**Draft for Consultation** 

# **Transfusion**

**Blood transfusion** 

NICE guideline Appendices J-K-L 18 May 2015

Draft for consultation

Commissioned by the National Institute for Health and Care Excellence











Transfusion

### 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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# Contents

Appendices J-K-L 51	10
Appendix J: GRADE tables51	10
Appendix K: Forest plots55	55
Appendix L: Network meta-analysis of alternatives to blood transfusion in surgical patients61	12
References	30

# **Appendices J-K-L**

# Appendix J: GRADE tables

J.1 Erythropoietin and iron

# J.1.1 Erythropoietin versus placebo

Quality as	sessment						No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Erythropoietin	Placebo/no erythropoietin	Relative (95% Cl)	Absolute	Quality	Importance
All-cause	mortality at 30 d	days										
7	Randomised 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 trans	fused										
12	Randomised 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 fewer to 236 fewer)	VERY LOW	

Quality as	ssessment						No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Erythropoietin	Placebo/no erythropoietin	Relative (95% CI)	Absolute	Quality	Importance
Number o	of units transfus	ed per patie	nt (Better indicat	ed by lower valu	ues)							
7	Randomised 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 a	dverse events											
6	Randomised 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	
Thrombo	sis											
5	Randomised 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	Randomised 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 stay (B	etter indicat	ted by lower value	es)								
1	Randomised trials	Serious <sub>a,h</sub>	No serious inconsistency	No serious indirectness	No serious imprecision	None	31	32	-	MD 3.00 lower (3.36 to 2.64 lower)	MODERATE	

(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.  $l^2=62\%$ . (d) Significant heterogeneity.  $l^2=60\%$ .

(e) Confidence interval crosses one default MID and line of no effect

(f) Heterogeneity. I<sup>2</sup>=30%.

(g) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect

(h) Unclear randomisation and allocation concealment

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

Ouality as	sessment						No. of patients		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 o	days										
2	Randomised 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	f patients trans	fused										
5	Randomised 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 fewer to 153 fewer)	LOW	
Length of	hospital stay (b	etter indicat	ed by lower value	es)								
1	Randomised 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 events											
1	Randomised 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	Randomised 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 J.1.3

Quality as	sessment						No of natients		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	of patients trans	fused		·	·					·		
2	Randomised 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.  $l^2=66\%$ .
- (c) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect

#### Erythropoietin plus IV iron versus placebo J.1.4

Quality as	sessment						No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Erythropoieti n + IV iron	Placebo	Relative (95% CI)	Absolute		
All-cause	mortality at 30 d	days										
2	Randomised 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	VERY LOW	

Quality as	ssessment						No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Erythropoieti n + IV iron	Placebo	Relative (95% Cl)	Absolute		
										90 more)		
Number o	of patients trans	fused										
4	Randomised 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	
Number o	of units transfus	ed per patie	ent (Better indicat	ed by lower valu	ues)							
2	Randomised 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 stay (B	etter indica	ted by lower valu	es)								
1	Randomised 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 a	dverse events											
1	Randomised trials	Very serious <sup>f</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/10 (0%)	0/10 (0%)	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.  $l^2=69\%$ . (d) Significant heterogeneity.  $l^2=93\%$ .

(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.

1 tio <b>J.1.5</b>	Oral iro	n versus IV i	ron
nal Clinic	Quality ass	essment	
cal Gu	No. of studies	Design	Risk bias
idel	Number of	patients transfo	used
ine Centre,	2	Randomised trials	Serio
201	Length of h	nospital stay (be	tter ir
ы	1	Dandomicod	No

No. of		Risk of							Relative			
studies	Design	bias	Inconsistency	Indirectness	Imprecision	Other	Oral iron	IV iron	(95% CI)	Absolute	Quality	Imp
Number	of patients transf	used										
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	CRIT
Length of	hospital stay (be	etter indicate	ed by lower value	es)								
1	Randomised trials	No serious risk of bias	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 veir	n thrombosis											
1	Randomised trials	No serious risk of bias	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 o	f life (Better indic	ated by low	er values)									
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	62	59	-	MD 0.00 higher (0.23 lower to 0.23 higher)	HIGH	
(a) Uncle (b) Confi (c) Confi	ar randomisation dence interval cro dence interval cro	n, allocation osses one dej osses one dej	concealment an fault MID (1.25) fault MID and lir	d unclear missin and line of no ej ne of no effect.	g data (Garrido- ffect.	Martin 20	012).					

No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Erythropoietin + IV iron	IV iron	Relative (95% Cl)	Absolute		
All-cause m	ortality at 30 da	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	patients transfu	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	erse 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	

(a) Unclear allocation concealment and blinding(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

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

Quality asse	essment						No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Erythropoietin+ Oral iron	Oral iron	Relative (95% Cl)	Absolute	Quality	Importance
All-cause m	ortality 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 more)	VERY LOW	
Number of	patients transfu	ised										
3	Randomised	Serious <sup>a</sup>	No serious	No serious	No serious	None	1/68	32/73	RR 0.06	412 fewer per	MODERATE	

1

Le	ngth of h	ospital stay (be	tter indicate	ed by lower values	5)							
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
Inf	fections											
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
De	eep vein t	thrombosis										
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
Ot	her thro	mbovascular eve	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

imprecision

indirectness

(1.5%)

(43.8%)

(0.02 to

0.25)

1000 (from

329 fewer to 430 fewer)

(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

inconsistency

(c) Unclear randomisation, blinding and allocation concealment.

(d) Open label. No blinding.

(e) Confidence interval crosses one default MID and line of no effect

#### Erythropoietin plus oral iron or IV iron versus oral or IV iron J.1.8 6

Quality ass	essment					No. of patients		Effect			
No. of	Design	Risk of bias Inconsistency	Indirectness	Imprecision	Other	EPO+ IV iron or	Placebo+IV iron	Relative	Absolute	Quality	Importance

studies							oral iron	or oral iron	(95% CI)			
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	

(a) Allocation concealment not reported.

(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

Quality as	sessment						No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intra-operative cell salvage	Standard treatment	Relative (95% Cl)	Absolute	Quality	Importance
No. expos	ed 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	

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Mortality	at up to 30 day	/S												
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 va	lues)										
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			
(d) The mo (b) The co (c) Downg (d) The co	ajority of the evi nfidence intervo iraded by one in nfidence intervo	al crosses o al crosses o acrement d al crosses b	at very high risk ne MID. ue to heterogene oth MIDs.	of blas. tity, 12=65%.										
Quality a	The confidence interval crosses both WIDS.													
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Post Op CS	Standard treatment	Relative (95% Cl)	Absolute	Quality	Importance		
No. expo	sed to allogenei	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	llogeneic blood	l transfused	d (Better indicate	ed by lower valu	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	No serious	Very serious <sup>c</sup>	None	1/25 (4%)	0/25 (0%)	RR 3 (0.13 to 70.3)	-	VERY LOW			
	citato	Serious					( . , . ,	(0,0)						

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	length of stay (E	Better indi	cated by lower va	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	
(a) The m (b) The co (c) The co	ajority of the even ofidence intervo ofidence intervo	idence was al crosses c al crosses b	s at very high risk one MID. ooth MIDs.	of bias.								
Quality a	ssessment						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% Cl)	Absolute	Quality	Importance
No. expo	sed to allogenei	ic 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	ction											
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 o	f hospital stay (E	Better indi	cated by lower va	alues)								
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	
() = 1	· ·· ··	., .										

(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 I	MIDs.
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Quality a	ssessment						No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intra-operative cell salvage +TXA	Intra-operative cell salvage	Relative (95% CI)	Absolute	Quality	Importance
No. expo	sed to allogenei	c 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) 2	161 fewer per 1000 from 83 fewer to 222 fewer)	VERY LOW	
Units of <b>b</b>	blood transfused	l (Better ir	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	- I t	MD 1.56 lower (1.84 to 1.29 lower)	VERY LOW	
Mortality	v 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)	) more per 1000 from 9 fewer to 147 nore)	VERY LOW	
Length of	f 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	
<ul><li>(a) The mo</li><li>(b) The co</li><li>(c) Downg</li><li>(d) The co</li></ul>	ajority of the evi nfidence interva graded by one in nfidence interva	dence is a l crosses c crement a l crosses b	t very high risk of one MID. lue to heterogene ooth MIDs.	bias. ity; 12=61%.								
Quality a	ssassmant						No of natients		Effect			
No. of		Risk of					Intra-operative		Relative			
studies	Design	bias	Inconsistency	Indirectness	Imprecision	Other	cell salvage +TXA	TXA	(95% CI)	Absolute	Quality	Importance
No. expo	sed to allogenei	c blood										
1	Randomised	Very	No serious	No serious	Very serious <sup>b</sup>	None	12/34	13/29	RR 0.79 (0.43	94 fewer per 1000	VERY LOW	

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	trials	serious	<sup>a</sup> inconsisten	cy indirectr	ness			(35.3%)	(44.8%)	to 1.45)	(f to	from 256 fewer o 202 more)		
Mortality	/ at 30 days													
1	Randomised trials	Very serious	No serious a inconsisten	No serio cy indirectr	ous Very ness	serious <sup>b</sup>	None	4/34 (11.8%)	0/29 (0%)	RR 7.71 to 137.5	(0.43 - 3)		VERY LOW	
Infection	S													
1	Randomised trials	Very serious	No serious a inconsisten	No serio cy indirectr	ness Very	serious <sup>b</sup>	None	5/34 (14.7%)	4/29 (13.8%)	RR 1.07 to 3.6)	(0.32 1 (f 3	0 more per 1000 from 94 fewer to 59 more)	VERY LOW	
Length o	f stay in hospita	l (Better	indicated by lo	ower values)										
1	Randomised trials	Very serious	No serious a inconsisten	No serio cy indirectr	ness Very	serious <sup>b</sup>	None	34	29	-	№ (3 7	/ID 2.1 higher 3.36 lower to 56 higher)	VERY LOW	
(a) The m (b) The co	ajority of the ev nfidence intervo	idence is al crosses	at very high ri both MIDs.	isk of bias.										
Quality a	ssessment							No. of patients		Effect				
No. of studies	Design	Risk of bias	Inconsisten	cy Indirecti	ness Impro	ecision	Other	Post-operative cell salvage +TX	АТХА	Relative (95% Cl)	Al	bsolute	Quality	Importance
No. of pa	tients with allo	geneic blo	ood transfusio	n										
1	Randomised trials	Very serious <sup>6</sup>	No serious inconsisten	No serio cy indirectr	ous No se ness impre	erious ecision	None	0/17 (0%)	0/17 (0%)	not poole	ed no	ot pooled	LOW	
(a) The m	ajority of the ev	idence is	at very high ri	isk of bias.							1			
Quality a	ssessment						No. of pa	atients			Fffect			
No. of studies	Ri Design bi	isk of ias In	nconsistency	Indirectness	Imprecision	Other	Intra-ope salvage + cell salva	erative cell - post-operative - ge +TXA	Intra-operative co salvage + post-op cell salvage	ell perative	Relative (95% CI	e ) Absolute	Quality	Importance
No. expo	sed to allogene	ic blood												
1	Randomised V	ery N	o serious	No serious	Very serious	<sup>b</sup> None	13/50		14/50		RR 0.93	20 fewer per	VERY	

	trials	serious <sup>a</sup> iı	nconsistency	indirectness		(2	26%)	(28%)		(0.49 to 1.77)	1000 (from 143 fewer to 216 more)	LOW	
Units of	blood transfus	ed (Better	indicated by lo	ower values)									
1	Randomised trials	Very N serious <sup>a</sup> ii	lo serious nconsistency	No serious S indirectness	Serious <sup>c</sup> N	lone 1	3	14		-	MD 0.25 higher (0.32 lower to 0.82 higher)	VERY LOW	
Mortality	y at 30 days		ľ					ľ				· · ·	
1	Randomised trials	Very N serious <sup>a</sup> ii	lo serious nconsistency	No serious I indirectness i	No serious M Mprecision	None 0 ((	/50 0%)	0/50 (0%)		Not pooled	Not pooled	LOW	
(a) The m (b) The co (c) The co	ajority of the o onfidence inter onfidence inter	evidence w val crosses val crosses	vas at very high s both MIDs. s one MID.	risk of bias.									
Quality a	issessment	Dialy of					No. of patients Intra-operative cell		Effect				
studies	Design	bias	Inconsistend	cy Indirectnes	s Imprecision	Other	cell salvage + post-opera	TXA	(95% CI)	Absc	lute	Quality	Importance
No. expo	osed to alloger	neic blood			-				-				
1	Randomised trials	l Very serious	No serious inconsistence	No serious cy indirectnes	Very s serious <sup>b</sup>	None	31/102 (30.4%)	33/111 (29.7%)	RR 1.02 (0.6 1.54)	58 to 6 mc 95 fe	ere per 1000 (from wer to 161 more)	VERY LOW	
Any infe	ction												
1	Randomised trials	l Serious	<sup>a</sup> No serious inconsistenc	No serious cy indirectnes	Very s serious <sup>b</sup>	None	6/102 (5.9%)	5/111 (4.5%)	RR 1.31 (0.4 4.15)	41 to 14 m (from more	ore per 1000 n 27 fewer to 142 e)	VERY LOW	
(a) The m (b) The co	ajority of the onfidence inter	evidence is val crosses	at very high ris s both MIDs.	sk of bias.									
Quality a	ssessment						No. of patients			Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	n Othe	Stanc er TXA High	lard treatment risk- adults	or placebo-	Relative (95% Cl)	Absolute	Quality	Importance

No. of pa	tients needing	g blood tra	insfusions								
38	Randomised trials	Serious <sup>a</sup>	Serious <sup>b</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
No. of u	nits of blood tr	ansfused -	All Patients (Be	tter indicated b	y lower values)						
17	Randomised trials	Serious <sup>a</sup>	Serious <sup>b</sup>	No serious indirectness	No serious imprecision	None	953	965	-	MD 0.0.83 lower (1.17 to 0.5 lower)	LOW
Mortalit	/										
31	Randomised 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 o	f hospital stay	(Better in	dicated by lower	values)							
3	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	89	93	-	MD 0.08 lower (0.35 lower to 0.18 higher)	MODERAT E
Infectior	s	·							·		
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	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	otic complication	ons									
10	Randomised trials	Serious <sup>a</sup>	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
<ul> <li>(a) Major</li> <li>(b) Down</li> <li>(c) Confid</li> <li>(d) Down</li> <li>Adults</li> </ul>	ity of the evide graded by one ence interval c graded by one <b>moderate</b>	nce was a increment crosses one increment <b>risk gro</b>	t high risk of bia due to heteroge MID. as the point est	s. eneity, 12=72%. imate varies wi	dely across stud	lies, une.	xplained by s	subgroup analysis.			

5

J.2.2

No. of	Docign	Risk of	Inconsistancy	Indiractnoss	Improvision	Othor	Intra-operative	Standard	Relative	Abcoluto		
	Design		inconsistency	munectness	Imprecision	other	cell salvage	treatment	(95% CI)	Absolute		
No. expo	ised to allogene	ic blood										
3	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	None	37/192 (19.3%)	48/192 (25%)	RR 0.74 (0.5 to 1.12)	5 65 fewer per 1000 (from 125 fewer to 30 more)	n VERY LOW	
) Major ) Confid	ity of the eviden lence interval cro	ice was at osses one l	very high risk of b MID.	ias.								
assessm	lent						atients					
tudies		bias	stency	iness	sion		erative cell salvage	d treatment	: (95% CI) :e			ince
osed to a	allogeneic bloor	ł										
	nised trials	rious <sup>a</sup>	)	ous indirectness	:		54 (12%)	77 (16.3%)	(0.41 to er 0.83) to	per 1000 (from 28 fewer 2 96 fewer)	W	
allogen	eic blood transf	used (Bett	er indicated by lo	ower values)								
	nised trials	rious <sup>a</sup>	t	ous indirectness	2				2    0	lower (1.31 to 0.33	W	
n				2115	rious <sup>e</sup>				(0.53 to pe	er 1000 (from 3 fewer to 3	W	
n	nised trials	rious <sup>a</sup>	ous inconsistency	indirectness			(1.5%)	(0.7%)	6.07) 31	/ more)		
n I length (	nised trials of stay (Better in	rious <sup>a</sup> ndicated b	inconsistency	indirectness			(1.5%)	(0.7%)	6.07) 3	/ more)		

National Clinical Guideline Centre, 2015 1 2 3

(c) Confidence interval crosses one MID.

(e) Confidence interval crosses both MIDs.

(d) Downgraded by one increment due to heterogeneity,  $l^2$ =88%.

Quality as	sessment							No. of J	patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectne	ss Impr	ecision	Other conside rations	Intra-o salvage operati	perative cell + post- ve cell salvage	Standard treatment	Relative (95% CI)	Absolute	Quality	Importance
No. expos	ed to allogenei	c blood												
2	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No seriou: indirectne	s Very ss	serious <sup>b</sup>	None	25/377 (6.6%)		58/720 (8.1%)	RR 0.84 (0.54 to 1.33)	13 fewer per 1 (from 37 fewer 27 more)	000 VERY to LOW	
Units of a	llogeneic blood	transfuse	d (Better indicat	ed by lower v	alues)									
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No seriou: indirectne	s No se ss impr	erious ecision	None	23		54	-	MD 0.81 highe (0.49 higher to 1.13 higher)	r LOW	
Infection														
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No seriou: indirectne	s Very ss	serious <sup>b</sup>	None	1/56 (1.8%)		0/62 (0%)	RR 3.32 (0.14 to 79.77)		VERY LOW	
Length of	stay (Better ind	licated by	lower values)											
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No seriou: indirectne	s Serio ss	us <sup>c</sup>	None	56		62	-	MD 0.2 higher lower to 0.6 higher)	(0.2 VERY LOW	
Mortality														
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectne	s Very ss	serious <sup>b</sup>	None	1/56 (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 as	uality assessment						No. of pa	atients		Effect				
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecisior	n Other	Intra-ope cell salva	erative Ige +TXA	Intra-operativo cell salvage	e Relative (95% CI)	Absolute	C	Quality	Importance

No. exposed to allogeneic blood													
1	L	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	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	
ι	Jnits of b	lood transfused	l (Better in	ndicated by lowe	er values)								
1	L	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>c</sup>	None	73	74	-	MD 0.46 lower (1.1 lower to 0.18 higher)	VERY LOW	
L	ength of.	stay in hospital	(Better in	ndicated by lowe	er values)								
1	L	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>c</sup>	None	73	74	-	MD 0.72 higher (0.85 lower to 2.29 higher)	VERY LOW	
(a) (b) (c)	) Majorit ) Confide ) Confide	y of the evidend nce interval cro nce interval cro	ce was at osses one l osses both	very high risk of MID. MIDs.	bias.								
c	Quality as	sessment			1	1		No. of patients		Effect	-		
			D' 1 C					<b>.</b>	Deat an entite	Deletive			
N S	lo. of tudies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Post-operative cell salvage +TXA	cell salvage	(95% CI)	Absolute	Quality	Importance
N S N	No. of tudies No. expos	Design ed to allogenei	bias biod	Inconsistency	Indirectness	Imprecision	Other	Post-operative cell salvage +TXA	cell salvage	(95% CI)	Absolute	Quality	Importance
N S N 2	No. of tudies No. expos 2	Design ed to allogeneio Randomised trials	kisk of bias c blood Very serious <sup>a</sup>	Inconsistency No serious inconsistency	Indirectness No serious indirectness	Imprecision Serious <sup>b</sup>	Other None	4/95 (4.2%)	11/98 (11.2%)	RR 0.37 (0.12 to 1.14)	Absolute 71 fewer per 1000 (from 99 fewer to 16 more)	Quality VERY LOW	Importance
N S 2 T	No. of tudies No. expos	Design ed to allogenei Randomised trials ic complication	kisk of bias c blood Very serious <sup>a</sup>	Inconsistency No serious inconsistency	Indirectness No serious indirectness	Imprecision Serious <sup>b</sup>	Other None	Post-operative cell salvage +TXA 4/95 (4.2%)	11/98 (11.2%)	Relative (95% CI) RR 0.37 (0.12 to 1.14)	Absolute 71 fewer per 1000 (from 99 fewer to 16 more)	Quality VERY LOW	Importance
N S 2 T 1	No. of tudies No. expos P	Design ed to allogenei Randomised trials tic complication Randomised trials	kisk of bias c blood Very serious <sup>a</sup> s Very serious <sup>a</sup>	Inconsistency No serious inconsistency No serious inconsistency	Indirectness No serious indirectness No serious indirectness	Imprecision Serious <sup>b</sup> Very serious <sup>c</sup>	Other None None	Post-operative cell salvage +TXA 4/95 (4.2%) 0/49 (0%)	Post-operative cell salvage 11/98 (11.2%) 2/49 (4.1%)	Relative (95% CI) RR 0.37 (0.12 to 1.14) RR 0.2 (0.01 to 4.06)	Absolute 71 fewer per 1000 (from 99 fewer to 16 more) 33 fewer per 1000 (from 40 fewer to 125 more)	Quality VERY LOW	Importance
N 5 2 1 ( <i>a</i> ) ( <i>b</i> ) ( <i>c</i> )	No. of tudies No. expos hrombot Majorit Confide Confide	Design ed to allogenei Randomised trials ic complication Randomised trials y of the evidence ince interval cro	Risk of bias c blood Very serious <sup>a</sup> s Very serious <sup>a</sup> ce is at very sess one l bosses both	Inconsistency No serious inconsistency No serious inconsistency ry high risk of bio MID. MIDs.	Indirectness No serious indirectness No serious indirectness as.	Imprecision Serious <sup>b</sup> Very serious <sup>c</sup>	Other None None	Post-operative cell salvage +TXA 4/95 (4.2%) 0/49 (0%)	2/49 (4.1%)	Relative (95% CI) RR 0.37 (0.12 to 1.14) RR 0.2 (0.01 to 4.06)	Absolute 71 fewer per 1000 (from 99 fewer to 16 more) 33 fewer per 1000 (from 40 fewer to 125 more)	Quality VERY LOW	Importance
N S 2 1 ( <i>a</i> ) ( <i>b</i> ) ( <i>c</i> )	No. of tudies No. expos Thrombot Majorit Confide Confide	Design ed to allogeneid Randomised trials cic complication Randomised trials y of the evidence interval cross sessment	Risk of bias c blood Very serious <sup>a</sup> s Very serious <sup>a</sup> ce is at ver posses one l posses both	Inconsistency No serious inconsistency No serious inconsistency ry high risk of bio MID. MIDs.	Indirectness No serious indirectness No serious indirectness as.	Imprecision Serious <sup>b</sup> Very serious <sup>c</sup>	Other None None	Post-operative cell salvage +TXA 4/95 (4.2%) 0/49 (0%) No. of patients	Post-operative cell salvage 11/98 (11.2%) 2/49 (4.1%)	Relative (95% CI) RR 0.37 (0.12 to 1.14) RR 0.2 (0.01 to 4.06) Effect	Absolute 71 fewer per 1000 (from 99 fewer to 16 more) 33 fewer per 1000 (from 40 fewer to 125 more)	Quality VERY LOW	Importance

							cell salvage +TX	XA					
No. exposed to allogeneic blood													
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	9/96 (9.4%)		13/101 (12.9%)	RR 0.73 (0.33 to 1.63)	35 fewer per 1000 (from 86 fewer to 81 more)	VERY LOW	
Units of b	lood transfuse	ed (Better	indicated by lowe	er values)									
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	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 as	ssessment						No. of patients			Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ТХА	Standard tr Adults- mo	reatment- derate risk	Relative (95% CI)	Absolute	Quality	Importance
No. expo	sed to allogene	eic transfu	isions										
52	Randomised 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 (( to 0.53)	0.38 193 fewer per 1000 (from 165 fewer to 218 fewer)	LOW	
No. of un	its of blood tra	ansfused -	All Patients (Bett	er indicated b	y lower value	s)							
9	Randomised trials	Serious <sup>a</sup>	Serious <sup>c</sup>	No serious indirectness	No serious imprecision	None	325	319		-	MD 0.88 lower (1.22 to 0.54 lower)	LOW	
Mortality													
9	Randomised 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 (( to 3.66)	0.15 1 fewer per 1000 (from 3 fewer to 10 more)	VERY LOW	
Length of	ength of hospital stay (Better indicated by lower values)												
9	Randomised trials	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	VERY LOW	

