A, D'Haese J, Camu F. Reduction of blood loss by tranexamic acid in total knee replacement. Journal of Bone and Joint Surgery British Volume. 1999; 81-B(Suppl II):234
- 115 Speekenbrink RG, Vonk AB, Wildevuur CR, Eijsman L. Hemostatic efficacy of dipyridamole, tranexamic acid, and aprotinin in coronary bypass grafting. Annals of Thoracic Surgery. 1995; 59(2):438-442
- 116 Taghaddomi RJ, Mashhadinezhad H, Attar ARS, Peivandi A. The effect of intravenous tranexamic acid on blood loss in lumbar hernial disc resection under inhalation and total intravenous anesthesia. Iranian Red Crescent Medical Journal. 2009; 11(3):265-270
- 117 Tanaka N, Sakahashi H, Sato E, Hirose K, Ishima T, Ishii S. Timing of the administration of tranexamic acid for maximum reduction in blood loss in arthroplasty of the knee. Journal of Bone and Joint Surgery British Volume. 2001; 83(5):702-705

- 118 Thomassen BJW, den Hollander PHC, Kaptijn HH, Nelissen RGHH, Pilot P. Autologous wound drains have no effect on allogeneic blood transfusions in primary total hip and knee replacement: a three-arm randomised trial. Bone and Joint Journal. 2014; 96-B(6):765-771
- 119 Thomassen BJW, Pilot P, Scholtes VAB, Grohs JG, Holen K, Bisbe E et al. Limit allogeneic blood use with routine re-use of patient's own blood: a prospective, randomized, controlled trial in total hip surgery. PloS One. 2012; 7(9):e44503
- 120Tripkovic B, Bukovic D, Sakic K, Sakic S, Bukovic N, Radakovic B. Quality of the blood sampled from surgical drainage after total hip arthroplasty. Collegium Antropologicum. 2008; 32(1):153-160
- 121 Uozaki Y, Watanabe G, Kotou K, Ueyama K, Doi Y, Misaki T. Effect of tranexamic acid on blood loss reduction after cardiopulmonary bypass. Japanese Journal of Thoracic and Cardiovascular Surgery. 2001; 49(5):273-278
- 122 Vanek T, Jares M, Fajt R, Straka Z, Jirasek K, Kolesar M et al. Fibrinolytic inhibitors in off-pump coronary surgery: a prospective, randomized, double-blind TAP study (tranexamic acid, aprotinin, placebo). European Journal of Cardio-Thoracic Surgery. 2005; 28(4):563-568
- 123 Vermeijden WJ, Van Klarenbosch J, Gu YJ, Mariani MA, Buhre WF, Scheeren TWL et al. Effects of cell-saving devices and filters on transfusion in cardiac surgery: A multicenter randomized study. Annals of Thoracic Surgery. 2015; 99(1):26-32
- 124 Vijay BS, Bedi V, Mitra S, Das B. Role of tranexamic acid in reducing postoperative blood loss and transfusion requirement in patients undergoing hip and femoral surgeries. Saudi Journal of Anaesthesia. 2013; 7(1):29-32
- 125 Wang G, Xie G, Jiang T, Wang Y, Wang W, Ji H et al. Tranexamic acid reduces blood loss after off-pump coronary surgery: a prospective, randomized, double-blind, placebo-controlled study. Anesthesia and Analgesia. 2012; 115(2):239-243
- 126 Wei M, Jian K, Guo Z, Wang L, Jiang D, Zhang L et al. Tranexamic acid reduces postoperative bleeding in off-pump coronary artery bypass grafting. Scandinavian Cardiovascular Journal. 2006; 40(2):105-109
- 127 Wiefferink A, Weerwind PW, van Heerde W, Teerenstra S, Noyez L, de Pauw BE et al. Autotransfusion management during and after cardiopulmonary bypass alters fibrin degradation and transfusion requirements. Journal of Extra-Corporeal Technology. 2007; 39(2):66-70
- 128 Wong J, Abrishami A, El Beheiry H, Mahomed NN, Roderick Davey J, Gandhi R et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. Journal of Bone and Joint Surgery American Volume. 2010; 92(15):2503-2513
- 129 Wong J, El Beheiry H, Rampersaud YR, Lewis S, Ahn H, De Silva Y et al. Tranexamic Acid reduces perioperative blood loss in adult patients having spinal fusion surgery. Anesthesia and Analgesia. 2008; 107(5):1479-1486
- 130 Wu CC, Ho WM, Cheng SB, Yeh DC, Wen MC, Liu TJ et al. Perioperative parenteral tranexamic acid in liver tumor resection: a prospective randomized trial toward a "blood transfusion"-free hepatectomy. Annals of Surgery. 2006; 243(2):173-180

- 131 Yang Y, Lv YM, Ding PJ, Li J, Ying-Ze Z. The reduction in blood loss with intra-articular injection of tranexamic acid in unilateral total knee arthroplasty without operative drains: a randomized controlled trial. European Journal of Orthopaedic Surgery and Traumatology. 2014; Epub
- 132 Yassen K, Bellamy MC, Sadek SA, Webster NR. Tranexamic acid reduces blood loss during orthotopic liver transplantation. Clinical Transplantation. 1993; 7(5):453-458
- 133 Yue C, Kang P, Yang P, Xie J, Pei F. Topical application of tranexamic acid in primary total hip arthroplasty: a randomized double-blind controlled trial. Journal of Arthroplasty. 2014; 29(12):2452-2456
- 134Zabeeda D, Medalion B, Sverdlov M, Ezra S, Schachner A, Ezri T et al. Tranexamic acid reduces bleeding and the need for blood transfusion in primary myocardial revascularization. Annals of Thoracic Surgery. 2002; 74(3):733-738
- 135 Zacharopoulos A, Apostolopoulos A, Kyriakidis A. The effectiveness of reinfusion after total knee replacement. A prospective randomised controlled study. International Orthopaedics. 2007; 31(3):303-308
- 136 Zhang XF, Dong JM, Gong ML, Shen SM, Zhou Y, Pan YF et al. Effectiveness of preoperative autologous plateletpheresis combined with intraoperative autotransfusion on the blood coagulation in orthopaedic patients. Zhonghua Wai Ke Za Zhi [Chinese Journal of Surgery]. 2008; 46(2):118-121
- 137 Zhao K, Xu J, Hu S, Wu Q, Wei Y, Liu Y. Autotransfusion of shed mediastinal blood after open heart surgery. Chinese Medical Journal. 2003; 116(8):1179-1182
- 138 Zohar E, Ellis M, Ifrach N, Stern A, Sapir O, Fredman B. The postoperative blood-sparing efficacy of oral versus intravenous tranexamic acid after total knee replacement. Anesthesia and Analgesia. 2004; 99(6):1679-1683