Quality assessment	No of patients	Effect	Quality	Importance

Transfusion GRADE tables

higher)

Infection	IS													
6	Randomised trials	Serious <sup>a</sup>	Serious <sup>d</sup>	No serious indirectness	Very serious	None	3/296 (1%)	3/290 (1%)		RR 0.93 ( to 3.93)	0.22 1 fewer (from 8 30 more	per 1000 fewer to e)	VERY LOW	
Thrombo	otic complicatio	ons												
48	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Serious <sup>f</sup>	None	44/2708 (1.6%)	46/24 (1.9%)	71 )	RR 0.67 ( to 1.04)	0.43 6 fewer (from 11 1 more)	per 1000 L fewer to	LOW	
<ul> <li>a) Majority of the evidence was at high risk of bias.</li> <li>b) Downgraded by one increment due to heterogeneity, l<sup>2</sup>=55%.</li> <li>c) Downgraded by one increment due to heterogeneity, l<sup>2</sup>=77%.</li> <li>d) Downgraded by one increment due to heterogeneity; the point estimate varies widely across studies, unexplained by subgroup analysis.</li> <li>(e) Confidence interval crosses both MIDs.</li> <li>(f) Downgraded by one increment due to heterogeneity, l<sup>2</sup>=61%.</li> <li>(g) Confidence interval crosses one MID.</li> </ul>														
No of studies	Design	Risk of bias	Inconsistency	/ Indirect	ness Imp	recisior	n Other considerat	ions	Intraop CS+Post op CS	Post op CS	Relative (95% CI)	A	bsolute	
Number o	f patients tran	sfused												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectnes	s	s <sup>2</sup>	none		23/321 (7.2%)	33/321 (10.3%)	RR 0.70 (0.42 to 1.16)	31 fewer 60 fewe	per 1000 (from er to 16 more)	⊕⊕OO LOW
Units of a	llogeneic bloo	d transfu	sed (Better indica	ated by lower	values)									
1	randomised	serious <sup>1</sup>	no serious	no serious	no ser	ious	none		23	33	-	MD 2.23	higher (1.92 to	⊕⊕⊕O
			inconsistency	indicotros	s inpred	151011						2.5	4 higher)	MODERATE

2 Confidence interval crosses one MID.

1 tio J.2.3	Adults -	low risk g	roup
nal Clinic	Quality a	ssessment	
cal Gu	No. of studies	Design	Risk o bias
idel	No. of pa	tients receivin	g allog
ine Centı	4	Randomised trials	Serio
,e, D	No. of pa	tients receivin	g allog
2015	1	Randomised	Serio

Quality as	ssessment						No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ТХА	Placebo- Low risk- adults	Relative (95% Cl)	Absolute	Quality	Importance
No. of pat	tients receivin	g allogene	eic transfusions (re	oute)								
4	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	6/315 (1.9%)	7/311 (2.3%)	RR 0.83 (0.3 to 2.29)	4 fewer per 1000 (from 16 fewer to 29 more)	VERY LOW	
No. of pat	tients receivin	g allogene	eic transfusions (re	oute) - Topica	I TXA							
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	0/200 (0%)	2/200 (1%)	RR 0.2 (0.01 to 4.14)	8 fewer per 1000 (from 10 fewer to 31 more)	VERY LOW	
No. of pat	tients receivin	g allogene	eic transfusions (re	oute) - Oral T>	ΚA							
1	Randomised trials	Serious <sup>a</sup>	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 indica	ted by lo	ower values)					
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.93 higher (0.73 to 1.2 higher)	MODERATE	
Blood los	s (type of surg	ery-topica	al TXA)) - Otolaryn	igeal surgery (	Better indicat	ed by lo	ower values)				,	
2	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.74 higher (0.73 to 0.76 higher)	MODERATE	
(a) Majorit (b) Confide	Majority of the evidence was at high risk of bias. Confidence interval crosses both MIDs.											
Children	ı - high risk	( group										

No. of patients

Effect

Quality

Importance

4

J.2.4

Quality assessment

No. of studies	Design	Risk of bias	Inconsistency	Indirectnes	s Imprecisio	on Othe	Inti ope er salv	ra- erative cells vage +TXA	Intra-operative cell salvage- type of surgery	Relative (95% Cl)	Absolute		
Number o	f patients tra	nsfused -	Post 2003										
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectnes	Very serio s	us <sup>2</sup> None	e 14/ (60	/23 ).9%)	15/21 (71.4%)	RR 0.85 (0.56 to 1.3)	107 fewer per 1000 (from 314 fewer to 214 more)	VERY LOW	
Total blood transfused - Post 2003 (Better indicated by lower values)													
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectnes	Very s serious <sup>b</sup>	None	e 23		21	-	MD 325 lower (685.06 lower to 35.06 higher)	VERY LOW	
Total bloo	d loss - Post 2	2003 (Bet	ter indicated by I	ower values)									
1	Randomised trials	Very serious <sup>a</sup>	No serious inconsistency	No serious indirectnes	Very s serious <sup>b</sup>	None	e 23		21	-	MD 855 lower (1408.15 to 301.85 lower)	VERY LOW	
a) Majorit b) Confide	y of the evide nce interval c	nce was a rosses bo	at very high risk o th MIDs.	of bias.									
Quality as	sessment							No. of pati	ents	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other		ТХА	Standard treatment	Relative : (95% CI)	Absolute	Quality	Importance
Post-opera	ative blood lo	ss - Post	2003 (Better indi	cated by lowe	er values)								
1	Randomise d trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None		96	24	-	MD 16 lower (21.13 to 10.87 lower)	MODERATE	
Length of	stay (Better ii	ndicated l	by lower values)										
1	Randomise d trials	Serious <sup>b</sup>	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	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.

# 1 2 National Clinical Guideline Centre, 2015 **Red blood cells**

**RBC thresholds** 

## Restrictive strategy versus liberal strategy (adults)

Quality a	ssessment						No. of patients		Effect			
No. of stu dies Desi	gn	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Blood transfusions (adults)	Control	Relative (95% CI)	Absolute	Quality	Importance
Number	of patients need	ding transf	usion						Ì			
23	Randomised trials	Serious <sup>a</sup>	Very serious <sup>b</sup>	No serious indirectness	No serious imprecision	None	1965/3981 (49.4%)	92%	RR 0.65 (0.58 to 0.74)	322 fewer per 1000 (from 239 fewer to 386 fewer)	VERY LOW	
Number	of patients nee	ding trans	fusion (sub-grou	ıps) - Peri-operati	ive surgical patie	nts						
11	Randomised trials	Serious <sup>a</sup>	Serious <sup>e</sup>	No serious indirectness	Serious <sup>d</sup>	None	928/2256 (41.1%)	87.8%	RR 0.61 (0.50 to 0.76)	342 fewer per 1000 (from 211 fewer to 439 fewer)	VERY 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	

Number	of patients need	ding transf	usion (sub-grou	ps) - chemothera	py and stem-cell	transplants							
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	of units of blood	d transfuse	ed in those trans	fused (Better ind	icated by lower v	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	sfused (sub-group	os) - Peri-operativ	e surgical patients	(Better indicated b	by lower v	values)				
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	sfused (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	sfused (sub-group	os) - Acute blood	loss/trauma (Better	a (Better indicated by lower 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	of units of blood	d transfuse	ed in those trans	sfused (sub-group	os) - Acute corona	ary syndrome (ACS)	(Better indicated	by 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		
<ul> <li>(a) Majori</li> <li>(b) Eviden</li> <li>(c) Eviden</li> <li>(d) Confide</li> <li>(e) l<sup>2</sup>=91%</li> <li>(f) l<sup>2</sup>=83%</li> <li>(g) l<sup>2</sup>=76%</li> <li>(h) Unclea</li> <li>(i) Unclea</li> </ul>	trials       inconsistency       indirectness       imprecision       to 0.69 lower)       ATE         a) Majority of the evidence is from studies at high risk of bias.       b) Evidence of high heterogeneity with 12 value of 93%.       c)       c)       Evidence of high heterogeneity, 12=84%.       d)       Confidence interval crosses one MID.       e)       l²=91%.       f)       l²=91%.       f)       l²=83%.       g)       l²=76%.       h)       Unclear randomisation. No blinding.       i)       Unclear randomisation and allocation concealment.       iiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiii												
Quality as	ssessment						No. of patients		Effect		Quality	Importance	

No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Length of hospi stay (adults)	tal Contr	Relative ol (95% CI)	Absolute			
Hospital le	ength of stay- su	bgroups (b	etter indicated I	oy 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 - F	Peri-operative su	irgical patients (Be	tter indicated	by lower values)							
9 Randomised Serious <sup>a</sup> No serious No serious No serious No serious No serious indirectness No serious imprecision None 1811 1813 - MD 0.01 higher (0.30 MD 0.01 higher (0.30 MD 0.02 higher) TE													
Hospital le	Hospital length of stay- subgroups - Critical care (Better indicated by lower values)												
1     Randomised trials     Serious <sup>d</sup> No serious indirectness     Serious <sup>c</sup> None     24     21     -     MD 4.2 lower (6.93 to LOW 1.47 lower)													
Hospital le	ength of stay- su	bgroups – A	ACS (Acute MI)	(Better indicated b	y lower value	s)							
1       Randomised Serious <sup>d</sup> No serious       No serious       Serious <sup>c</sup> None       24       21       -       MD 4.2 lower (6.93 to LO 1.47 lower)													
Hospital le	ength of stay- su	bgroups - A	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		
<ul> <li>(a) Majorit</li> <li>(b) l<sup>2</sup>=55%.</li> <li>(c) Confide</li> <li>(d) Unclear</li> <li>(e) Unclear</li> </ul>	y of the evidenco nce interval cros randomisation blinding.	e is from st sses one MI and allocat	udies at high risi D. ion concealmen	k of bias. t.									
Quality as	sessment						No. of patients	Ef	fect		Qualit Y	Importanc e	
No. of studies	Design	Risk of bias	Inconsistenc Y	Indirectness	Imprecisio n	Other considerations	Mortality Co (adults) of	ontr Ro (9	lative 5% Cl)	Absolute			
30-day mo	ortality												
20	Randomised trials	Serious a	Serious <sup>b</sup>	No serious indirectness	Serious <sup>c</sup>	None	397/3798 5. (10.5%)	1% RI (C 1.	: 0.92 .74 to 14)	4 fewer per 1000 (from 13 fewer to 7 more)	VERY LOW		
30-day mo	ortality (sub-gro	ups) - Perio	perative surgica	l patients									

11	Randomised trials	Serious <sup>a</sup>	No serious inconsistenc y	No serious indirectness	Very serious <sup>d</sup>	None	76/2145 (3.5%)	2.4%	RR 0.90 2 (0.66 to ( 1.23) 1	? fewer per 1000 from 8 fewer to 6 nore)	VERY LOW		
30-day m	ortality (sub-gro	oups) - Criti	cal care										
5	randomised trials	Serious <sup>a</sup>	no serious inconsistenc Y	no serious indirectness	Serious <sup>e</sup>	none	289/1105 (26.2%)	25%	RR 0.98 5 (0.73 to ( 1.31) 1	5 fewer per 1000 from 67 fewer to 77 nore)	LOW		
30-day m	ortality (sub-gro	ups) – ACS	(Acute MI)										
2 randomised trials serious a serious no serious inconsistenc y ery serious se													
30-day m	ortality (sub-gro	ups) - Acut	e blood loss/tra	uma									
2	randomised trials	Serious <sup>a</sup>	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) f	l0 fewer per 1000 from 10 fewer to 58 ewer)	LOW		
(b) Effects (c) Confide (d) Confide (e) Confide Quality as	<ul> <li>) Majority of the evidence is from studies at high risk of bias.</li> <li>) Effect sizes on forest plot are not consistent with each other.</li> <li>) Confidence interval crosses one MID.</li> <li>1) Confidence interval crosses both default MIDs and line of no effect.</li> <li>&gt;) Confidence interval crosses one default MID and line of no effect.</li> </ul>												
No. of		Risk of				Other	New cardiac	:	Relative				
studies	Design	bias	Inconsistency	Indirectness	Imprecision	considerations	events (adul	ts) Contr	ol (95% CI)	Absolute	Quality	Importance	
New Card	liac events (MI, (	CHF) - sub-	total analysis - N	lyocardial infarctio	n			_					
15       Randomised trials       Serious inconsistency       No serious indirectness       Very serious <sup>a</sup> None       77/3197       1.8%       RR 1.13 (0.76 2 more per 1000       VERY         15       trials       inconsistency       indirectness       Very serious <sup>a</sup> None       77/3197       1.8%       RR 1.13 (0.76 2 more per 1000       VERY         15       more       Very serious <sup>a</sup> None       (2.4%)       to 1.67)       (from 4 fewer to 12 LOW more)													
New Card	liac events (MI,	CHF)- sub-t	otal analysis - Co	ongestive heart fail	ure								
7	Randomised trials	Serious <sup>b</sup>	Serious <sup>c</sup>	No serious indirectness <sup>d</sup>	Very serious	s <sup>a</sup> None	83/2106 (3.9%)	4.2%	RR 1.00 (0.5 to 1.83)	4 0 fewer per 1000 (from 19 fewer to 35 more)	VERY LOW		

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(a) Confidence interval crosses both MIDs.

(b) Majority of the evidence was from studies at high risk of bias.

(c)  $l^2 = 61\%$ .

(d) Pulmonary oedema reported in 3 studies which is a surrogate outcome.

No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Infection - adults	ents Control	Rela	ative % CI)	Absolute	Quality		Importance
Infection	(Pneumonia, su	urgical site	infection, sept	icaemia, UTI, i	nfections not	t specified) – Pn	eumonia		·				ĺ	
8	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	None	146/1725 (8.5%)	4.1%	RR ( 1.12	0.9 (0.73 to 1)	4 fewer per 1000 (from 11 fewer to 5 more)	LOW		
Infection	nfection (Pneumonia, surgical site infection, septicaemia, UTI, infections not specified) - Surgical site/Wound infection													
2	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	56/1069 (5.2%)	6.2%	RR ( to 1	0.73 (0.52 1.01)	17 fewer per 1000 (from 30 fewer to 1 more)	LOW		
Infection	(Pneumonia, su	urgical site	infection, sept	icaemia, UTI, i	nfections not	t specified) - Sep	oticaemia/Ba	cteraemi	а					
2	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	ne 1/114 0.8% RR 1 (0.06 to 0 fewer per 1000 (from (0.88%) 15.62) 8 fewer to 117 more)		LOW					
Infection	(Pneumonia, su	urgical site	infection, sept	icaemia, UTI, i	nfections not	t specified) - Info	ection (not sp	pecified)						
4	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	172/1204 (14.3%)	10%	RR ( to 1	0.89 (0.74 1.07)	11 fewer per 1000 (from 26 fewer to 7 more)	LOW		
(a) Majorii (b) Confide	ty of the eviden ence interval cro	ce was fro osses one l	om studies at hi MID.	gh risk of bias.										
<b>.</b>														
Quality as	ssessment	Dick of				Other	No. of patien	its		Effect				
studies	Design	Risk of esignRisk of biasOther InconsistencyOther Indirectness		considerations	(adults)	Cont	rol	(95% CI)	Absolute	Quali	ity	Importance		
All advers	se events (as de	fined by t	he study)											
3	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious S indirectness	Serious <sup>b</sup>	None	179/957 (18.7%)	0.2%	'n	RR 0.83 (0.7 to 0.97)	2 0 fewer per 1000 (fro 0 fewer to 1 fewer)	om LOW		
Transfusio	on associated c	irculatory	overload (TAC	))										

2	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	2/932 (0.21%)	1.8%	RR 0.13 (0. to 0.54)	03 16 fewer per 1000 (f 8 fewer to 17 fewer)	rom MODERATE	
Transfu	sion Related Ad	cute Lung II	njury (TRALI)									
2	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/932 (0%)	0%	Not pooled	Not pooled	MODERATE	
'a) Majo 'b) Confi <b>Restrict</b>	rity of the evide dence interval t <b>ive strategy</b>	ence is fron crosses one <b>versus li</b>	n studies at higi MID. i <b>beral strate</b> i	h risk of bias. <b>gy (childre</b> n	)							
Quality	assessment						No. of patients		Effect		_	
No. of studies	Design I	Risk of bias	Inconsistency	Indirectness	Imprecision	o Other	Blood transfusion (children)	Control	Relative (95% Cl) A	bsolute	Quality	Importance
Total RE	BC ml/patient (	Better indio	cated by lower	values)								
1	Randomised S trials	Serious <sup>a</sup>	serious inconsistency <sup>b</sup>	No serious indirectness	No serious imprecisior	None	53	54	- N 0	/ID 73.0 lower (1.0352 to .4248 lower)	MODERATE	
Numbe	r of patients ne	eding trans	sfusion –childre	n								
2	Randomised S trials	Serious <sup>c</sup>	No serious inconsistency	No serious indirectness	No serious imprecisior	None	157/350 (44.9%)	97.2%	RR 0.46 5 (0.41 to 4 0.52)	25 fewer per 1000 (from 67 fewer to 573 fewer)	MODERATE	
Number	r of patients ne	eding trans	sfusion (sub-gro	oup)-children -	Critical care							
1	Randomised S trials	Serious <sup>d</sup>	No serious inconsistency	No serious indirectness	No serious imprecisior	None	146/320 (45.6%)	97.8%	RR 0.47 5 (0.41 to 4 0.53)	18 fewer per 1000 (from 60 fewer to 577 fewer)	MODERATE	
Number	r of patients ne	eding trans	sfusion (sub-gro	oup)-children -	Congenital c	ardiac disea	ase					
1	Randomised S trials	Serious <sup>e</sup>	No serious inconsistency <sup>f</sup>	No serious indirectness	No serious imprecisior	None nd	11/30 (36.7%)	96.7%	RR 0.38 6 (0.24 to 3 0.61)	00 fewer per 1000 (from 77 fewer to 735 fewer)	MODERATE	
Number	r of units trans	fused-child	ren (Better indi	cated by lowe	r values)							
2	Randomised	Serious <sup>c</sup>	Very serious <sup>b</sup>	No serious	No serious	None	350	340	- N	1D 0.65 lower (0.98 to	VERY LOW	

Quality a	sessment						No. of nation	Effect	+				
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Mortality (children)	Control	Relati (95%	tive 5 CI)	Absolute	Quality	Importance
Mortality	(30 days)					-			-				
2	randomised	serious <sup>1</sup>	no serious	serious <sup>2</sup>	very serious	<sup>3</sup> none	14/350 (4%)	3.9%	RR 0.	.93 (0.46 87)	3 fewer per 1000 (from fewer to 34 more)	1 21 VERY LOW	
a) Most ir b) Lacroix c) Confide	trials formation is fi 2007- Include ence interval ci	rom studies a d infants <1 y rosses both de	inconsistency it high risk of bic iear. efault MIDs (0.7.	s. 5 and 1.25) and	l line of no effe	ct.							
a) Most ir b) Lacroix c) Confide Quality as	trials formation is fi 2007- Include ence interval cr	rom studies a d infants <1 y rosses both d	nt high risk of bia rear. efault MIDs (0.7	s. 5 and 1.25) and	line of no effe	ct.	No. of patients		E	Effect			
a) Most ir b) Lacroix c) Confide Quality as No. of studies	trials formation is fi 2007- Include ence interval co ssessment Design	rom studies a d infants <1 y rosses both d Risk of bias	Inconsistency It high risk of bio lefault MIDs (0.7	s. 5 and 1.25) and Indirectness	line of no effe	ct. Other	No. of patients Length of hospi stay (children)	tal Contr	E' R :rol (S	Effect Relative 95% CI)	Absolute	Quality	Importa
a) Most ir b) Lacroix c) Confide Quality as No. of studies ICU lengt	trials formation is fi 2007- Include ence interval cr ssessment Design n of stay (Bette	rom studies a d infants <1 y rosses both d Risk of bias er indicated b	Inconsistency It high risk of bic lear. efault MIDs (0.7 Inconsistency y lower values)	s. 5 and 1.25) and Indirectness	line of no effe	ct. Other	No. of patients Length of hospi stay (children)	tal Contr	E R (S	Effect Relative 95% CI)	Absolute	Quality	Importa

Transfusion GRADE tables

studies		bias					(children)		(	95% CI)				
Pulmona	ry oedema													
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	Serious <sup>b</sup>	Very serious <sup>c</sup>	None	0/320 (0%)	1	1.6% F t	RR 0.09 (0.01 to 1.62)	15 fewer per 1000 16 fewer to 10 mo	(from Vi re)	ERY LOW	
(a) Unclea (b) Pulmoi (c) Confide	<ul> <li>i) Unclear randomisation sequence generation.</li> <li>ii) Pulmonary oedema not protocol specified new cardiac event. Included children less than 1 year.</li> <li>c) Confidence interval crosses both default MIDs and line of no effect.</li> </ul>													
Quality a	ssessment						No. of pati	ents	Effect					
No. of studies	Design	Risk of bia	is Inconsistency	/ Indirectness	Imprecision	Other	Infection (children)	Control	Relative (95% Cl)	Absolu	te	Quality	Import	ance
Infection	(Nosocomial i	nfections)												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	65/320 (20.3%)	24.9%	RR 0.82 ( to 1.09)	(0.61   45 few 97 few	er per 1000 (from er to 22 more)	VERY LOW	V	
(a) Unclea	r randomisatio	on and blin	dina.											

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

#### **RBC** targets J.3.2 8

# Blood transfusions (adults)

Quality as:				No of patients		Effect			Importance			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Blood transfusions (adults)	Control	Relative (95% CI)	Absolute	2ry	
Number o	f patients need	ling transf	usion (all stud	ies)								

5	randomised trials	serious <sup>1</sup>	serious <sup>2</sup>	no serious indirectness	no serious imprecision	none	644/1169 (55.1%)	91.8%	RR 0.61 (0.55 to 0.67)	358 fewer per 1000 (from 303 fewer to 413 fewer)	????? LOW			
Number	Number of patients needing transfusion (sub-groups) - Peri-operative surgical patients													
1	randomised trials					none	118/249 (47.4%)	198/253 (78.3%)	RR 0.61 (0.52 to 0.7)	305 fewer per 1000 (from 235 fewer to 376 fewer)				
								78.3%		305 fewer per 1000 (from 235 fewer to 376 fewer)				
Number	of units of bloo	d transfus	ed in those tra	ansfused (Better i	ndicated by lowe	r values)								
3	randomised trials	serious <sup>1</sup>	serious <sup>3</sup>	no serious indirectness	no serious imprecision	none	748	886	-	MD 1.72 lower (2.41 to 1.02 lower)	????? LOW			

Transfusion GRADE tables

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

# Length of hospital stay (adults)

(	Quality ass	sessment						No of patients		Effect		Ouality	Importance
9	No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Length of hospital stay (adults)	Control	Relative (95% CI)	Absolute		inpertunce
	lospital le	ngth of stay (Be	tter indica	ted by lower values)									
	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	

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

Mortality (adults)

Quality as	sessment						No of patients	;	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecisic	Other considerations	Mortality (adults)	Control	Relative (95% Cl)	Absolute		
30-day mo	ortality											
5	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	126/1193 (10.6%)	9.2%	RR 0.78 (0.63 to 0.97)	20 fewer per 1000 (from 3 fewer to 34 fewer)	⊕⊕OO LOW	
Majority of the evidence is from studies at high risk of bias. Confidence interval crosses one MID. New cardiac events (adults)												
Quality as	sessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	mprecision	Other considerations	New cardiac events (adults)	Control	Relative (95% CI)	Absolute		
New Card	iac events (MI,	CHF)- sub-	total analysis - Myo	ocardial infarction								
					2							
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious s indirectness	serious <sup>2</sup>	none	3/418 (0.72%)	2.9%	RR 0.25 (0.07 to 0.88)	22 fewer per 1000 (from 3 fewer to 27 fewer)	⊕⊕OO LOW	
1 New Cardi	randomised trials iac events (MI,	serious <sup>1</sup> CHF)- sub-	no serious inconsistency total analysis - Con	no serious sindirectness gestive heart failu	serious <sup>2</sup> re	none	3/418 (0.72%)	2.9%	RR 0.25 (0.07 to 0.88)	22 fewer per 1000 (from 3 fewer to 27 fewer)	⊕⊕OO LOW	

<sup>1</sup> Majority of the evidence is from studies at high risk of bias.
 <sup>2</sup> Confidence interval crosses one MID.
 <sup>3</sup> One study reports acute pulmonary oedema which is a surrogate outcome for congestive heart failure.

Infection - adults for guiding allogeneic red blood cell transfusion
Quality as	ssessment						No of patien	ts	Effect		Quality	Importan
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Infection - adults	Control	Relative (95% CI)	Absolute		
infection	(Pneumonia, surgio	al site infe	ection, septicemia, L	JTI) - Pneumonia								
2	no methodology chosen					none	90/443 (20.3%)	96/477 (20.1%)	RR 0.95 (0.73 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)		
nfection	(Pneumonia, surgio	al site infe	ection, septicemia, L	JTI) - Infection (no	ot specified)							
l	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	30/249 (12%)	9.9%	RR 1.22 (0.74 to 2.01)	22 more per 1000 (from 26 fewer to 100 more)	???? VERY LOW	

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

#### Adverse events (adults)

Quality as	sessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adverse events (adults)	Control	Relative (95% Cl)	Absolute		
All adverse	e events (as def	ined by th	ie study)									
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	179/444 (40.3%)	48.1%	RR 0.84 (0.72 to 0.97)	77 fewer per 1000 (from 14 fewer to 135 fewer)	⊕OOO VERY LOW	

<sup>1</sup> Evidence from study at high risk of bias.
 <sup>2</sup> Adverse event not defined in study.
 <sup>3</sup> Confidence interval crosses one MID.

## Blood transfusion (children)

Quality a	ssessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Blood transfusion (children)	Control	Relative (95% Cl)	Absolute	Quanty	importance
Total RB	C 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 of patients needing transfusion -children (critical care)												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	146/320 (45.6%)	97.8%	RR 0.47 (0.41 to 0.53)	518 fewer per 1000 (from 460 fewer to 577 fewer)	⊕⊕⊕O MODERATE	

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

#### Mortality (children)

Quality as	ssessment						No of patients	i	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mortality (children)	Control	Relative (95% Cl)	Absolute		
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%)	4.4%	RR 0.99 (0.48 to 2.04)	0 fewer per 1000 (from 23 fewer to 46 more)	⊕OOO VERY LOW	

<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 as	sessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Length of hospital stay (children)	Control	Relative (95% CI)	Absolute	Quanty	
ICU length	of stay (Better	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)	⊕OOO VERY LOW	

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

## New cardiac events (children)

Quality as	ssessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	New cardiac events (children)	Control	Relative (95% CI)	Absolute		
Pulmonai	ry oedema											
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	None	0/320 (0%)	1.6%	RR 0.09 (0.01 to 1.62)	15 fewer per 1000 (from 16 fewer to 10 more)	⊕OOO VERY LOW	

<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.

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National Clinical Guideline Centre, 2015 1

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itional Cli	Quality as	sessment						No of patients		Effect		Quality
nical G	No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Infection (children)	Control	Relative (95% Cl)	Absolute	
ûuid	Infection	(Nosocomial inf										
eline	1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	65/320 (20.3%)	24.9%	RR 0.82 (0.61 to 1.09)	45 fewer per 1000 (from 97 fewer to 22 more)	⊕⊕OO LOW
1 2	<sup>1</sup> Evidence from study at high risk of bias. <sup>2</sup> Confidence interval crosses one MID.											
2015 <b>J.3.3</b>	RBC do	ses										

#### **RBC doses**

None

4

#### 54**5** J.4 Platelets

Platelet thresholds and targets J.4.1 6

#### Prophylactic transfusion versus no prophylactic transfusion - adults who are haematology patients (non-bleeding patients) J.4.1.1 7

Quality	assessment						No of patient	s	Effect			
No of studies	of Risk of dies Design bias Inconsistency Indirectness Imprecision C mber of patients with bleeding events (WHO grade 2 or higher)						Prophylactic transfusion	No prophylactic transfusion - adults who are haematology patients	Relative (95% Cl)	Absolute	Quality	Importance
Number	of patients w	ith bleeding	g events (WHO g	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	

Quality Importance

Number	r of patients w	ith major b	leeding events	(WHO grade 3	or 4)							
2	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	8/493 (1.6%)	6.3%	RR 0.3 (0.14 to 0.65)	44 fewer per 1000 (from 22 fewer to 54 fewer)	MODERATE	
Serious	adverse event	s (including	sepsis and res	piratory deter	ioration)							
1	Randomised trials	Serious <sup>d</sup>	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	
Transfu	sion related se	rious advei	rse event (urtica	arial and angic	edema)							
1	Randomised trials	Serious <sup>d</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>e</sup>	None	1/299 (0.33%)	0%	RR 3.02 (0.12 to 73.84)	-	VERY LOW	
Numbei	r of patients ne	eeding plate	elet transfusion									
1	Randomised trials	Serious <sup>d</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	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	
Number	r of units (plate	elets) trans	fused per patie	nt (better indi	cated by lowe	r values	;)					
1	Randomised trials	Serious <sup>d</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	299	301	-	MD 1.3 higher (0.75 to 1.85 higher)	MODERATE	
Mortali	ty (all cause)							•				,
1	Randomised trials	No serious risk of bias	No serious inconsistency	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 eff	ects of transfu	sion (not sp	pecified)									
1	Randomised trials	No serious risk of bias	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	

(a) Most information is from studies at high risk of bias.
(b) <sup>12</sup>=92%.

(c) Confidence interval crosses one default MID and line of no effect.

(d) Study at high risk of bias.

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

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

Quality a	assessment						No of patient	S	Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Prophylactic transfusion	No prophylactic transfusion - children who are haematology patients	Relative (95% Cl)	Absolute	Quality	Importance
Number	of patients wi	ith major	bleeding events (	WHO grade 3 o	or 4)							
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	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	
Mortalit	y (all cause) (3	years)										
1	Randomised trials	Serious <sup>a</sup>	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	
Mortalit	y from bleedir	ng (3 year	s)									
1	Randomised trials	Serious <sup>a</sup>	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	

(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.

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

Quality a	assessment						No of patient	s	Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Low platelet thresholds	High platelet thresholds - Adults who are haematology patients	Relative (95% Cl)	Absolute	Quality	Importance
Mortalit	y (all cause)											

4 5

4	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	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	
Mortali	ity (all cause) -	Patients	undergoing che	motherapy								
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	
Mortali	ity (all cause) -	Patients	undergoing ster	n-cell transpla	ant							
2	Randomised trials	Serious <sup>a</sup>	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	
Numbe	r of patients w	vith bleed	ing events (WH	O grade 2 or h	nigher)							
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	
Numbe	r of patients w	vith major	bleeding event	s (WHO grade	e 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	
Numbe	r of patients w	vith major	bleeding event	s - Patients ur	ndergoing che	mother	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	
Numbe	r of patients w	vith major	bleeding event	s - Patients ur	ndergoing ster	m-cell ti	ransplant					
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	ons (Bacteraen	nia)										
1	Randomised trials	Serious <sup>j</sup>	No serious inconsistency	No serious indirectness	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	
Advers	e events			·	·							
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	
Numbe	r of units (plat	elets) tra	nsfused per pat	ient (Better in	dicated by lov	wer valu	ies)					
3	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	None	250	242	-	MD 1.96 lower (3.03 to 0.89 lower)	MODERATE	

MD 2.09 lower (3.2 to

MD 0.2 higher (4.27

lower to 4.67 higher)

0.99 lower)

MODERATE

MODERATE

#### J.4.2 Platelet doses

12

#### Low platelet dose versus medium platelet dose 13 J.4.2.1

Quality	assessment						No. of pati	ents	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Low dose	Medium dose	Relative (95% Cl)	Absolute	Quality	Importance
Number	r 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	
Mortalit	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	

161

81

No serious No serious None 172

No serious No serious None 78

inconsistency indirectness imprecision

inconsistency indirectness imprecision

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%	RR 1.01 (0.3 to 3.48)	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%	RR 1.31 (0.81 to 2.13)	20 more per 1000 (from 12 fewer to 72 more)	LOW	

(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. (b) Confidence interval crosses both MIDs.

(c) Confidence interval crosses one MID.

#### High platelet dose versus medium platelet dose

Quality ass	essment						No. of pa	itients	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	High dose	Medium dose	Relative (95% Cl)	Absolute	Quality	Importance
Number of patients with bleeding (WHO grade 2 and above)												
2	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	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 inconsistency	No serious indirectness	Very serious <sup>b</sup>	None	7/432 (1.6%)	1%	RR 1.71 (0.51 to 5.81)	7 more per 1000 (from 5 fewer to 48 more)	VERY LOW	
Infections												
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	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 adv	verse event											
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	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	

(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.

(b) Confidence interval crosses both MIDs.

(c) Confidence interval crosses one MID.

1 tio J.4.2.3 L	ow plate	elet dose ver	sus high	platelet dos	e
nal Clini	Quality as	sessment			
cal Guide	No. of studies	Design	Risk of bias	Inconsistency	Ir
line	Number o	f patients with	bleeding (	WHO grade 2 a	nd
e Centre,	1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	N ir
20	Mortality	at 30 days			
15	1	Pandomicod	Sorious <sup>a</sup>	No corious	N

Quality as	ssessment						No. of pati	ents	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider ations	Low dose	High 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 1.42)	8 more per 1000 (from 36 fewer to 68 more)	LOW	
Mortality at 30 days												
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	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	5											
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	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 a	dverse event											
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	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	

(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.

(b) Confidence interval crosses one MID.

(c) Confidence interval crosses both MIDs.

#### J.5 PCC 5

- J.5.1 PCC thresholds 6
  - None

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# 1 I J.5.2 2 I Clinical Guideline Centre, 2015 PCC targets

None

PCC doses

## Low dose PCC (25 IU/kg) versus high dose PCC (40 IU/kg)

Quality	assessment						No. of patie	ents	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Low dose (25 IU /kg)	High dose (40 IU /kg) [RCT]	Relative (95% Cl)	Absolute	Quality	Importance
Mortalit	y											
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	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 inconsistency	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 ever	nt								
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	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 thror	nbotic 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 II	NR (<1.2) achi	ieved										
1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	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	

(a) Allocation concealment not reported. Open label study.(b) Confidence interval crosses both default MIDs and line of no effect.

(c) Confidence interval crosses one default MID.

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

Quality	assessment						No. of patier	nts	Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Fixed dose (1040 IU)	Variable dose (cohort study)	Relative (95% Cl)	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	ein 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	

(a) Observational study and is therefore more prone to selection bias.

(b) Confidence interval crosses both default MIDs and line of no effect.

(c) Confidence interval crosses one default MID.

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

Quality	assessment						No. of patients		Effect			
No. of studies Target I	Design NR at 15 minu	Risk of bias tes after	of Inconsistency Indirectness Imprecision Other ID FIX/7 IU/kg) Individu Inconsistency Indirectness Imprecision Other ID FIX/7 IU/kg) Individu				Individualised dosing regimen [RCT]	Relative (95% CI)	Absolute	Quality	Importance	
1RandomisedSeriousNo seriousNo seriousNo serious1trialsinconsistencyindirectnessimprecision						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	
serious	adverse event	S										

Z														
ational C		1	Randomised trials	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	None	2/47 (4.3%)	4.3%	RR 1 (0.15 to 6.81)	0 fewer per 1000 (from 37 fewer to 250 more)	LOW	
1		(a) Alloc	ation concealr	nent not r	eported. Open l	abel study.								
2 <u>a</u>		(b) Confi	idence interva	crosses b	oth default MI	os and line of i	no effect.							
Gu														
3 idelii	J.6	Mon	itoring f	or ac	ute react	ions								
ne		None												
+ Cen		None												
Itre														
5 , <sub>20</sub>	J./	Elect	ronic de	cisioi	n suppor	τ								
6 015		None												
0		None												
-	10	Floct	ronic na	tiont	idantifia	ation								
сл Сл	<b>J.O</b>	Elect	rome pa	tient	laentinc	ation								
48		None												
-														
0	۱۵	Datio	nt infor	matic	'n									
9	1.2	Falle		matic	///									
10		None												
11														
12														

# **Appendix K: Forest plots**

## 2 K.1 Erythropoietin and iron

#### 3 K.1.1 Erythropoietin versus placebo

#### Figure 1: All-cause mortality at 30 days

	EPC	)	placebo/no E	PO		Risk Ratio			Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl			M-H, Fixe	ed, 95% CI	
D'Ambra 1997	9	126	0	56	5.1%	8.53 [0.50, 144.01]					
de Andrade 1996	1	213	0	103	5.0%	1.46 [0.06, 35.48]	←			-	
Heiss 1996	2	17	1	10	9.3%	1.18 [0.12, 11.39]	_			-	
Kettelhack 1998	5	52	2	57	14.2%	2.74 [0.56, 13.52]					
Sowade 1997	4	38	4	38	29.7%	1.00 [0.27, 3.71]					
Weltert 2010	3	158	3	162	22.0%	1.03 [0.21, 5.00]				•	-
Wurnig 2001	0	119	1	60	14.8%	0.17 [0.01, 4.10]	←	•			
Total (95% CI)		723		486	100.0%	1.55 [0.79, 3.07]					
Total events	24		11								
Heterogeneity: Chi <sup>2</sup> =	4.50, df=	6 (P =	0.61); I <sup>z</sup> = 0%					-	0.5		+
Test for overall effect:	Z=1.27 (	(P = 0.2	:0)				0.1	0.2	Favours EPO	Favours placebo	/no EPC

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#### Figure 2: Number of patients transfused

	EPC	)	placebo/no	D EPO		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	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]	_ <b></b>
Feagan 2000	23	123	35	78	10.8%	0.42 [0.27, 0.65]	<b>_</b>
Heiss 1996	9	17	4	10	1.3%	1.32 [0.55, 3.20]	
Kettelhack 1998	16	48	15	54	3.5%	1.20 [0.67, 2.16]	
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]	<b>← →</b>
Weltert 2010	35	158	59	162	14.6%	0.61 [0.43, 0.87]	<b>-</b>
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]	•
Total events	295		348				
Heterogeneity: Chi <sup>2</sup> =	29.24, df	= 11 (F					
Test for overall effect:	Z = 8.56 (	(P < 0.0	10001)				U.1 U.2 U.5 1 2 5 Eavours EPO Eavours placebo/no EP(

baseline											
	EPO	)	placebo/no	D EPO		Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI				
1.3.1 not anaemic at	baseline										
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]					
Sowade 1997	4	36	19	36	4.8%	0.21 [0.08, 0.56]	<b>← − −</b>				
Weltert 2010	35	158	59	162	14.6%	0.61 [0.43, 0.87]	<b>_</b>				
Wurnig 2001	41	124	28	51	10.0%	0.60 [0.42, 0.86]					
Subtotal (95% CI)		567		379	54.5%	0.61 [0.52, 0.72]	◆				
Total events	180		183								
Heterogeneity: Chi <sup>2</sup> =	7.02, df=	4 (P =	0.13); I <sup>z</sup> = 40	3%							
Test for overall effect:	Z = 5.95 (	P < 0.0	0001)								
1.3.2 others											
Faris 1996	25	118	36	67	11.5%	0.39 [0.26, 0.60]	_ <b></b>				
Feagan 2000	23	123	35	78	10.8%	0.42 [0.27, 0.65]	<b>_</b>				
Heiss 1996	9	17	4	10	1.3%	1.32 [0.55, 3.20]					
Kettelhack 1998	16	48	15	54	3.5%	1.20 [0.67, 2.16]	<b>-</b>				
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]					
Subtotal (95% CI)		404		313	45.5%	0.57 [0.47, 0.68]	◆				
Total events	115		165								
Heterogeneity: Chi <sup>2</sup> =	21.83, df	= 6 (P =	= 0.001); I <b>²</b> =	73%							
Test for overall effect:	Z = 6.18 (	(P < 0.0	0001)								
Total (95% CI)		971		692	100.0%	0.59 [0.53, 0.67]	◆				
Total events	295		348								
Heterogeneity: Chi <sup>2</sup> =	29.24, df:	= 11 (P	= 0.002); l <sup>2</sup>	= 62%							
Test for overall effect:	Z = 8.56 (	P < 0.0	0001)				0.1 0.2 0.5 1 2 5 10 Eavours EPO Eavours placebo/po EPO				
Test for subgroup diff	erences:	Chi <sup>z</sup> = (	0.44, df = 1 (	P = 0.51	), I <sup>z</sup> = 0%						

# 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	ebo/no E	PO		Mean Difference		Mean	Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fix	ed, 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: Chi <sup>2</sup> = 1	4.92, df	= 6 (P =	: 0.02);	l² = 609	6				10	<u> </u>	<u> </u>	5 1
Test for overall effect: Z	Z = 6.91 (	(P < 0.0	0001)						-10	Favours EP	O Favours	placebo/n

(1) 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

	50	<b>.</b>							
		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
1.5.1 not anaemic at ba	aseline								
D'Ambra 1997	1.546	3.247	119	1.33	2.01	52	6.0%	0.22 [-0.58, 1.02]	+
Subtotal (95% CI)			119			52	6.0%	0.22 [-0.58, 1.02]	<b>•</b>
Heterogeneity: Not appl	licable								
Test for overall effect: Z	= 0.53 (	P = 0.6	0)						
1.5.2 others									
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]	
Subtotal (95% CI)			382			256	94.0%	-0.75 [-0.95, -0.55]	•
Heterogeneity: Chi <sup>2</sup> = 9.	.66, df=	5 (P = 0	0.09); I <sup>a</sup>	²= 48%					
Test for overall effect: Z	= 7.26 (	(P < 0.0)	0001)						
Total (95% CI)			501			308	100.0%	-0.69 [-0.89, -0.49]	•
Heterogeneity: Chi <sup>2</sup> = 1	4.92, df	= 6 (P =	0.02);	l <sup>2</sup> = 60%	6				
Test for overall effect: Z	= 6.91 (	(P < 0.0)	0001)						-10 -5 0 5 10 Eavours EPO Eavours placebo/no EPO
Test for subgroup differ	ences:	Chi <sup>z</sup> = 5	i.26, df	= 1 (P =	0.02), P	²= 81.0	1%		
Footnotes									

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

1

#### Figure 3: Serious adverse events

-	EPC	)	placebo/no	EPO		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
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]	
Karkouti 2006	0	10	0	10		Not estimable	
Scott 2002	2	29	0	29	1.6%	5.00 [0.25, 99.82]	
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: Chi <sup>2</sup> =	5.72, df=	4 (P =	0.22); I <sup>z</sup> = 30	)%			
Test for overall effect:	Z=0.33	(P = 0.7	74)				Favours EPO Favours placebo/n

#### 2

#### Figure 4: Thrombosis

	EPC	)	placebo/no	EPO		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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]	-
Total events	29		13				
Heterogeneity: Chi <sup>2</sup> =	3.25, df=	4 (P =	0.52); I <sup>z</sup> = 0%	5			
Test for overall effect:	Z = 0.99	(P = 0.3	32)				Favours EPO Favours placebo/no EPO

#### Figure 5: Length of hospital stay

	E	PO		placeb	oo/no E	PO		Mean Difference	Mean Di	fference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed	1, 95% CI	
Kosmadakis 2003	10	0.5	31	13	0.9	32	100.0%	-3.00 [-3.36, -2.64]		•	
Total (95% CI)	nlicabla		31			32	100.0%	-3.00 [-3.36, -2.64]		 	
Test for overall effect:	Z = 16.4	2 (P	< 0.000	001)					-100 -50 Favours EPO	Ó 50 Favours pl	) 10 lacebo/n

1

#### Figure 6: Infection (pneumonia)

•										
	EPC	)	placebo/n	IO EPO		Risk Ratio		Ris	k Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% Cl	
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:	oplicable Not appli	cable					0.01	0.1 Favours EPC	1 10 Favours palce	10 bo

2

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

#### Figure 7: All-cause mortality at 30 days

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

4

#### Figure 8: Number of patients transfused

	-	-												
		IV iro	n	placebo/no IV	/ iron		Risk Ratio			Risk	Ratio			
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		I	M-H, Fixe	d, 95%	CI		
Ì	Edwards 2009	2	34	5	26	6.6%	0.31 [0.06, 1.45]	4	•					
	Garrido-Martin 2012	20	54	26	52	30.7%	0.74 [0.48, 1.15]				_			
	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]				•			
	Serrano-Trenas 2011	33	100	41	100	47.5%	0.80 [0.56, 1.16]				_			
	Total (95% CI)		239		228	100.0%	0.77 [0.59, 0.99]			•				
	Total events	67		85										
	Heterogeneity: Chi <sup>2</sup> = 2.7	77, df = 4	(P = 0.1	60); I² = 0%								<u>+</u>	÷	- 1
	Test for overall effect: Z =	= 2.02 (P	= 0.04)	I				0.1	Favour	s IV iron	Favou	z Irs plac	;ebo/i	no

5

#### 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		IV, F	ixed, 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 app Test for overall effect: Z	licable . = 0.61	(P = (	0.54)						-100	-50 Favours IV ii	0 on Fav	50 ours plac	100 ebo/no IV ir

#### Figure 10: Serious adverse events

-	IV iro	n	placebo/no	IV iron		Risk Ratio		Ris	k Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fi	xed, 95% C	I	
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:	olicable Not applic	able					0.1	0.2 0.5 Favours IV iro	1 2 n Favours	5 placebo	10 p/no IV

2

#### **Figure 11: Infections**

0											
	IV iro	n	placebo/no	IV iron		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fix	ed, 95%	6 CI	
Serrano-Trenas 2011	16	100	13	100	100.0%	1.23 [0.63, 2.42]		_			
Total (95% CI)		100		100	100.0%	1.23 [0.63, 2.42]		•			
Total events	16		13								
Heterogeneity: Not applic	cable	- 0 55	<b>`</b>				0.01	0.1	<del> </del> 1	10	100
	- 0.00 (i	- 0.55	)					Favours IV iron	Favou	urs place	bo/no IV i

3

4

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

#### Figure 12: Number of patients transfused

0											
	Oral ir	on	placebo/no ora	al iron		Risk Ratio		Risk Ra	tio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H, Fixed,	95% CI		
Garrido-Martin 2012	27	53	26	52	67.3%	1.02 [0.70, 1.49]			_		
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 = <sup>-</sup>	1 (P = 0	0.09); l² = 66%					0.5 1		<u>_</u>	10
Test for overall effect: 2	Z = 0.98 (I	<b>P</b> = 0.3	3)				Favour	s Oral iron F	∠ avours pla	cebo/n	o oral ir

#### 5

## 6 K.1.4 Erythropoietin plus IV iron versus placebo

#### Figure 13: All-cause mortality at 30 days

	EPO+ IV	iron	placebo/no	IV iron		Risk Ratio	Risk R	atio	
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			
Yoo 2011	0	37	1	37	100.0%	0.33 [0.01, 7.93]			_
Total (95% CI)		77		77	100.0%	0.33 [0.01, 7.93]			_
Total events	0		1						
Heterogeneity: Not app Test for overall effect:	olicable Z = 0.68 (P	e = 0.50)				1	0.1 0.2 0.5 1 Favours EPO+ IV iron p	25 blacebo/no IV iro	10 n

#### Figure 14: Number of patients transfused

	EPO+ IV	iron	place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	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]	▲
Total events	43		84				
Heterogeneity: Chi <sup>z</sup> = Test for overall effect:	9.79, df= Z= 4.90 (	3 (P = 0 P ≺ 0.00	1.02); I² = 1001)	69%			0.1 0.2 0.5 1 2 5 1 Favours EPO+ IV iron Favours placebo

#### Figure 15: Number of units transfused per patient

	EPO-	+ IV in	iron placebo			)		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]				
Total (95% CI)			91			91	100.0%	-0.76 [-1.00, -0.52]	•			
Heterogeneity: Chi² = Test for overall effect:	= 14.28, df = 1 (P = 0.0002); I² = 93% t: Z = 6.23 (P < 0.00001)								-10 -5 0 5 Favours EPO+ IV iron Favours placebo			

#### 2

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

	EPO+IV	iron	place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
4.3.1 anaemic at base	eline						
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 Subtotal (95% Cl)	22	37 <b>141</b>	32	37 <b>142</b>	38.1% <b>100.0%</b>	0.69 [0.51, 0.92] <b>0.51 [0.39, 0.67]</b>	<b>▲</b>
Total events	43		84				
Heterogeneity: Chi² = !	9.79. df = 3	3 (P = 0	.02); I <sup>2</sup> =	69%			
Test for overall effect: .	Z = 4.90 (F	° < 0.00	1001)				
4.3.2 others							
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not applic	able					
Total (95% CI)		141		142	100.0%	0.51 [0.39, 0.67]	•
Total events	43		84				-
Heterogeneity: Chi <sup>2</sup> =	9.79, df = 3	3 (P = 0	.02); I <sup>z</sup> =	69%			
Test for overall effect: 2	Z = 4.90 (F	, ≤ 0.00	1001)				U.1 U.2 U.5 1 2 5 10
Test for subgroup diffe	erences: N	lot appl	icable				Favours EFO+10 IION Favours placebo

#### Figure 17: Length of hospital stay

		-										
	EPO+ IV iron placebo		D		Mean Difference	Mean Difference						
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	1	IV, Fixe	l, 95% CI	
Yoo 2011	11.3	4.1	37	13.5	8	37	100.0%	-2.20 [-5.10, 0.70	]		+	
Total (95% CI)			37			37	100.0%	-2.20 [-5.10, 0.70]	]	-	-	
Heterogeneity: Not a Test for overall effect	pplicable t: Z = 1.49	(P = (	D.14)						-10 -	+ -5 20+ IV iron	0 5 Eavours pl	1 acebo

#### Figure 18: Serious adverse events

	EPC	)	place	bo		Risk Ratio			Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl			M-H, Fixe	ed, 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:	plicable Not appli	cable					⊢ 0.1	0.2	0.5 Favours EPO	Favour	s Placeb	5 1 0

#### 2

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

#### Figure 19: Number of patients transfused

	Oral in	on	IV iro	n		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	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: Chi <sup>2</sup> = (	0.72, df=	1 (P = 1	0.39); I <b>²</b> =	0%			
Test for overall effect: 2	Z = 1.12 (I	P = 0.2	6)				Favours Oral iron Favours IV iron

#### 4

#### Figure 20: Length of hospital stay

	Or	al iro	n	IV	iron			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
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 a Test for overall effect	pplicable :: Z = 1.20	) ) (P =	0.23)						-100 -50 0 50 10 Favours Oral iron Favours IV iron

#### 5

#### Figure 21: Deep vein thrombosis (DVT)

•	Oral i	ron	IV iro	on -		Risk Ratio	Risk Rat	io
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 9	5% CI
Bisbe 2014	0	62	1	59	100.0%	0.32 [0.01, 7.64]		
Total (95% CI)		62		59	100.0%	0.32 [0.01, 7.64]		
Total events	0		1					
Heterogeneity: Not ap Test for overall effect:	oplicable Z = 0.71	(P = 0.4	18)				0.01 0.1 1 Favours Oral iron Fa	10 10 vours IV iron

#### 6

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



#### 1

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

#### Figure 23: All-cause mortality at 30 days



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#### 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% Cl	M-H, Random, 95% Cl
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]	
Total (95% CI)		50		51	100.0%	0.76 [0.35, 1.65]	
Total events	9		12				
Heterogeneity: Tau <sup>2</sup> = 0	0.00; Chi² :	= 0.20, c	∄f = 1 (P =	= 0.65);	ł		
Test for overall effect: 2	Z = 0.68 (P	= 0.49)		Fav	ours EPO+ IV iron Favours IV iron		

4

#### Figure 25: Serious adverse events

-	EPO+IV	iron	IV iro	n		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Karkouti 2006	0	10	0	10		Not estimable	
Kateros 2010	0	38	0	41		Not estimable	
Total (95% CI)		48		51		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
lest for overall effect:	NOT applic	apie					Favours EPO+IV iron Favours IV iron

#### 5

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

#### Figure 26: All-cause mortality at 30 days

	EPO+ Ora	l iron	Oral in	on		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Podesta 2000	9	97	10	103	82.9%	0.96 [0.41, 2.25]	
Stowell 2009	1	340	2	340	17.1%	0.50 [0.05, 5.49]	• • •
Total (95% CI)		437		443	100.0%	0.88 [0.39, 1.96]	
Total events	10		12				
Heterogeneity: Chi <sup>2</sup> =	0.25, df = 1	(P = 0.8	62); I² = 0'	%			
Test for overall effect:	Z = 0.32 (P	= 0.75)					Favours EPO+ Oral iron Favours Oral iron

#### Figure 27: Number of patients transfused



1

#### Figure 28: Length of hospital stay

0 0		•							
	EPO+ Oral iron Oral iron				n		Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% (	CI 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	3]
Total (95% CI)			38			43	100.0%	-0.22 [-0.61, 0.18	1
Heterogeneity: Chi <sup>2</sup> =	0.63, df=	:1(P:	= 0.43)	; I² = 0%	, ,				
l'est for overall effect.	Z=1.08	(P = 0	.28)						Favours EPO+ Oral iron Favours Oral iron

2

#### **Figure 29: Infections**

•	EPO+ Oral iron		Oral iron			Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	
Larson 2001	1	16	2	16	100.0%	0.50 [0.05, 4.98]		
Total (95% CI)		16		16	100.0%	0.50 [0.05, 4.98]		
Total events	1		2					
Heterogeneity: Not ap	oplicable							1
Test for overall effect:	Z = 0.59 (P	= 0.55)					Favours EPO+oral iron Favours oral iron	'

3

#### Figure 30: Deep vein thrombosis (DVT)

	EPO+ Ora	l iron	Oral in	ron		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 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]	-
Total events	16		7				
Heterogeneity: Not ap Test for overall effect:	= 0.06)					0.01 0.1 1 10 10 Favours EPO+Oral iron Favours Oral iron	

4

#### Figure 31: Other thrombovascular events

0					-		
	EPO+ Ora	l iron	Oral in	on		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Stowell 2009	12	340	7	340	100.0%	1.71 [0.68, 4.30]	
Total (95% CI)		340		340	100.0%	1.71 [0.68, 4.30]	
Total events	12		7				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 1.15 (P :	= 0.25)					Eavours EPO+oral iron Eavours oral iron

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

#### Figure 32: Mortality (all-cause)



2

#### Figure 33: Serious adverse events

0							
	EPO+oral or I	V iron	Oral or IV	V iron		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	I 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:	oplicable Z = 0.74 (P = 0.	.46)					0.01 0.1 1 10 11 Favours EPO+oral or IV Favours Oral or IV iron

3

#### 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% Cl	M-H, Fix	ed, 95% Cl	
Olijhoek 2001	0	58	0	52		Not estimable			
Total (95% CI)		58		52		Not estimable			
Total events	0		0						
Heterogeneity: Not ap	oplicable							1 10	1
Test for overall effect:						Favours EPO+oral or IV iron	Favours oral or IV iron		

#### 4

## 5 K.2 Alternatives to blood transfusion in surgical patients-6 combinations of cell salvage and tranexamic acid

#### 7 K.2.1 Adults - high risk

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

-						-	-
	Intra Op	CS	Standard treat	ment		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Year	M-H, Random, 95% Cl
1.1.1 Post 2003							
Mercer 2004	21	40	31	41	17.8%	0.69 [0.49, 0.98] 2004	
Murphy 2005	4	30	7	31	1.7%	0.59 [0.19, 1.81] 2005	
Damgaard 2006	17	30	21	29	14.0%	0.78 [0.53, 1.15] 2006	
Aghdaii 2012	7	25	8	25	2.9%	0.88 [0.37, 2.05] 2012	
Vermeijden 2015 Subtotal (95% CI)	98	189 <b>314</b>	108	177 303	63.6% 1 <b>00.0%</b>	0.85 [0.71, 1.02] 2015 0.81 [0.70, 0.93]	▲
Total events	147		175				
Heterogeneity: Tau <sup>2</sup> = 0	0.00; Chi <sup>2</sup> :	= 1.41,	df = 4 (P = 0.84)	; l <sup>2</sup> = 0%			
Test for overall effect: Z	Z = 2.93 (P	= 0.00	3)				
Total (95% CI)		314		303	100.0%	0.81 [0.70, 0.93]	•
Total events	147		175				
Heterogeneity: Tau <sup>2</sup> = 0	0.00; Chi <sup>2</sup> :	= 1.41,	df = 4 (P = 0.84)	; l <sup>2</sup> = 0%		H H	
Test for overall effect: Z	Z = 2.93 (P	9 = 0.00	3)			0	Eavours Intra On CS Eavours Standard Tt
Test for subgroup differ	ences: No	t applic	able				

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

		Intr	a op C	s	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	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	-		
	Bowley 2006	6.47	5.14	21	11.17	6.06	23	3.0%	-4.70 [-8.01, -1.39]	2006			
	Goel 2007	1.54	1.1	24	2.4	1.29	25	28.3%	-0.86 [-1.53, -0.19]	2007			
	Aghdaii 2012	0.4	0.8	25	0.7	1	25	33.6%	-0.30 [-0.80, 0.20]	2012			
	Subtotal (95% CI)			110			113	100.0%	-0.78 [-1.37, -0.19]		◆		
	Heterogeneity: Tau <sup>2</sup> =	0.21; Cł	ni² = 8.	68, df =	= 3 (P =	0.03);	$l^2 = 65^{\circ}$	%					
	Test for overall effect:	Z = 2.59	(P = 0	0.010)									
	Total (95% CI)			110			113	100.0%	-0.78 [-1.37, -0.19]		•		
	Heterogeneity: Tau <sup>2</sup> =	0.21; Cł	ni² = 8.	68, df =	= 3 (P =	0.03);	$l^2 = 65^{\circ}$	%					
Test for overall effect: $Z = 2.59$ (P = 0.010)										-10	-5 U 5 10 Eavours Intra on CS Eavours Standard Tt		
	Test for subgroup diffe	erences:	Not ap	plicabl	е								

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



#### Figure 38: ICS versus standard treatment- Infection

	Intra Op	CS	Standar	d Tt		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	Year	M-H, Random, 95% Cl		
1.4.1 Post 2003										
Mercer 2004	5	40	14	41	72.2%	0.37 [0.15, 0.92]	2004			
Murphy 2005	0	30	2	31	6.9%	0.21 [0.01, 4.13]	2005 —			
Damgaard 2006	2	30	3	29	20.9%	0.64 [0.12, 3.58]	2006			
Goel 2007	0	24	0	25		Not estimable	2007			
Subtotal (95% CI)		124		126	100.0%	0.40 [0.18, 0.87]		$\bullet$		
Total events	7		19							
Heterogeneity: Tau <sup>2</sup> = 0	0.00; Chi <sup>2</sup> :	= 0.52,	df = 2 (P =	= 0.77);	l <sup>2</sup> = 0%					
Test for overall effect: 2	Z = 2.31 (F	9 = 0.02	)							
Total (95% CI)		124		126	100.0%	0.40 [0.18, 0.87]		•		
Total events	7		19							
Heterogeneity: Tau <sup>2</sup> = 0	0.00; Chi <sup>2</sup>	= 0.52,	df = 2 (P =	= 0.77);	l <sup>2</sup> = 0%					
Test for overall effect: 2	Z = 2.31 (F	P = 0.02	)			0.0	Eavours Intra On CS Eavours Standard Tt			
Test for subgroup diffe	rences: No	t applic	able							

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



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

0						•				
	Post op	CS	Standar	d Tt		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Rano	dom, 95% Cl	
2.1.1 Post 2003										
Zhao 2003	19	30	30	30	83.5%	0.64 [0.49, 0.84]	2003			
Naumenko 2003	2	32	1	33	1.6%	2.06 [0.20, 21.64]	2003			
Pleym 2005	1	23	3	24	1.9%	0.35 [0.04, 3.11]	2005			
Sirvinskas 2007	6	41	19	49	12.9%	0.38 [0.17, 0.86]	2007			
Subtotal (95% CI)		126		136	100.0%	0.60 [0.45, 0.81]		•		
Total events	28		53							
Heterogeneity: Tau <sup>2</sup> =	0.01; Chi <sup>2</sup>	= 3.11,	df = 3 (P =	= 0.37);	l <sup>2</sup> = 4%					
Test for overall effect:	Z = 3.30 (F	<b>P</b> = 0.00	10)							
Total (95% CI)		126		136	100.0%	0.60 [0.45, 0.81]		•		
Total events	28		53							
Heterogeneity: Tau <sup>2</sup> =	0.01; Chi <sup>2</sup>	= 3.11,	df = 3 (P =	= 0.37);	l² = 4%			01	1 10	100
Test for overall effect:	Z = 3.30 (F	P = 0.00	10)				0.01	U.I Eavoure Poet On CS	Eavoure Standard Tt	100
Test for subgroup diffe	rences: No	ot applic	able					1 avours 1 0st Op 00		

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



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

	Post Op	CS	Standar	rd Tt	Risk Ratio			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
2.3.1 Post 2003								
Pleym 2005	1	25	0	25	100.0%	3.00 [0.13, 70.30]	2005	
Subtotal (95% CI)		25		25	100.0%	3.00 [0.13, 70.30]		
Total events	1		0					
Heterogeneity: Not app	olicable							
Test for overall effect:	Z = 0.68 (P	= 0.49	)					
Total (95% CI)		25		25	100.0%	3.00 [0.13, 70.30]		
Total events	1		0					
Heterogeneity: Not app	olicable							
Test for overall effect: Z = 0.68 (P = 0.49)							0.0	Favours Post On CS Favours Standard Tt
Test for subgroup diffe	rences: No	t applic	able					

#### Figure 43: PCS versus standard treatment- Infection

	Post Op	CS	Standar	rd Tt		Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Rano	lom, 95% Cl		
2.4.1 Post 2003											
Sirvinskas 2007 Subtotal (95% CI)	1	41 41	8	49 <b>49</b>	100.0% 1 <b>00.0%</b>	0.15 [0.02, 1.15] 0.15 [0.02, 1.15]	2007 -		+		
Total events Heterogeneity: Not app Test for overall effect: 2	1 olicable Z = 1.83 (F	P = 0.07	8								
Total (95% CI)		41		49	100.0%	0.15 [0.02, 1.15]	-		-		
Total events Heterogeneity: Not app Test for overall effect: 2 Test for subgroup differ	1 olicable Z = 1.83 (F rences: No	P = 0.07 ot applic	8 ) able				0.01	0.1 Favours Post Op CS	1 10 Favours Standard Tt	100	

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



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

	(Intra+Post)	Op CS	Standar	d Tt		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
3.1.1 Post 2003								
Murphy 2004	41	98	64	102	82.1%	0.67 [0.51, 0.88]	2004	
Wiefferink 2007 Subtotal (95% CI)	8	15 113	10	15 117	17.9% 1 <b>00.0%</b>	0.80 [0.44, 1.45] 0.69 [0.54, 0.89]	2007	•
Total events	49		74					
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> = 0.3	30, df = 1	(P = 0.58	); l <sup>2</sup> = 0	%			
Test for overall effect:	Z = 2.91 (P = 0	.004)						
Total (95% CI)		113		117	100.0%	0.69 [0.54, 0.89]		◆
Total events	49		74					
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: Test for subgroup diffe	0.00; Chi <sup>2</sup> = 0.3 Z = 2.91 (P = 0 rences: Not ap	80, df = 1 .004) plicable	(P = 0.58	); I <sup>2</sup> = 0	%			0.01 0.1 1 10 100 Favours (Intra+Post)Op CS Favours Standard Tt

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

	(Intra+Post)C	Dp CS	Standar	d Tt		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
3.3.1 Post 2003								
Murphy 2004 Subtotal (95% CI)	1	99 <b>99</b>	3	97 <b>97</b>	100.0% 1 <b>00.0%</b>	0.33 [0.03, 3.09] 0.33 [0.03, 3.09]	2004	
Total events Heterogeneity: Not app Test for overall effect: 2	1 blicable Z = 0.98 (P = 0.	.33)	3					
Total (95% CI)		99		97	100.0%	0.33 [0.03, 3.09]		
Total events	1		3					
Heterogeneity: Not app	licable						H	
Test for overall effect: 2	Z = 0.98 (P = 0.	.33)					, c	Foyours (Intro+Post)Op CS Foyours Standard Tt
Test for subgroup diffe	rences: Not app	olicable						

#### Figure 47: ICS plus PCS versus standard treatment- Infection

	(Intra+Post)	Op CS	Standar	d Tt		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Yea	Ir M-H, Random, 95% CI
3.4.1 Post 2003							
Murphy 2004 Subtotal (95% CI)	2	99 <b>99</b>	2	97 <b>97</b>	100.0% 1 <b>00.0%</b>	0.98 [0.14, 6.82] 200 0.98 [0.14, 6.82]	4
Total events Heterogeneity: Not ap Test for overall effect:	2 plicable Z = 0.02 (P = 0	.98)	2				
Total (95% CI)		99		97	100.0%	0.98 [0.14, 6.82]	
Total events Heterogeneity: Not ap Test for overall effect: Test for subgroup diffe	2 plicable Z = 0.02 (P = 0 prences: Not app	.98) plicable	2				0.01 0.1 1 10 100 Favours (Intra+Post)Op CS Favours Standard Tt

#### 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

•					•	•		
	ICS+T	XA	ICS			Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	CI M-H, Fixed, 95% CI	
5.1.1 Post 2003								
Casati 2004	9	52	13	50	9.3%	0.67 [0.31, 1.42]	· · · · · · · · · · · · · · · · · · ·	
Diprose 2005	20	60	27	60	19.0%	0.74 [0.47, 1.17]		
Jimenez 2007	9	24	19	26	12.8%	0.51 [0.29, 0.90]		
Kuitunen 2005	5	20	12	20	8.4%	0.42 [0.18, 0.96]		
Later 2009	57	99	73	103	50.4%	0.81 [0.66, 1.00]		
Subtotal (95% CI)		255		259	100.0%	0.71 [0.60, 0.85]	◆	
Total events	100		144					
Heterogeneity: Chi <sup>2</sup> = 4	.41, df = 4	4 (P = 0	).35); l² =	9%				
Test for overall effect: 2	Z = 3.71 (I	P = 0.0	002)					
Total (95% CI)		255		259	100.0%	0.71 [0.60, 0.85]	•	
Total events	100		144					
Heterogeneity: Chi <sup>2</sup> = 4	.41, df = 4	4 (P = 0	).35); l² =	9%				
Test for overall effect: 2	Z = 3.71 (I	P = 0.0	002)				Eavours ICS+TXA Eavours ICS	
Test for subgroup differ	rences: N	ot appli	cable					

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

	IC	S+TX/	4		ICS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	CI IV, Fixed, 95% CI
5.2.1 Post 2003									
Diprose 2005	0.87	1.52	60	1.68	3.51	60	8.2%	-0.81 [-1.78, 0.16]	6]
Jimenez 2007	1.58	0.49	24	3.21	0.55	26	91.8%	-1.63 [-1.92, -1.34]	l]
Subtotal (95% CI)			84			86	100.0%	-1.56 [-1.84, -1.29]	j I
Heterogeneity: Chi <sup>2</sup> = 2	2.53, df :	= 1 (P	= 0.11)	; l <sup>2</sup> = 61	%				
Test for overall effect:	Z = 11.0	9 (P <	0.0000	)1)					
									_
Total (95% CI)			84			86	100.0%	-1.56 [-1.84, -1.29]	]
Heterogeneity: Chi <sup>2</sup> = 2	2.53, df :	= 1 (P	= 0.11)	; l <sup>2</sup> = 61	%				
Test for overall effect:	Z = 11.0	9 (P <	0.0000	)1)					Favoure ICS+TXA Favoure ICS
Test for subgroup diffe	rences:	Not ap	plicabl	е					

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

	ICS+T	XA	ICS			Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixe	ed, 95% Cl	
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		_		
Later 2009	1	99	1	103	100.0%	1.04 [0.07, 16.41]				
Subtotal (95% CI)		143		209	1 <b>00.0%</b>	1.04 [0.07, 16.41]				
Total events	1		2							
Heterogeneity: Not app	licable									
Test for overall effect: Z	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							0.1		100
Test for overall effect: 2	Z = 0.03 (H	- = 0.9	3)				0.01 Eave		1 10 Eavoure ICS	100
Test for subgroup differ	ences: N	ot appli	cable				Fav	0015 103 +1 AA	1 avouis 103	

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



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



#### 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	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
6.3.1 Post 2003							
Reyes 2011 Subtotal (95% CI)	5	34 <b>34</b>	4	29 <b>29</b>	100.0% 1 <b>00.0%</b>	1.07 [0.32, 3.60] 1.07 [0.32, 3.60]	
Total events	5		4				
Heterogeneity: Not app	licable						
Test for overall effect: 2	Z = 0.10 (P = 0)	).92)					
Total (95% CI)		34		29	100.0%	1.07 [0.32, 3.60]	
Total events Heterogeneity: Not app Test for overall effect: 2	5 licable Z = 0.10 (P = 0	).92)	4				0.01 0.1 1 10 100 Favours Intra Op CS+TXA Favours TXA

#### 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	<b>`</b>		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	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 ap	0 plicable		0				
Test for overall effect:	Not applicable						
Total (95% CI)		17		17		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not applicable						Eavours Poat On CS+TXA Eavours TXA
Test for subgroup diffe	erences: Not an	plicable					

#### 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

<b>.</b>	•				•		<i>i i i</i>
	ICS +PCS	+TXA	ICS +P	CS		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
9.3.1 Post 2003							
Murphy 2006 Subtotal (95% CI)	0	50 <b>50</b>	0	50 <b>50</b>		Not estimable Not estimable	
Total events Heterogeneity: Not app Test for overall effect: N	0 Iicable Not applicabl	е	0				
Total (95% CI)		50		50		Not estimable	
Total events Heterogeneity: Not app Test for overall effect: N Test for subgroup differ	0 Ilicable Not applicabl rences: Not a	e applicabl	0 e				0.01 0.1 1 10 100 Favours ICS+PCS+TXA Favours ICS+PCS

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



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

	ICS +PCS +	⊦TXA	TXA			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
10.3.1 Post 2003							
Klein 2008 Subtotal (95% CI)	6	102 1 <b>02</b>	5	111 111	100.0% 1 <b>00.0%</b>	1.31 [0.41, 4.15] 1.31 [0.41, 4.15]	
Total events Heterogeneity: Not app Test for overall effect: 2	6 blicable Z = 0.45 (P =	0.65)	5				
Total (95% CI)		102		111	100.0%	1.31 [0.41, 4.15]	
Total events Heterogeneity: Not app Test for overall effect: 2 Test for subgroup diffe	6 blicable Z = 0.45 (P = rences: Not a	0.65) pplicabl	5 e				0.01 0.1 1 10 100 Favours ICS+PCS+TXA Favours TXA

Figure 63: TAA versus standard treatment- Number exposed to allogeneic transfusion	Figure 63:	TXA versus standard	treatment- Number ex	posed to allogeneic	transfusions
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Study or Subaroup	Evente	Total	Evente	Total	Weight	M-H Random 95% C	M-H Random 95% Cl
1 1 1 Pro 2003	Lvents	Total	Lvents	Total	weight	M-H, Kanuolii, 55 /6 G	
1.1.1 FIE 2003	05	4.40	00	4.40	0.00/	0 5 4 10 00 0 771	
Armellin 2001	35	143	63	140	3.9%	0.54 [0.39, 0.77]	-
Blauhut 1994	(	15	9	14	2.1%	0.73 [0.37, 1.41]	
Jasati 2001	2	20	4	20	0.5%	0.50 [0.10, 2.43]	
Coffey 1995	9	16	8	14	2.3%	0.98 [0.53, 1.84]	
Jorbeau 1995	15	41	12	20	2.7%	0.61 [0.36, 1.05]	
Jalmau 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]	
awzy 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	16	44	2.3%	0.89 [0.49, 1.64]	
Katoh 1997	7	62	10	31	1.5%	0.35 [0.15, 0.83]	
Katsaros 1996	11	104	27	106	2.2%	0.42 [0.22, 0.79]	
(rohn 2002	2	16	9	14	0.7%	0.19 [0.05, 0.75]	• • • • • • • • • • • • • • • • • • •
Aenichetti 1996	12	24	18	24	3.1%	0.67 [0.42, 1.06]	
'ugh 1995	22	22	23	23	5.6%	1.00 [0.92, 1.09]	+
peekenbrink 1995	13	15	11	15	3.8%	1.18 [0.82, 1.70]	<b>_</b>
ubtotal (95% CI)		638		588	43.8%	0.74 [0.58, 0.95]	
otal events	221		291				
leterogeneity: Tau <sup>2</sup> =	0.17; Chi <sup>2</sup>	= 91.6	9, df = 15	(P < 0.0	0001); l² =	= 84%	
est for overall effect:	Z = 2.35 (F	P = 0.02	2)				
.1.2 Post 2003							
HN 2012	20	38	27	38	3.8%	0.74 [0.51, 1.07]	
ndreasen 2004	6	20	5	17	1.2%	1.02 [0.38, 2.76]	
aric 2007	51	97	51	96	4.5%	0.99 [0.76, 1.29]	_ <del></del>
ell Amore 2012	8	44	10	43	1.6%	0.78 [0.34, 1.79]	
sfandiari 2013	22	75	43	75	3.5%	0.51 [0.34, 0.76]	———
ihaffari 2012	15	50	23	50	2.8%	0.65 [0.39, 1.10]	
havidel 2014	60	100	74	100	5.0%	0.81 [0.67, 0.99]	
ares 2003	2	22	7	25	0.6%	0.32 [0.08, 1.40]	•
arski 2005	24	147	41	165	3.2%	0.66 [0.42, 1.03]	
undin 2014	15	50	22	50	2.7%	0.68 [0.40, 1.15]	
lansour 2004	7	20	12	20	2.0%	0.58 [0.29, 1.17]	
/lehr-Aein 2007	5	33	8	33	1.2%	0.63 [0.23, 1.71]	
louraei 2013	15	40	21	40	2.9%	0.71 [0.43, 1.17]	
'leym 2003	7	40	8	39	1.3%	0.85 [0.34, 2.13]	
aberi 2010	0	50	0	50		Not estimable	
antos 2006	7	29	12	31	1.7%	0.62 [0.29, 1.36]	
hi 2013	166	274	221	278	5.5%	0.76 [0.68, 0.85]	-
hi2013A	42	58	54	59	5.1%	0.79 [0.66, 0.94]	
aghaddomi 2009	8	50	27	50	2.0%	0.30 [0.15, 0.59]	
anek 2005	3	32	6	30	0.8%	0.47 [0.13. 1.71]	
Vang 2012	37	116	54	115	4.0%	0.68 [0.49. 0.94]	
Vei 2006	3	36	8	40	0.8%	0.42 [0.12, 1.45]	
Vu 2006	0	106	17	108	0.2%	0.03 [0.00, 0.48]	←─────
Subtotal (95% CI)	5	1527		1552	56.2%	0.72 [0.65, 0.80]	♦
otal events	523		751			·····	
Heterogeneity: Tau <sup>2</sup> =	0.01; Chi <sup>2</sup> 7 = 6.05 (	= 29.0	0, df = 21	(P = 0.1	1); l² = 28	%	
	∠ – 0.03 (r	2165	550 r <i>j</i>	2140	100 0%	0 72 [0 64 0 94]	
0141 (35 /0 01)	711	210J	1040	2140	100.0 /0	0.72 [0.04, 0.01]	▼
Total avanta	144		1042				1
otal events	0.07.01	407	00 IK	-		300/	
Total events leterogeneity: Tau <sup>2</sup> =	0.07; Chi <sup>2</sup>	= 125.	33, df = 3	7 (P < 0.	00001); l²	= 70%	0.1 0.2 0.5 1 2 5

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

		тха		Sta	ndard <sup>-</sup>	Гt		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.2.1 Pre 2003									
Armellin 2001	1.68	1.2	35	1.93	1.3	63	9.9%	-0.25 [-0.76, 0.26]	
Blauhut 1994	1.71	0.95	7	2.44	1.13	9	5.9%	-0.73 [-1.75, 0.29]	
Corbeau 1995	2.19	0.46	15	2.83	1.45	12	7.0%	-0.64 [-1.49, 0.21]	
Dalmau 2000	7.72	5.44	29	8.38	6.13	37	1.3%	-0.66 [-3.46, 2.14]	
Horrow 1990	0.92	0.8	18	0.76	1.08	20	9.1%	0.16 [-0.44, 0.76]	
Katoh 1997	1.42	2.74	62	3.03	4.57	31	2.9%	-1.61 [-3.36, 0.14]	
Speekenbrink 1995	3.31	1.62	13	4.27	3.15	11	2.2%	-0.96 [-3.02, 1.10]	
Uozaki 2001	4.1	2.23	6	9.16	6.6	6	0.4%	-5.06 [-10.63, 0.51]	←
Yassen 1993	7.9	3.3	10	12.4	8	10	0.4%	-4.50 [-9.86, 0.86]	←
Zabeeda 2002	0.52	0.9	25	1.68	1	25	9.7%	-1.16 [-1.69, -0.63]	
Subtotal (95% CI)			220			224	48.7%	-0.66 [-1.14, -0.18]	$\bullet$
Heterogeneity: Tau <sup>2</sup> =	0.23; Cł	ni² = 18	3.16, df	= 9 (P =	= 0.03);	$I^2 = 50^6$	%		
Test for overall effect:	Z = 2.69	) (P = 0	0.007)						
1.2.2 Post 2003									
AHN 2012	0.8	0.8	38	1.4	1.2	38	10.3%	-0.60 [-1.06, -0.14]	
Ghavidel 2014	1.25	0.53	100	1.65	0.55	100	12.5%	-0.40 [-0.55, -0.25]	*
Maddali 2007	2.03	0.78	111	3.17	0.97	111	12.1%	-1.14 [-1.37, -0.91]	<b>T</b>
Shi 2013	3.93	4.66	274	6.51	7.33	278	5.9%	-2.58 [-3.60, -1.56]	
Shi2013A	4.84	5.85	58	9.36	11.41	59	1.0%	-4.52 [-7.80, -1.24]	•
Wang 2012	0.91	1.59	116	1.62	2.57	115	9.5%	-0.71 [-1.26, -0.16]	
Wei 2006	1.27	0.07	36	1.33	0	40		Not estimable	
Subtotal (95% CI)			733			741	51.3%	-1.02 [-1.53, -0.52]	←
Heterogeneity: Tau <sup>2</sup> =	0.28; Cł	ni² = 47	7.03, df	= 5 (P -	< 0.000	01); I² =	89%		
Test for overall effect:	Z = 3.96	6 (P < 0	0.0001)						
Total (95% CI)			953			965	100.0%	-0.83 [-1.17, -0.50]	◆
Heterogeneity: Tau <sup>2</sup> =	0.23; Cł	ni² = 65	5.57, df	= 15 (P	< 0.00	001); l²	= 77%		
Test for overall effect:	Z = 4.87	' (P < (	0.00001	D)					-4 -2 0 2 4
Test for subgroup diffe	rences:	Chi <sup>2</sup> =	1.04, c	lf = 1 (P	= 0.31)	), $I^2 = 3$ .	7%		Favours IXA Favours Standard Tt

#### Figure 65: TXA versus standard treatment- Mortality

		aara	Standa	rd Tt	ioi cancy	Risk Ratio	Risk Ratio
Study or Subaroup	Events	Total	Events	Total	Weight	M-H Fixed 95% C	M-H Fixed 95% Cl
1 3 1 Pre 2003	Lventa	Total	Lventa	Total	Weight	W-11, 1 IXed, 3370 0	
Armollin 2001	1	150	2	150	7 40/	0 22 [0 04 2 47]	<b>▲</b>
AIMellin 2001	1	150	3	150	7.4%	0.33 [0.04, 3.17]	
Blaunul 1994	0	15	0	14	0.00/		4
Boylan 1996	0	25	3	20	9.6%	0.12 [0.01, 2.11]	
Coffey 1995	0	16	1	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	1	22	4	19	10.6%	0.22 [0.03, 1.77]	• •
Hardy 1998	0	43	0	45		Not estimable	
Kaspar 1997	1	16	0	16	1.2%	3.00 [0.13, 68.57]	
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]	$\bullet$
Total events	7		19				
Heterogeneity: $Chi^2 = 4$	4.39. df = 8	3 (P = 0	$(.82):  ^2 =$	0%			
Test for overall effect:	7 – 2 41 (F	P = 0.0	2)	0,0			
	<b>Z</b> = <b>Z</b> .+1 (1	- 0.0	<u>~</u> )				
1.3.2 Post 2003							
	1	50	4	50	0.00/	0.25 [0.02, 2.46]	<b>←</b>
Abdi-Azili 2000	1	21	4	20	9.9/0	2 27 [0.03, 2.10]	·
Anureasen 2004	1	21	0	23	1.2%	3.27 [0.14, 70.21]	`
Baric 2007	1	97	3	96	1.5%	0.33 [0.03, 3.12]	•
Dell Amore 2012	0	44	0	43	<b>F</b> 00/	Not estimable	
Estandiari 2013	2	75	2	75	5.0%	1.00 [0.14, 6.91]	
Fawzy 2009	0	19	0	19		Not estimable	
Ghaffari 2012	0	50	0	50		Not estimable	
Jares 2003	0	22	0	25		Not estimable	
Karski 2005	3	147	1	165	2.3%	3.37 [0.35, 32.02]	
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]	<b>←</b>
Wang 2012	0	116	0	115		Not estimable	
Wu 2006	0	106	0	108		Not estimable	
Subtotal (95% CI)	-	1292	-	1321	43.0%	0.68 [0.33, 1.41]	
Total events	10		16				-
Heterogeneity: Chi <sup>2</sup> – 4	5 03 df - 7	7 (P - (	1 66)· 12 -	0%			
Tost for overall effect:	7 - 1 04 (0	2 - 03	0) 0)	070			
	∠ = 1.04 (f	= 0.3	0)				
Total (95% CI)		1891		1880	100.0%	0.52 [0.31, 0.87]	•
Total events	17		35				
Heterogeneity: Chi <sup>2</sup> =	10.05, df =	16 (P	= 0.86): l <sup>2</sup>	= 0%			
Test for overall effect:	Z = 2.47 (F	⊃ = 0.0	1)				0.05 0.2 1 5 20
Test for subgroup diffe	erences: Cl	ni² = 0.	, 96, df = 1	(P = 0.3)	33), l <sup>2</sup> = 0%	6	Favouis INA Favouis Standard t

#### Figure 66: TXA versus standard treatment- Length of hospital stay

	-	ТХА		Stan	dard	Tt		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	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	0.8	36	7.3	1.2	40	34.4%	-0.20 [-0.65, 0.25]	<b>+</b>
Subtotal (95% CI)			89			93	100.0%	-0.08 [-0.35, 0.18]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; Cł	ni² = (	).87, df	= 2 (P =	0.65	); I <sup>2</sup> = 0	%		
Test for overall effect:	Z = 0.62	2 (P =	0.53)						
Total (95% CI)			89			93	100.0%	-0.08 [-0.35, 0.18]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; Cł	ni² = (	).87, df	= 2 (P =	0.65	); I <sup>2</sup> = 0	%		
Test for overall effect:	Z = 0.62	2 (P =	0.53)						-10 -5 0 5 10 Eavoure TXA Eavoure Standard T
Test for subgroup diffe	erences:	Not a	applicat	ole					Tavouis IAA Favouis Stanuaru I

#### Figure 67: TXA versus standard treatment- Thrombotic complications

•	ТХА	<b>\</b>	Standar	rd Tt		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
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]	
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)	; l <sup>2</sup> = 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]	
Hosseini 2014	0	35	0	36		Not estimable	
Lundin 2014	2	50	5	50	35.7%	0.40 [0.08, 1.97]	
Nouraei 2013	0	40	0	40		Not estimable	
Subtotal (95% CI)		282		282	82.1%	0.50 [0.18, 1.44]	-
Total events	5		10				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	<sup>2</sup> = 0.14	, df = 1 (P	= 0.71)	; l <sup>2</sup> = 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>	<sup>e</sup> = 0.21	, df = 3 (P	= 0.98)	; l² = 0%		
Test for overall effect:	Z = 1.53 (	P = 0.1	3)				Favours TXA Favours Standa
Test for subgroup diffe	erences: C	hi² = 0.	06, df = 1	(P = 0.8)	30), l <sup>2</sup> = 0%	%	

2

#### **Figure 68: Infections**

-	TXA	L.	Standa	rd Tt		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
1.5.1 Post 2003							
Lundin 2014 Subtotal (95% CI)	10	50 <b>50</b>	16	50 <b>50</b>	100.0% 1 <b>00.0%</b>	0.63 [0.31, 1.24] <b>0.63 [0.31, 1.24]</b>	
Total events Heterogeneity: Not app Test for overall effect:	10 olicable Z = 1.34 (I	P = 0.1	16 8)				
Total (95% CI)		50		50	100.0%	0.63 [0.31, 1.24]	•
Total events Heterogeneity: Not app Test for overall effect: Test for subgroup diffe	10 olicable Z = 1.34 (I rences: N	P = 0.1 ot appli	16 8) cable				0.01 0.1 1 10 100 Favours TXA Favours Standard

3

#### 4 K.2.2 Adults - moderate risk

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

•	Intra Or	20.0	Standard troa	tmont		Pick Patio		Pick Patio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
1.1.1 Post 2003						, , ,		
Zhang 2008	10	20	16	20	43.4%	0.63 [0.38, 1.02]	2008	
Hortstmann 2013	4	102	9	102	11.4%	0.44 [0.14, 1.40]	2013	
Cip 2013	23	70	23	70	45.3%	1.00 [0.62, 1.61]	2013	- <b>-</b>
Subtotal (95% CI)		192		192	100.0%	0.74 [0.50, 1.12]		◆
Total events	37		48					
Heterogeneity: Tau <sup>2</sup> =	0.04; Chi <sup>2</sup>	= 2.75,	df = 2 (P = 0.25	); l <sup>2</sup> = 279	%			
Test for overall effect:	Z = 1.43 (F	P = 0.15	)					
Total (95% CI)		192		192	100.0%	0.74 [0.50, 1.12]		-
Total events	37		48					
Heterogeneity: Tau <sup>2</sup> =	0.04; Chi <sup>2</sup>	= 2.75,	df = 2 (P = 0.25	); l <sup>2</sup> = 279	%			
Test for overall effect:	Z = 1.43 (F	P = 0.15	)				0.0	Favours Intra Op CS Favours Standard Tt
Test for subgroup diffe	rences: No	ot applic	able					

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

-								-				
	Intra	а ор С	s	Star	ndard	Tt		Mean Difference		Mean D	fference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI Yea	ar	IV, Rando	om, 95% Cl	
1.2.1 Post 2003												
Thomasson 2012	2.33	0	96	2.54	0	101		Not estimable 201	2			
Hortstmann 2013 Subtotal (95% CI)	2	0	102 <b>198</b>	2	0	102 <b>203</b>		Not estimable 201 Not estimable	3			
Heterogeneity: Not ap Test for overall effect:	plicable Not appli	icable	•									
Total (95% CI) Heterogeneity: Not ap Test for overall effect: Test for subgroup diffe	plicable Not appli erences: I	icable Not ar	198 pplicabl	le		203		Not estimable	-10	-5 Favours Intra op CS	0 5 Favours Standard Tt	10

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

	Post op	o CS	Standar	d Tt		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Year	M-H, Random, 95% Cl
2.1.1 Post 2003							
Atay 2010 i	9	17	15	19	9.5%	0.67 [0.40, 1.11]	
Atay 2010 ii	1	20	8	21	2.5%	0.13 [0.02, 0.96]	
So-osman 2014ii	33	321	54	658	10.2%	1.25 [0.83, 1.89]	+
Cheng 2005	4	26	13	34	6.1%	0.40 [0.15, 1.09] 2005	
So-Osman 2006	22	47	10	22	9.2%	1.03 [0.59, 1.78] 2006	
Dramis 2006	3	32	10	17	5.3%	0.16 [0.05, 0.50] 2006	
Moonen 2007	5	80	15	80	6.3%	0.33 [0.13, 0.87] 2007	
Smith 2007	6	76	17	82	6.9%	0.38 [0.16, 0.92] 2007	<b>_</b>
Zacharopoulos 2007	5	30	10	30	6.4%	0.50 [0.19, 1.29] 2007	
Abuzakuk 2007	13	52	12	52	8.2%	1.08 [0.55, 2.15] 2007	
Tripkovic 2008	4	30	24	30	6.5%	0.17 [0.07, 0.42] 2008	
Amin 2008	12	92	13	86	7.9%	0.86 [0.42, 1.79] 2008	
Horstmann 2014	6	59	11	56	6.5%	0.52 [0.21, 1.31] 2014	
Thomassen 2014	29	382	12	190	8.5%	1.20 [0.63, 2.30] 2014	
Subtotal (95% CI)		1264		1377	100.0%	0.58 [0.41, 0.83]	$\bullet$
Total events	152		224				
Heterogeneity: Tau <sup>2</sup> = 0	0.28; Chi <sup>2</sup>	= 38.89	, df = 13 (	P = 0.0	002); l <sup>2</sup> = 6	7%	
Test for overall effect: 2	Z = 3.01 (F	<b>P</b> = 0.00	3)				
Total (95% CI)		1264		1377	100.0%	0.58 [0.41, 0.83]	•
Total events	152		224				
Heterogeneity: Tau <sup>2</sup> = 0	0.28; Chi <sup>2</sup>	= 38.89	, df = 13 (	P = 0.0	002); l <sup>2</sup> = 6	7%	
Test for overall effect: 2	Z = 3.01 (F	P = 0.00	)3)				U.UT U.T T 10 100 Eavours Post On CS Eavours Standard Tt
Test for subgroup difference	rences: No	ot applic	able				Favours Fost Op 05 Favours Stanuaru Tt

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

-								-					
	Pos	st op C	s	Sta	ndard	Γt		Mean Difference			Mean Diff	erence	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year		IV, Randon	n, 95% CI	
2.2.1 Post 2003													
So-osman 2014ii	1.26	0.7	33	2.68	0.9	54	16.1%	-1.42 [-1.76, -1.08]			-		
Atay 2010 i	0.82	1.07	17	1.68	1.44	19	11.7%	-0.86 [-1.68, -0.04]					
Atay 2010 ii	0.05	0.22	20	0.71	0.96	21	15.5%	-0.66 [-1.08, -0.24]					
So-Osman 2006	2.36	0.89	22	1.9	0.7	10	14.1%	0.46 [-0.11, 1.03]	2006		- t•	F	
Kirkos 2006	0.54	0.86	78	1.06	1.174	77	16.2%	-0.52 [-0.84, -0.20]	2006		-		
Altinel 2007	1.02	1.12	16	2.29	1.22	16	11.8%	-1.27 [-2.08, -0.46]	2007				
Tripkovic 2008	0.22	0.98	30	1.74	1.15	30	14.4%	-1.52 [-2.06, -0.98]	2008		-		
Subtotal (95% CI)			216			227	100.0%	-0.82 [-1.31, -0.33]			•		
Heterogeneity: Tau <sup>2</sup> =	0.36; Cł	ni² = 42	2.75, df	= 6 (P ·	< 0.000	01); l² =	= 86%						
Test for overall effect:	Z = 3.28	8 (P = 0	0.001)										
Total (95% CI)			216			227	100.0%	-0.82 [-1.31 -0.33]			•		
	0.00.01	- 12 44	2.0	0 (D	0.000		0.000	0.02 [ 1.01, 0.00]			•		
Heterogeneity: Tau <sup>2</sup> =	0.36; Cr	$11^2 = 4_2$	2.75, ar	= 6 (P ·	< 0.000	01); I <sup>2</sup> =	86%		-10	-5	ō	5	10
Test for overall effect:	Z = 3.28	B(P = 0)	0.001)							Favours Po	ost op CS	avours Standard	Тt
Test for subgroup diffe	rences:	Not an	oplicabl	e									

#### Figure 73: PCS versus standard treatment- Infection



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



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

(Intra+Post)	Dp CS	Standar	d Tt		Risk Ratio	Risk Ratio
Events	Total	Events	Total	Weight	M-H, Random, 95% CI Yea	r M-H, Random, 95% Cl
2	56	4	62	7.4%	0.55 [0.11, 2.91]	
23	321 377	54	658 <b>720</b>	92.6% 1 <b>00.0%</b>	0.87 [0.55, 1.40] 201 0.84 [0.54, 1.33]	4
25		58				
0.00; Chi <sup>2</sup> = 0.2	27, df = 1	(P = 0.60	); I <sup>2</sup> = 0	%		
Z = 0.74 (P = 0.	.46)					
	377		720	100.0%	0.84 [0.54, 1.33]	<b></b>
25		58				
0.00; Chi <sup>2</sup> = 0.2 Z = 0.74 (P = 0. rences: Not ap	27, df = 1 .46) olicable	(P = 0.60	); I <sup>2</sup> = 0	%		0.01 0.1 1 10 100 Favours (Intra+Post)Op CS Favours Standard Tt
	(Intra+Post) Events 2 23 25 0.00; Chi <sup>2</sup> = 0.2 Z = 0.74 (P = 0 25 0.00; Chi <sup>2</sup> = 0.2 Z = 0.74 (P = 0 rences: Not ap	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $

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


#### Figure 77: ICS plus PCS versus standard treatment- Mortality

	(Intra+Post)	Standa	d Tt		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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 app	olicable						
Test for overall effect:	Z = 0.74 (P = 0	.46)					Favours ICS+PCS Favours Standard Tt

1

#### Figure 78: ICS plus PCS versus standard treatment- Infection



2

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

	(Intra+Post)Op CS			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	
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]		
Heterogeneity: Not app Test for overall effect: 2	olicable Z = 0.98 (F	P = 0.33	5)						-100 -50 0 50 Favours ICS+PCS Favours Star	100 Idard Tt

3

4

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

					-	-	-
	ICS+P	cs	PCS	5		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
So-osman 2014i	23	321	33	321	100.0%	0.70 [0.42, 1.16]	
Total (95% CI)		321		321	100.0%	0.70 [0.42, 1.16]	•
Total events	23		33				
Heterogeneity: Not app Test for overall effect:	plicable Z = 1.39 (	P = 0.1	6)				0.01 0.1 1 10 100 Favours ICS+PCS Favours PCS

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

	ICS	S+PC	s	F	PCS			Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Rand	om, 95% Cl		
So-osman 2014i	3.49	0.5	23	1.26	0.7	33	100.0%	2.23 [1.92, 2.54]					
Total (95% CI)			23			33	100.0%	2.23 [1.92, 2.54]					
Heterogeneity: Not app Test for overall effect: 2	olicable Z = 13.9	1 (P	< 0.000	01)					-100 -: Favour	 50 's ICS+PCS	0 s Favours P	+	100

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

	ICS+T	XA	ICS			Risk Ratio	Risk Ratio
Study or Subgroup	Events	nts Total Events To			Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
4.1.1 Post 2003							
Wong 2008 Subtotal (95% Cl)	23	73 <b>73</b>	30	74 74	100.0% 1 <b>00.0%</b>	0.78 [0.50, 1.20] <b>0.78 [0.50, 1.20]</b>	
Total events	23		30				
Heterogeneity: Not app	licable						
Test for overall effect: Z	Z = 1.13 (F	P = 0.26	6)				
Total (95% CI)		73		74	100.0%	0.78 [0.50, 1.20]	•
Total events	23		30				
Heterogeneity: Not app	licable					F	
Test for overall effect: Z	Z = 1.13 (F	P = 0.26	6)			U	Favours ICS+TXA Favours ICS
Test for subgroup differ	ences: N	ot appli	cable				

#### 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	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]	$\tau$
Heterogeneity: Not app	olicable								
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 app	olicable								
Test for overall effect:	Z = 1.40	(P =	0.16)						Favours ICS+TXA Favours ICS
Test for subgroup diffe	rences:	Not a	pplicab	le					

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



#### PCS+TXA **Risk Ratio Risk Ratio** PCS Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% Cl 5.1.1 Post 2003 Alvarez 2008 46 6 49 53.7% 0.18 [0.02, 1.42] 1 0.60 [0.15, 2.37] **0.37 [0.12**, 1.14] Oremus 2014 49 49 46.3% 3 5 Subtotal (95% CI) 98 100.0% 95 Total events 4 11 Heterogeneity: Chi<sup>2</sup> = 0.95, df = 1 (P = 0.33); l<sup>2</sup> = 0% Test for overall effect: Z = 1.73 (P = 0.08) Total (95% CI) 98 100.0% 0.37 [0.12, 1.14] 95 Total events 4 11 Heterogeneity: Chi<sup>2</sup> = 0.95, df = 1 (P = 0.33); l<sup>2</sup> = 0% 0.01 0.1 10 100 Test for overall effect: Z = 1.73 (P = 0.08) Favours PCS +TXA Favours PCS Test for subgroup differences: Not applicable

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

1 2

#### Figure 86: PCS plus TXA versus PCS- Thrombotic complications



#### 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	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
7.1.1 Post 2003							
Thomasson 2012	9	96	13	101	100.0%	0.73 [0.33, 1.63]	
Subtotal (95% CI)		96		101	100.0%	0.73 [0.33, 1.63]	$\bullet$
Total events	9		13				
Heterogeneity: Not app	olicable						
Test for overall effect: 2	Z = 0.77 (P =	0.44)					
Total (95% CI)		96		101	100.0%	0.73 [0.33, 1.63]	-
Total events	9		13				
Heterogeneity: Not app	olicable						
Test for overall effect: 2	Z = 0.77 (P =	0.44)					Favours ICS+PCS+TXA Favours TXA
Test for subaroup diffe	rences: Not a	applicabl	е				

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

•	ICS +P	ICS +PCS +TXA TXA						Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
7.2.1 Post 2003									
Thomasson 2012 Subtotal (95% CI)	2.33	0	96 96	2.54	0	101 101		Not estimable Not estimable	
Heterogeneity: Not a Test for overall effect	pplicable : Not appli	cable							
Total (95% CI) Heterogeneity: Not ay Test for overall effect Test for subgroup dif	pplicable : Not appli ferences:	cable Not ap	96 plicab	le		101		Not estimable Fav	-100 -50 0 50 100 ours ICS+PCS+TXA Favours TXA

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

	TXA	\	Standar	d Tt	• • • • • • • • •	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
1.1.1 Pre 2003							
Benoni 1996	8	43	24	43	2.8%	0.33 [0.17, 0.66]	
Benoni 2000 Benoni 2001	9	20	15	19	3.5%	0.57 [0.33, 0.98]	
Ellis 2001	4	10	0 7	20	0.6%	0.56 [0.20, 1.54]	←
Engel 2001	0	12	3	12	0.0%	0.14 [0.02, 0.30]	←
Hiipala 1995	10	15	12	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]	←
Lanaka 2001 Subtotal (95% CI)	47	73 272	26	26 223	5.3% 24 9%	0.65 [0.55, 0.78]	
Total events	100		155			0.10 [0.02, 0.00]	<b>→</b>
Heterogeneity: Tau <sup>2</sup> = 0.16	5; Chi <sup>2</sup> = 2	9.02, df	f = 9 (P = )	0.0006);	l² = 69%		
Test for overall effect: Z =	4.33 (P <	0.0001)	)	,			
1.1.2 Post 2003							
Aguilera 2013	2	41	12	42	1.0%	0.17 [0.04, 0.72]	
Ridolegui 2013	0	79 25	13	25	0.0%	0.06 [0.01, 0.57]	· · · · · · · · · · · · · · · · · · ·
Bradshaw 2012	0	26	1	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]	<b></b>
Charoench2011	28	50	45	50	4.9%	0.62 [0.48, 0.81]	
Claeys 2007	1	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]	
Eftekharian 2015	0	28	2	28	0.3%	Not estimable	
Farrokhi 2011	10	38	15	38	2.9%	0.67 [0.34, 1.29]	
Garneti 2004	16	25	14	25	3.9%	1.14 [0.72, 1.80]	
Georgiadis 2013	0	50	4	51	0.3%	0.11 [0.01, 2.05]	<b>←</b>
Gill 2009	1	5	4	5	0.7%	0.25 [0.04, 1.52]	
Good 2003	3	27	14	24	1.5%	0.19 [0.06, 0.58]	
Gungorduk 2011 Hustod 2002	2	330	7	330	0.9%	0.29 [0.06, 1.37]	
Imai2012	2	20 95	0	20	1.0 /0	Not estimable	
Ishida 2011	0	50	1	50	0.2%	0.33 [0.01, 7.99]	· · · · · · · · · · · · · · · · · · ·
Johansson 2005	8	47	23	53	2.7%	0.39 [0.19, 0.79]	
Karimi 2012	0	16	1	16	0.2%	0.33 [0.01, 7.62]	· · · · · · · · · · · · · · · · · · ·
Kazemi 2010	4	32	11	32	1.7%	0.36 [0.13, 1.02]	
Kim 2014 i	1	90 72	б 20	90	0.5%	0.17 [0.02, 1.36]	
Lee 2013	9	34	20	34	2.0%	0.45 [0.24 0.84]	
Lemay 2004	0	20	8	19	0.3%	0.06 [0.00, 0.91]	←────
MacGillivray 2010	13	40	10	20	3.0%	0.65 [0.35, 1.22]	
Martin 2014	7	50	10	50	2.1%	0.70 [0.29, 1.69]	
Niskanen 2005	5	19	8	20	2.0%	0.66 [0.26, 1.66]	
Orpen 2006 Rejesseren 2000	1	15	3	14	0.5%	0.31 [0.04, 2.65]	
Ravirai2012	7	88	18	88	2.3%	0.39 [0.17 0.88]	
Roy 2012	2	25	7	25	1.0%	0.29 [0.07, 1.24]	· · · · · · · · · · · · · · · · · · ·
Sa-Ngasoongsong 2011	1	24	8	24	0.6%	0.13 [0.02, 0.92]	< <u>←</u>
Sa-ngasoongsong 2013	6	90	10	45	1.9%	0.30 [0.12, 0.77]	
Sadeghi 2007	12	32	20	35	3.5%	0.66 [0.39, 1.12]	
Seo 2013 Shahid 2013	10	50 38	47	50 36	3.3%	0.21 [0.12, 0.37]	· · · · · · · · · · · · · · · · · · ·
Vijav 2013	7	45	12	45	2.4%	0.39 [0.18 0.84]	
Wong 2010	5	64	.0	35	1.7%	0.30 [0.11, 0.84]	
Yamasaki 2004	0	20	0	20		Not estimable	
Yang 2015	10	40	19	40	3.0%	0.53 [0.28, 0.99]	
Yue 2015	3	52	11	49	1.3%	0.26 [0.08, 0.87]	
Zonar 2004 Subtotal (95% CI)	3	20 2245	12	20 2074	1.5% 75 1%	0.25 [0.08, 0.75]	
Total events	297	2273	641	2014	10.170	0.77 [0.00, 0.00]	▼
Heterogeneity: $Tau^2 = 0.12$ Test for overall effect: Z = 3	2; Chi² = 7 8.71 (P < 9	9.34, df 0.0000 <sup>-</sup>	f = 41 (P = 1)	0.0003	); l² = 48%	9	
Total (95% CI)		2517		2297	100.0%	0.45 [0.38, 0.52]	•
Total events	397		796				
Heterogeneity: $Tau^2 = 0.12$ Test for overall effect: Z = 2	2; Chi² = 1 9.90 (P < 0	09.71, ( 0.0000 <sup>-</sup>	df = 51 (P 1)	< 0.000	01); l <sup>2</sup> = 54	4%	0.1 0.2 0.5 1 2 5 10 Favours TXA Favours Standard #
Test for subgroup difference	ces: Chi² =	= 0.06, o	df = 1 (P =	: 0.81), I	<sup>2</sup> = 0%		

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

-		тха		Sta	ndard	tt		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.2.1 Pre 2003								· · ·	
Hiipala 1995	2.25	0.87	10	3.58	1.57	12	6.3%	-1.33 [-2.37, -0.29]	
Hiipala 1997	2.29	0.52	17	3.46	1.25	34	11.9%	-1.17 [-1.66, -0.68]	
Jansen 1999	0.46	1.45	21	2.5	2.47	21	5.1%	-2.04 [-3.26, -0.82]	
Subtotal (95% CI)			48			67	23.4%	-1.30 [-1.71, -0.88]	◆
Heterogeneity: Tau <sup>2</sup> =	0.00; Cł	ni² = 1.	68, df =	= 2 (P =	0.43);	$I^{2} = 0\%$	þ		
Test for overall effect:	Z = 6.12	2 (P < 0	0.00001	)					
1.2.2 Post 2003									
Antinolfi 2014	0.8	0.8	20	2.2	1	20	11.0%	-1.40 [-1.96, -0.84]	
Caglar 2008	1.8	0.54	15	1.6	0.66	10	11.8%	0.20 [-0.29, 0.69]	
Charoench2011	0.71	0.78	50	1.89	0.87	50	13.8%	-1.18 [-1.50, -0.86]	-
Charoench2012	0.55	0.62	120	1.55	0.98	120	14.9%	-1.00 [-1.21, -0.79]	-
Kazemi 2010	0.31	0.64	32	0.84	0.9	32	13.1%	-0.53 [-0.91, -0.15]	
MacGillivray 2010	0.76	0.75	40	1.11	0.97	20	11.9%	-0.35 [-0.83, 0.13]	
Subtotal (95% CI)			277			252	76.6%	-0.72 [-1.12, -0.32]	•
Heterogeneity: Tau <sup>2</sup> =	0.20; Ch	ni² = 33	3.96, df	= 5 (P	< 0.00	001); l²	= 85%		
Test for overall effect:	Z = 3.55	6 (P = 0	0.0004)						
Total (95% CI)			325			319	100.0%	-0.88 [-1.22, -0.54]	•
Heterogeneity: Tau <sup>2</sup> =	0.19; Cł	ni² = 39	9.70, df	= 8 (P ·	< 0.00	001); l²	= 80%		
Test for overall effect:	Z = 5.12	2 (P < 0	0.00001	)					-4 -2 U 2 4
Test for subgroup diffe	erences:	Chi² =	3.82, c	df = 1 (P	= 0.0	5), l <sup>2</sup> = 1	73.8%		Tavours TXA Favours Stanua

#### Figure 91: TXA versus standard treatment- Mortality

<b>U</b>	ТХА	Standar		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									
Hiipala 1997	0	39	1	38	44.0%	0.33 [0.01, 7.74]	+		
Subtotal (95% CI)		39		38	44.0%	0.33 [0.01, 7.74]			
Total events	0		1						
Heterogeneity: Not app	licable								
Test for overall effect: 2	Z = 0.69 (	P = 0.4	9)						
1.3.2 Post 2003									
Alshryda 2013	0	79	0	78		Not estimable			
Crescenti 2011	0	100	0	100		Not estimable			
Pfizer 2011	0	41	0	42		Not estimable			
Sadeghi 2007	0	32	1	35	41.5%	0.36 [0.02, 8.62]	←		-
Seo 2013	0	50	0	50		Not estimable			
Wong 2010	0	64	0	35		Not estimable			
Xu 2013	0	88	0	86		Not estimable			
Zuffrey 2010	1	57	0	57	14.5%	3.00 [0.12, 72.13]			
Subtotal (95% CI)		511		483	56.0%	1.04 [0.15, 7.45]			
Total events	1		1						
Heterogeneity: Chi <sup>2</sup> = 0	.85, df =	1 (P = 0	).36); l² =	0%					
Test for overall effect: 2	Z = 0.04 (	P = 0.9	7)						
Total (95% CI)		550		521	100.0%	0.73 [0.15, 3.66]			
Total events	1		2						
Heterogeneity: Chi <sup>2</sup> = 1	.20, df = 2	2 (P = 0	).55); l² =	0%			1 05		
Test for overall effect: 2	Z = 0.39 (	P = 0.7	0)				0.05	Eavours TXA Favours Standa	20∠ ard Tt
Test for subgroup differ	ences: C	hi² = 0.3	38, df = 1	(P = 0.5)	54), l <sup>2</sup> = 0%	6			iu il

Bare ser inat									1
		ТХА		Sta	ndard	tt		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
1.4.1 Pre 2003									
Ellis 2001	10	3	10	10	2	10	2.2%	0.00 [-2.23, 2.23]	
Subtotal (95% CI)			10			10	2.2%	0.00 [-2.23, 2.23]	
Heterogeneity: Not app	olicable								
Test for overall effect:	Z = 0.00	(P = 1	1.00)						
1.4.2 Post 2003									
Abdal-aleem 2013	2	0.52	373	2	0.54	367	31.8%	0.00 [-0.08, 0.08]	+
Aguilera 2013	6.8	2.4	41	7.5	2.6	42	7.6%	-0.70 [-1.78, 0.38]	
Bidolegui 2014	4.1	8.3	25	3.8	9.4	25	0.5%	0.30 [-4.62, 5.22]	
Crescenti 2011	9	4.3	100	9	4.3	100	6.5%	0.00 [-1.19, 1.19]	
Kazemi 2010	13	12.4	32	15.5	7.44	32	0.5%	-2.50 [-7.51, 2.51]	
Lee 2013	15.4	3.3	34	15.2	3.1	34	4.3%	0.20 [-1.32, 1.72]	_ <del>_</del> _
Sadeghi 2007	4.3	1.6	32	5.8	1.5	35	12.7%	-1.50 [-2.24, -0.76]	
Yue 2015	5.1	0.5	52	4.9	0.7	49	27.9%	0.20 [-0.04, 0.44]	•
Zohar 2004	8	2	20	9	2	20	6.1%	-1.00 [-2.24, 0.24]	
Subtotal (95% CI)			709			704	97.8%	-0.26 [-0.62, 0.09]	•
Heterogeneity: Tau <sup>2</sup> =	0.10; Cł	ni² = 23	3.45, df	= 8 (P =	= 0.003	3); l² = (	66%		
Test for overall effect:	Z = 1.47	(P=0	0.14)						
Total (95% CI)			719			714	100.0%	-0.25 [-0.59, 0.09]	•
Heterogeneity: Tau <sup>2</sup> =	0.09; Cł	ni² = 23	3.45, df	= 9 (P =	= 0.00	5); l <sup>2</sup> = (	62%		
Test for overall effect:	Z = 1.44	(P = 0	).15)						-10 -5 0 5 10
		•	'						

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

Test for subgroup differences:  $Chi^2 = 0.05$ , df = 1 (P = 0.82), l<sup>2</sup> = 0%

1

### Figure 93: TXA versus standard treatment- Infections

	TXA		Standard Tt			Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	l	M-H, Fixe	∋d, 95% Cl		
1.5.1 Post 2003											
Bidolegui 2014	0	25	0	25		Not estimable					
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]	←		•		$\rightarrow$
Charoench2012	2	120	1	120	27.1%	2.00 [0.18, 21.76]	_				$\rightarrow$
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	1 <b>00.0%</b>	0.93 [0.22, 3.93]				_	
Total events	3		3								
Heterogeneity: Chi <sup>2</sup> = 1	.03, df = 2	2 (P = 0	).60); l <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 ovents	3	024	3	0.0	1001070	0.000 [0.22, 0.000]					
Hotorogonoity: $Chi^2 = 1$	03 df - 1	) (P _ (	0 60). 12 -	0%			<b>⊢</b> →		<u> </u>		
Tost for overall effect: 7	103,  ur = 2	≤ (F = 0 ⊃ = 0 0′	7.00), i= = ' ?\	0 /0			0.1 0.2	2 0.5	1 2	5	10
Tost for subgroup differ	0.10 (r	0.94 at appli	<i>_)</i>					Favours TXA	Favours Sta	Indard 7	Γt
restion subgroup differ	ences. No	Ji appli	Lane								

#### Figure 94: TXA versus standard treatment- Thrombotic complications

		iiuui	Standar	d Tt		Risk Ratio	Risk Ratio
Study or Subaroup	Events	Total	Events	Total	Weiaht	M-H. Random, 95% C	M-H. Random, 95% Cl
1.6.1 Pre 2003							
Benoni 1996	4	43	3	43	9.4%	1.33 [0.32, 5.61]	
Engel 2001	2	12	0	12	2.3%	5.00 [0.27, 94.34]	
Hiipala 1995	0	15	2	13	2.2%	0.17 [0.01, 3.34]	
Hiipala 1997	2	39	2	38	5.3%	0.97 [0.14, 6.57]	
Jansen 1999	0	21	2	21	2.2%	0.20 [0.01, 3.93]	
Sorin 1999	0	21	2	21	2.2%	0.20 [0.01, 3.93]	
Subtotal (95% CI)	•	151		148	23.6%	0.82 [0.33, 2.03]	
Hotorogopoity: Tou2 – 0.00	0 • Chi2 – 4	74 df.	- F (P - 0	45).12 -	0%		
Test for overall effect: $Z = 0.00$	0.43 (P = 0	0.66)	= 5 (F = 0.	43), 1- =	0 /0		
1.6.2 Post 2003							
Abdal-aleem 2013	0	373	0	367		Not estimable	
Alshryda 2013	2	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	1	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	0.00/	Not estimable	
Crescenti 2011	1	100	3	100	3.8%	0.33 [0.04, 3.15]	
Dakir 2014 Forrokhi 2011	0	20	0	20		Not estimable	
Garpeti 2004	0	30 25	0	30 25		Not estimable	
Georgiadis 2013	4	50	q	51	15 7%	0.45 [0.15, 1.38]	— <b>•</b> –
Gill 2009	0	5	0	5	13.770	Not estimable	
Good 2003	2	27	2	24	5.5%	0.89 [0.14, 5.83]	
Gungorduk 2011	0	330	0	330		Not estimable	
Husted 2003	0	20	0	20		Not estimable	
Imai2012	10	95	3	22	13.4%	0.77 [0.23, 2.57]	
Johansson 2005	0	47	0	53		Not estimable	
Kakar 2009	0	25	0	25		Not estimable	
Kazemi 2010	0	32	1	32	1.9%	0.33 [0.01, 7.89]	
Kim 2014 i	0	90	1	90	1.9%	0.33 [0.01, 8.08]	
Kim 2014 ii	0	73	0	73		Not estimable	
Lee 2013	0	34	0	34		Not estimable	
Lemay 2004 Malbatra 2011	0	20	0	19		Not estimable	
Martin 2014	0	20 50	0	20 50		Not estimable	
Niskanen 2005	0	19	0	20		Not estimable	
Orpen 2006	0	15	0	14		Not estimable	
Pfizer 2011	3	41	0	40	2.3%	6.83 [0.36, 128,20]	
Rajesparan 2009	1	36	2	37	3.5%	0.51 [0.05, 5.42]	
Raviraj2012	0	88	1	87	1.9%	0.33 [0.01, 7.98]	
Roy 2012	0	25	0	25		Not estimable	
Sa-Ngasoongsong 2011	0	24	0	24		Not estimable	
Sa-ngasoongsong 2013	3	90	4	45	9.2%	0.38 [0.09, 1.60]	
Seo 2013	0	50	2	50	2.1%	0.20 [0.01, 4.06]	
Snahid 2013	0	38	0	36		Not estimable	
Van EISt 2013 Vijov 2012	0	41	0	26		Not estimable	
Wong 2010	2	40	1	40	2 0%		
Xu 2013	2	88	2	86	5.3%	0.98 [0.14, 6.78]	
Yang 2015	0	40	0	40	0.270	Not estimable	
Yue 2015	1	52	0	49	1.9%	2.83 [0.12. 67.87]	— <u> </u>
Zhang 2007	0	51	0	51		Not estimable	
Zuffrey 2010	5	57	3	0		Not estimable	
Subtotal (95% CI)		2669		2432	76.4%	0.65 [0.39, 1.07]	•
Total events	37		35				
Heterogeneity: $Tau^2 = 0.00$ Test for overall effect: Z = $T$	); Chi² = 8. 1.68 (P = 0	.88, df : 0.09)	= 15 (P = 0	0.88); l²	= 0%		
Total (95% CI)		2820		2580	100.0%	0.69 [0.44, 1.07]	•
Total events	45		46				
Heterogeneity: Tau <sup>2</sup> = 0.00	; Chi <sup>2</sup> = 13	3.73, di	f = 21 (P =	0.88); I	<sup>2</sup> = 0%		
Test for overall effect: Z = Test for subgroup difference	Favours TXA Favours Standard Tt						

- 1
- .
- 2
- 3

#### 1 K.2.3 Adult- Low risk group

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

	ТХА		Placel	bo		Risk Ratio	Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl					
3.1.1 Topical TXA												
Albirmawy 2013 Subtotal (95% Cl)	0	200 <b>200</b>	2	200 <b>200</b>	32.7% <b>32.7%</b>	0.20 [0.01, 4.14] <b>0.20 [0.01, 4.14]</b>						
Total events	0		2									
Heterogeneity: Not app	licable											
Test for overall effect: Z	<u>z</u> = 1.04 (l	P = 0.30	D)									
3.1.2 Oral TXA												
Rannikko 2004 Subtotal (95% Cl)	6	70 <b>70</b>	5	66 <b>66</b>	67.3% <b>67.3%</b>	1.13 [0.36, 3.53] 1.13 [0.36, 3.53]						
Total events	6 liaabla		5									
Test for overall effect: Z	Z = 0.21 (I	P = 0.83	3)									
	`		,									
3.1.3 TXA iv												
Sankar 2012	0	25	0	25		Not estimable						
Tsutsumimoto 2011 Subtotal (95% CI)	0	20 <b>45</b>	0	20 <b>45</b>		Not estimable Not estimable						
Total events	0		0									
Heterogeneity: Not app	licable											
Test for overall effect: N	lot applic	able										
Total (95% CI)		315		311	100.0%	0.83 [0.30, 2.29]	-					
Total events	6		7									
Heterogeneity: Chi <sup>2</sup> = 1	.13, df =	1 (P = 0	).29); l² =	12%								
Test for overall effect: Z	Test for overall effect: Z = 0.37 (P = 0.71) Favours TXA Favours Placebo											
Test for subgroup differences: Chi <sup>2</sup> = 1.10, df = 1 (P = 0.29), $l^2 = 9.2\%$												

# 2 3

#### Figure 96: TXA versus standard treatment- Blood loss



#### Figure 97: Thrombotic complications

		•								
	TXA		Place	bo		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl			
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								
							Favours TXA Favours Placebo			
Test for subgroup differences: Not applicable										

1

#### 2 K.2.4 Children - high risk

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



3

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

	Intra O	p CS+	ТХА	Intra	a Op (	cs		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	IV, Fixed, 95% CI
1.2.1 Post 2003									
Sethna 2005 Subtotal (95% CI)	615	460	23 23	940	718	21 <b>21</b>	100.0% 1 <b>00.0%</b>	-325.00 [-685.06, 35.06] -325.00 [-685.06, 35.06]	
Heterogeneity: Not app Test for overall effect: 2	licable Z = 1.77 (I	P = 0.0	8)						
Total (95% CI)			23			21	100.0%	-325.00 [-685.06, 35.06]	
Heterogeneity: Not app Test for overall effect: 2 Test for subgroup differ	licable Z = 1.77 (I rences: No	P = 0.0 ot appli	8) cable						-1000 -500 0 500 1000 Favours Intra Op CS+TXA Favours Intra Op CS

4

Figure 100: ICS plus TXA versus ICS- Total blood loss



0									
	T	XA		PI	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.1.1 Pre 2003									
Zonis 1996	21.2	12	40	27.2	20.3	42	33.8%	-6.00 [-13.18, 1.18]	-
Subtotal (95% CI)			40			42	33.8%	-6.00 [-13.18, 1.18]	◆
Heterogeneity: Not app	plicable								
Test for overall effect 2	Z=1.64	(P =	0.10)						
2.1.2 Post 2003									
Chauhan 2003	20	9	96	36	12	24	66.2%	-16.00 [-21.13, -10.87]	
Subtotal (95% CI)			96			24	66.2%	-16.00 [-21.13, -10.87]	◆
Heterogeneity: Not app	plicable								
Test for overall effect 2	Z = 6.12	(P <	0.0000	01)					
Total (95% CI)			136			66	100.0%	-12.62 [-16.79, -8.45]	•
Heterogeneity: Chi <sup>2</sup> = 4	4.94, df	= 1 ()	P = 0.0	3); I <sup>z</sup> = 8	0%				-100 -50 0 50 100
Test for overall effect 2	Z = 5.93	(P <	0.0000	01)					Favours TXA Favours Placebo
Test for subgroup diffe	erences	: Chř	<sup>2</sup> = 4.94	l, df = 1	(P = 0)	03), P	= 79.7%		

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

#### Figure 102: Length of hospital stay

	TXA			Standard Tt Mean Difference						Mear	n Diffe	erence	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, F	ixed,	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 ap Test for overall effect:	plicable Z = 0.42	: (P =	0.68)						-100	-50 Favours T	Ó XA F	50 avours sta	100 andard tt

# 1 K.3 Red blood cells

#### 2 K.3.1 RBC thresholds - adults

Figure 103: Number of patients needing allogeneic transfusions											
-	Restric	tive	Liber	al		Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl				
1.2.4 Peri-operative	surgical patient	ts									
Bracey 1999	74	212	104	216	4.7%	0.72 [0.58, 0.91]					
Bush 1997	40	50	43	49	5.1%	0.91 [0.77, 1.08]	-+				
Carson 1998	19	42	41	42	3.9%	0.46 [0.33, 0.65]					
Carson 2011	415	1009	974	1009	5.5%	0.43 [0.40, 0.46]	+				
Fan 2014	41	94	52	92	4.2%	0.77 [0.58, 1.03]					
Foss 2009	22	60	44	60	3.7%	0.50 [0.35, 0.72]	_ <b>-</b>				
Grover 2005	37	109	46	109	3.9%	0.80 [0.57, 1.13]					
Hajjar 2010	118	249	198	253	5.2%	0.61 [0.52, 0.70]	-				
Johnson 1992	15	20	18	18	4.4%	0.76 [0.58, 0.99]					
Lotke 1999	16	62	65	65	3.4%	0.26 [0.17, 0.40]					
Markatou 2012	9	25	19	27	2.4%	0.51 [0.29, 0.91]					
Shehata 2012	13	25	22	25	3.4%	0.59 [0.39, 0.88]					
So-Osman 2010	109	299	119	304	4.9%	0.93 [0.76, 1.14]					
Subtotal (95% CI)		2256		2269	54.8%	0.61 [0.50, 0.76]	◆				
Total events	928		1745								
Heterogeneity: Tau² =	0.12; Chi <sup>2</sup> = 13	9.86, d	f=12 (P	< 0.000	001); I <b>2</b> = 9	31%					
Test for overall effect:	Z = 4.58 (P < 0.	00001)	)								
1.2.5 Critical care											
Hebert 1995	18	33	35	36	4.1%	0.56 [0.41, 0.77]					
Hebert 1999	280	418	420	420	5.6%	0.67 [0.63, 0.72]	T I				
Hoist 2014	326	502	490	496	5.6%	0.66 [0.62, 0.70]	-				
Pinneirodeaimeida 2	U15 47	101	32	97	3.8%	1.41 [0.99, 2.01]					
VValsh 2013 Subtotal (05% CI)	40	1105	49	49	5.2% 2/ 2%	0.79 [0.68, 0.91]	▲				
Total quanta	744	1105	4000	1030	24.2 /0	0.75 [0.04, 0.04]	•				
Hotorogonoity: Touã -	0.00: Chi8 = 00	22 df.	1020 - 470 - 0	00043	· 18 - 0.204						
Test for overall effect:	- 0.02, CHF = 23 7 = 4.56 (P < 0	.33, ui× 000011	-4(r-0 )		,1 - 0370						
rescion overall ellect.	2 - 4.50 (1 - 0.		,								
1.2.9 Acute blood los	s/trauma										
Blair 1986	5	26	24	24	1.8%	0.21 [0.10, 0.44]					
Colomo 2008	68	109	95	105	5.2%	0.69 [0.59, 0.81]	-				
Topley 1956	8	12	10	10	3.4%	0.68 [0.45, 1.04]	<b>_</b>				
Villanueva 2013A	219	444	384	445	5.5%	0.57 [0.52, 0.63]	÷.				
Subtotal (95% CI)		591		584	15.7%	0.58 [0.46, 0.74]	◆				
Total events	300		513								
Heterogeneity: Tau² =	0.04; Chi <sup>2</sup> = 12	.62, df:	= 3 (P = 0	.006);	I <b>²</b> = 76%						
Test for overall effect:	Z = 4.43 (P < 0.	00001;	)								
			1								
1.2.10 Chemounerapy	and stem-cell	transp	names								
Webert 2008	26	29	29	31	5.2%	0.96 [0.82, 1.12]	T				
Sublotal (95% CI)	20	29	20	21	<b>J.</b> 270	0.90 [0.02, 1.12]	T				
i otal events	20		29								
Heterogeneity: Not ap	iplicable Z = 0.54 (D = 0	5 M									
rest for overall effect:	∠ = 0.54 (P = 0.	59)									
Total (95% CI)		3981		3982	100.0%	0.65 [0.58. 0.74]	◆				
Total events	1965		3313				•				
Heterogeneity: Tau <sup>2</sup> =	0.07° Chi≊ = 25	6 61 d	f= 22 (P	< N N N	101) <sup>,</sup> P= 0						
Test for overall effect:	Z = 6.96 /P < 0	00001	· ** ()	0.000			0.1 0.2 0.5 1 2 5 10				
Test for subaroun diff	erences: Chi <sup>2</sup> =	17.78	df = 3 (P	= 0.00	05). <b>F</b> = 8	3.1%	Favours Restrictive Favours Liberal				
				2.00							

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

	Res	strictiv	e	L	iberal			Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl			
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]				
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]				
Subtotal (95% CI)			172			225	54.1%	-0.55 [-0.91, -0.18]	•			
Heterogeneity: Tau <sup>2</sup> = 0.05; Chi <sup>2</sup> = 5.75, df = 4 (P = 0.22); l <sup>2</sup> = 30%												
Test for overall effect: Z = 2.93 (P = 0.003)												
4.5.0.0.10												
1.5.2 Critical care												
Hebert 1999	3.88	4.49	280	5.6	5.3	420	11.3%	-1.72 [-2.45, -0.99]	<b>T</b>			
Subtotal (95% CI)			280			420	11.3%	-1.72 [-2.45, -0.99]	•			
Heterogeneity: Not ap	plicable	! 										
lest for overall effect:	Test for overall effect: Z = 4.62 (P < 0.00001)											
1.5.3 Acute blood los	s/traum	a										
Blair 1986	2.6	1.34	5	4.6	1.47	24	7.7%	-2.00 [-3.31, -0.69]	_ <b></b>			
Topley 1956	7.2	7.13	8	11.34	6.87	10	0.7%	-4.14 [-10.66, 2.38]	<			
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]	♦			
Heterogeneity: Tau <sup>2</sup> =	: 0.00; C	hi² = 0	.43, df=	= 2 (P =	0.81);	l <sup>2</sup> = 0%						
Test for overall effect:	Z = 10.9	)1 (P ≺	0.0000	01)								
1.5.4 Acuto coronan	eundro	mo (A)	(2)									
Concern 204.2	Synuro	4 00	(3) (5)	4 50	4 4 2		42.400	4 00 1 4 40 0 00				
Carson 2013 Subtotal (05% CI)	0.49	1.03	55	1.58	1.13	55 55	13.1%	-1.09 [-1.49, -0.69]				
Subtotal (95% CI)			55			55	13.170	-1.09 [-1.49, -0.09]	•			
Toot for overall effect:	7 – 5 20	; )/D ~ ^	00004	ix.								
restior overall ellect.	2 = 5.28	) (P < (	.00001	0								
Total (95% CI)			964			1179	100.0%	-1.13 [-1.67, -0.59]	▲			
Heterogeneity: Tau <sup>2</sup> =	0.53; C	hi <b>²</b> = 5	4.93, di	f= 9 (P -	< 0.00	001); I <sup>z</sup>	= 84%					
Test for overall effect:	Z= 4.12	2 (P < 0	).0001)						-10 -5 U 5 1 Eavoure Restrictive Eavoure Liberal			
Test for subgroup differences: Chi <sup>2</sup> = 38.36, df = 3 (P < 0.00001), l <sup>2</sup> = 92.2%												

#### Figure 105: Length of stay in hospital (adults)

		Res	strictiv	/e	L	iberal			Mean Difference	Mean Difference
_	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
	2.2.1 Peri-operative s	urgical	patier	nts						
	Bracey 1999	7.5	2.9	212	7.9	4.9	216	15.6%	-0.40 [-1.16, 0.36]	- <b>e</b> +
	Bush 1997	10	6	50	11	9	49	3.2%	-1.00 [-4.02, 2.02]	
	Carson 1998	6.4	3.4	42	6.3	3.4	42	9.2%	0.10 [-1.35, 1.55]	<del></del>
	Carson 2011	4	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	60	18.4	14.4	60	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]	
	Shehata 2012	9	12	25	7	4	25	1.3%	2.00 [-2.96, 6.96]	
	So-Osman 2010 Subtotal (95% CI)	9.6	5	299 1811	10.2	7.4	304 1813	13.0% 83.0%	-0.60 [-1.61, 0.41] 0.01 [-0.30, 0.32]	+
	Heterogeneity: Tau <sup>2</sup> – (	0 02· Cł	ni² – 8	47 df -	- 8 (P -	0 30).	$l^2 - 6\%$		····]	Ī
	Test for overall effect: 7	7 – 0 04	(P – (	- 107) 107)	- 0 (1 =	0.00),	1 - 0 /	,		
		_ = 0.01	(	,						
	2.2.2 Critical care									
	Hebert 1999 Subtotal (95% CI)	34.8	19.5	418 <b>418</b>	35.5	19.4	420 <b>420</b>	4.0% <b>4.0%</b>	-0.70 [-3.33, 1.93] -0.70 [-3.33, 1.93]	
	Heterogeneity: Not apr	licable								
	Test for overall effect: 2	Z = 0.52	(P = (	).60)						
			. (	,						
	2.2.3 ACS (Acute MI)									
	Cooper 2011	4.3	3.3	24	8.5	5.6	21	3.8%	-4.20 [-6.93, -1.47]	
				24			21	3.0%	-4.20 [-0.93, -1.47]	
	Heterogeneity: Not app		(D (							
	lest for overall effect: 2	2 = 3.01	(P = (	).003)						
	2.2.4 Acute blood los	s/traum	a							
	Villanueva 2013A	9.6	8.7	444	11.5	12.8	445	9.3%	-1.90 [-3.34, -0.46]	
	Subtotal (95% CI)			444			445	9.3%	-1.90 [-3.34, -0.46]	$\bullet$
	Heterogeneity: Not app	licable								
	Test for overall effect: 2	Z = 2.59	(P = 0	0.010)						
	Total (95% CI)			2697			2699	100.0%	-0.52 [-1.11, 0.06]	•
	Heterogeneity: Tau <sup>2</sup> = 0	0.42; Cł	ni² = 24	4.72, df	= 11 (P	9 = 0.0	1); l² = {	55%		
	Test for overall effect: 2	Z = 1.75	(P = 0	0.08)	·					Favours Restrictive Favours Liberal
	Test for subgroup difference	rences:	Chi² =	15.25,	df = 3 (	P = 0.0	002), I²	= 80.3%		

#### Figure 106: Mortality at 30 days (all-cause) -adults

	Destrie	41.00		-		Dials Datia	Dial: Datia
Study or Subgroup	Evente	Total	Evente	Total	Weight	M H Random 05% CL	KISK Källö M H Bandom 95% Cl
3.2.1 Perioperative surgica	al patients	S	Lvento	Total	weight	m-n, Random, 55% Cr	m-n, Randoni, 55 / Cr
Bracev 1999	3	215	6	222	2.2%	0.52 (0.13, 2.04)	
Bush 1997	4	50	4	49	2.3%	0.98 [0.26, 3.70]	
Carson 1998	1	42	. 1	42	0.6%	1.00 [0.06, 15,47]	
Carson 2011	43	1009	52	1007	13.5%	0.83 (0.56, 1.22)	
Foss 2009	5	60	0	60	0.5%	11.00 [0.62, 194.63]	
Grover 2005	0	109	1	109	0.4%	0.33 [0.01, 8.09]	
Hajjar 2010	15	249	13	253	6.4%	1.17 [0.57, 2.41]	
Lotke 1999	0	62	0	65		Not estimable	
Markatou 2012	0	25	2	27	0.5%	0.22 [0.01, 4.28]	
Shehata 2012	4	25	1	25	1.0%	4.00 [0.48, 33.33]	
So-Osman 2010	1	299	2	304	0.8%	0.51 [0.05, 5.58]	
Subtotal (95% CI)		2145		2163	28.2%	0.90 [0.66, 1.23]	•
Total events	76		82				
Heterogeneity: Tau <sup>2</sup> = 0.00;	Chi <sup>2</sup> = 7.6	69, df =	9 (P = 0.9	57); I² =	0%		
Test for overall effect: $Z = 0$ .	.67 (P = 0.	51)					
3.2.2 Critical care							
Hohort 1995	0	22	a	26	5.2%	0 07 10 42 2 221	
Hebert 1999	78	/18	9 99	420	18.2%	0.37 [0.42, 2.22]	-
Holst 2014	168	502	175	496	21.7%	0.00 [0.01, 1.04]	
Pinheirodealmeida 2015	23	101		97	6.0%	2 76 [1 30 5 87]	
Walsh 2013	12	51	16	49	7 7%	0.72 [0.38, 1.36]	
Subtotal (95% CI)		1105		1098	58.8%	0.98 [0.73, 1.31]	
Total events	289		306			. / .	
Heterogeneity: Tau <sup>2</sup> = 0.05;	Chi <sup>2</sup> = 9.9	33. df=	4 (P = 0.1)	04); l <sup>2</sup> =	60%		
Test for overall effect: Z = 0.	.16 (P = 0.	87)		~			
3.2.3 ACS (Acute MI)	_						
Carson 2013	7	54	1	55	1.0%	7.13 [0.91, 56.02]	
Cooper 2011	2	24	1	21	0.8%	1.75 [0.17, 17.95]	
Subtotal (95% CI)		78		10	1.8%	3.85 [0.82, 18.00]	
Listere reneitr Tev? - 0.00	9	74 de -	4 (D = 0.1	_ קו עקר	0.07		
Test for sucrell effect: 7 = 1	CHF = 0.8	31, ui =	1 (P = 0.)	37); ==	0%		
Test for overall effect. $Z = 1$ .	.71 (P = 0.	09)					
3.2.4 Acute blood loss/trau	ıma						
Blair 1986	0	26	2	24	0.5%	0.19 [0.01, 3.67]	
Villanueva 2013A	23	444	41	445	10.7%	0.56 [0.34, 0.92]	
Subtotal (95% CI)		470		469	11.2%	0.55 [0.34, 0.89]	•
Total events	23		43				
Heterogeneity: Tau <sup>2</sup> = 0.00;	$Chi^2 = 0.5$	52, df =	1 (P = 0	47); l² =	0%		
Test for overall effect: Z = 2.	.44 (P = 0.	01)					
Total (05% CI)		2700		2006	100.0%	0.02 [0.74.4.44]	
Total (95% CI)	~~~	21,88		2800	100.0%	0.92 [0.74, 1.14]	•
I OTAL EVENTS	397		433	0.000	7 000		
Heterogeneity: Tau* = 0.05; Toot for everall effects 7 = 0	Chin= 26	uob, df÷ ⊿bo	= 18 (P =	0.09);1	-= 32%		0.005 0.1 1 10 20
Test for overall effect: Z = 0.	.79 (≓=U. 	43)	w = 2/D =	0.065	<b>R</b> = 64.40	v.	Favours Restrictive Favours Liberal
reation subgroup dimerenc	es. Unit =	-7.71, C	an – 3 (F =	0.00),	r — 01.15	0	

#### Figure 107: New cardiac events (adults)

					/		
	Restric	ctive	Liber	al		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
4.1.1 Myocardial infarction	1						
Bracey 1999	1	212	0	216	1.5%	3.06 [0.13, 74.61]	
Bush 1997	1	50	2	49	2.7%	0.49 [0.05, 5.23]	
Carson 2011	38	1009	23	1007	32.3%	1.65 [0.99, 2.75]	
Carson 2013	7	54	5	55	11.1%	1.43 [0.48, 4.22]	
Fan 2014	0	94	1	92	1.5%	0.33 [0.01, 7.91]	
Foss 2009	1	60	0	60	1.5%	3.00 [0.12, 72.20]	
Grover 2005	0	109	1	109	1.5%	0.33 [0.01, 8.09]	
Hebert 1999	3	418	12	420	8.6%	0.25 [0.07, 0.88]	
Holst 2014	13	488	6	489	13.6%	2.17 [0.83, 5.67]	+
Johnson 1992	0	20	1	18	1.5%	0.30 [0.01, 6.97]	
Lotke 1999	1	62	0	65	1.5%	3.14 [0.13, 75.72]	
Pinheirodealmeida 2015	1	101	0	97	1.5%	2.88 [0.12, 69.91]	
Shehata 2012	1	25	0	25	1.5%	3.00 [0.13, 70.30]	
Villanueva 2013A	8	444	13	445	15.8%	0.62 [0.26, 1.47]	
Walsh 2013	2	51	2	49	4.0%	0.96 [0.14, 6.56]	
Subtotal (95% CI)		3197		3196	100.0%	1.13 [0.76, 1.67]	<b>*</b>
Total events	77		66				
Heterogeneity: Tau <sup>2</sup> = 0.06;	Chi <sup>2</sup> = 15	5.50, df=	= 14 (P =	0.34);1	²=10%		
Test for overall effect: Z = 0.	.61 (P = 0	.54)					
4.4.2 Congostivo hoart fail							
4.1.2 Congestive heart fail	ule	4000		4007	05.50	4 00 10 70 0 4 00	
Carson 2011	35	1009	27	1007	25.5%	1.29 [0.79, 2.12]	
Carson 2013	(	54	2	55	10.5%	3.56 [0.78, 16.40]	
FOSS 2009	2	60	U 45	100	3.6%	5.00 [0.25, 102.00]	
Hepert 1999	22	418	45	420	25.6%	0.49 [0.30, 0.80]	
Junnson 1992 Disheiredeelmeide 2047	U _	20	1	18	3.3%	0.30 [0.01, 6.97]	
Pinnelrodealmeida 2015	5	101	2	97	9.7%	2.40 [0.48, 12.08]	
villandeva 2013A Subtotal (95% CI)	12	444 2106	21	445 2102	21.9%	0.57 [0.29, 1.15]	
Total quanta	0.2	2100	00	2102	100.0%	1.00 [0.54, 1.65]	Ť
Listere geneity Tev? - 0.24	83 05-40	50 df.	98 - C (D - C	0.000.12	- 64.00		
<ul> <li>meterogeneity: rauf = 0.31;</li> <li>Toot for everall effect: 7 = 9.</li> </ul>	01 /D = 0	0.00, dT=	= 0 (P = l	).02); I*	= 01%		
Test for overall effect: $Z = 0$ .	.01 (P = 0	.99)					
							+
							0.002 0.1 i 10
Test for subaroup difference	es: Chi <sup>z</sup> =	:011 d	lf = 1 (P =	:074)	I² = 0%		Favours Restrictive Favours Liberal
rearran agradioup amorano		0.11,0		9.1 Th			

inguic 100.	meetic	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	ia a i co j				
	Restric	tive	Liber	al		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
5.1.1 Pneumonia							
Carson 1998	0	42	2	42	1.5%	0.20 [0.01, 4.04]	· · · · ·
Carson 2011	48	1007	60	1005	36.7%	0.80 [0.55, 1.16]	
Carson 2013	0	54	0	55		Not estimable	
Fan 2014	3	94	3	92	1.9%	0.98 [0.20, 4.72]	
Foss 2009	1	60	2	60	1.2%	0.50 [0.05, 5.37]	
Hebert 1999	87	418	86	420	52.5%	1.02 [0.78, 1.33]	+
Markatou 2012	3	25	10	27	5.9%	0.32 [0.10, 1.04]	
Shehata 2012	4	25	0	25	0.3%	9.00 [0.51, 158.85]	
Subtotal (95% CI)		1725		1726	100.0%	0.90 [0.73, 1.11]	•
Total events	146		163				
Heterogeneity: Chi <sup>2</sup> =	= 7.82, df =	6 (P = 0	).25); l² =	23%			
Test for overall effect	t: Z = 1.00 (	P = 0.32	2)				
5.1.2 Surgical site/V	Vound infe	ction					
Carson 2011	56	1009	74	1007	95.5%	0.76 [0.54, 1.06]	<b>I</b>
Foss 2009	0	60	3	60	4.5%	0.14 [0.01, 2.71]	
Subtotal (95% CI)		1069		1067	100.0%	0.73 [0.52, 1.01]	$\bullet$
Total events	56		77				
Heterogeneity: Chi <sup>2</sup> =	= 1.22, df =	1 (P = 0	0.27); l <sup>2</sup> =	18%			
Test for overall effect	t: Z = 1.88 (	P = 0.06	5)				
5 1 2 Sonticomia/Ba	otoromia						
	loterennia	<b>F</b> 4	0				
Carson 2013	0	54	0	55	100.00/		
FOSS 2009 Subtotal (95% CI)	1	60 114	1	115	100.0%	1.00 [0.06, 15.62]	
Total aventa	1	114	1	115	100.070	1.00 [0.00, 10.02]	
Hotorogonoity: Not a	nnlicabla		1				
Test for overall effect	ppiloable	P - 1 00	ור				
	l. ∠ = 0.00 (	F = 1.00	)				
5.1.5 Infection (not	specified)						
Bracev 1999	5	212	3	216	1 5%	1 70 [0 41 7 02]	
Hajjar 2010	30	212	25	253	12.8%	1 22 [0 74 2 01]	
So-Osman 2010	18	243	20	304	15.0%	0.59 [0.34, 1.03]	_ <b>_</b> _
Villanueva 2013A	110	233	135	115	60.7%	0.88 [0.72 1.00]	
Subtotal (95% CI)	119	1204	135	1218	100.0%	0.89 [0.74, 1.07]	
Total events	172		194				Ť
Heterogeneity: Chi <sup>2</sup> -	= 4.39 df -	3 (P = 0	1 22)· 12 -	32%			
Test for overall effect	1.00, 0.1 =	P = 0.22	···	02/0			
		. – 0.24	-,				
							0.01 0.1 1 10 100
Test for subaroup dif	ferences: C	hi² – 1 3	31 df – 3	(P - 0)	73) l <sup>2</sup> – 09	%	Favours [experimental] Favours [control]

#### Figure 108: Infections (adults)

Test for subgroup differences:  $Chi^2 = 1.31$ , df = 3 (P = 0.73), l<sup>2</sup> = 0%

#### Adverse events (adults) Figure 109:

	Restric	tive	Liberal			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Holst 2014	0	488	1	489	0.7%	0.33 [0.01, 8.18]	
Nielsen 2012A	0	25	0	23		Not estimable	
Villanueva 2013A	179	444	214	445	99.3%	0.84 [0.72, 0.97]	<b>—</b>
Total (95% CI)		957		957	100.0%	0.83 [0.72, 0.97]	•
Total events	179		215				
Heterogeneity: Chi <sup>2</sup> = 0 Test for overall effect: 2	).32, df = <sup>-</sup> Z = 2.38 (I	1 (P = 0 P = 0.02	2.57); l² = 2)	0%			I         I

Figure 110:	Adverse	ever	nts (ad	ults)-	тасо		
	Restrict	ive	Liber	al		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I 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 a	pplicable						
Test for overall effec	t: Z = 2.78 (P	9 = 0.00	)5)				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	1	M-H, Fixe	ed, 95% Cl		
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 app	olicable									100	
Test for overall effect:	Not applic	able					Favours Re	estrictive	Favours Liberal	100	

#### 2 K.3.2 RBC thresholds - children

#### Figure 112: Total RBC ml/patient (children)

	Res	rictiv	/e	Li	beral	I		Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	I IV, Fixed	I, 95% CI	
Degastbakker 2013	186	70	53	259	90	54	100.0%	-73.00 [-103.52, -42.48	] •		
Total (95% CI)	nlicabla		53			54	100.0%	-73.00 [-103.52, -42.48			
Test for overall effect:	Z = 4.69	(P < I	0.0000	1)					-100 -50 Favours Restrictive	Ö 5i Favours (	0 10 Liberal

#### 3

#### Figure 113: Number of units transfused-children

	Resrictive Liberal							Mean Difference		Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl		IV, Fixed	, 95% CI	
Cholette 2011	0.43	0.6	30	2.1	1.2	30	45.6%	-1.67 [-2.15, -1.19]		•		
Lacroix 2007	1.9	3.4	320	1.7	2.1	310	54.4%	0.20 [-0.24, 0.64]				
Total (95% CI)			350			340	100.0%	-0.65 [-0.98, -0.33]				
Heterogeneity: Chi² = Test for overall effect:	31.69, d Z = 3.95	lf=1 i(P <	(P < 0.0 0.0001	) ) )	I² = 9	7%			-100 Favours	-50 ( Restrictive	) 5 Favours	i0 10 Liberal

#### 4

#### 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% Cl	M-H, Fixe	ed, 95% Cl	
Cholette 2011	11	30	29	30	8.5%	0.38 [0.24, 0.61]			
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: Chi <sup>2</sup> =	0.69, df =	1 (P =	0.41); <b>I<sup>2</sup></b> =			0.01 0.1	1 10 10		
Test for overall effect.	Z = 13.01	(P < 0.	.00001)				Favours Restrictive	Favours Liberal	

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

	Resric	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		
7.4.1 Congenital card	liac disea	IS								
Cholette 2011 Subtotal (95% CI)	11	30 <b>30</b>	29	30 <b>30</b>	8.5% <mark>8.5%</mark>	0.38 [0.24, 0.61 0.38 [0.24, 0.61				
Total events	11		29							
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 4.00 (	(P < 0.0	0001)							
7.4.2 Critical care							_			
Lacroix 2007 Subtotal (95% CI)	146	320 <b>320</b>	310	317 <b>317</b>	91.5% <b>91.5%</b>	0.47 [0.41, 0.53 0.47 [0.41, 0.53				
Total events	146		310							
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z=12.37	(P < 0	.00001)							
Total (95% CI)		350		347	100.0%	0.46 [0.41, 0.52	ı •			
Total events	157		339							
Heterogeneity: Chi <sup>2</sup> =	0.69, df=	1 (P =	0.41); I <sup>z</sup> =	:0%						
Test for overall effect:	Z = 13.01	(P < 0	.00001)				Eavours [experimental]	Eavours [control]		
Test for subgroup diff	erences:	Chi² = I	0.69, df=	1 (P =	0.41), I <sup>z</sup> =	:0%	r areare texperimental	i areare [control]		

#### 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% Cl	M-H, Fixed, 95% Cl		
Cholette 2011	0	30	1	30	9.6%	0.33 [0.01, 7.87]			
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 = Test for overall effect:	0.43, df= Z=0.21 (	1 (P = P = 0.8	0.51); I² = 3)	:0%			0.01 0.1 1 10 10 Favours restrictive Favours liberal		

#### 2

#### Figure 117: ICU length of stay (children)

	Restrictive			Li	beral	1		Mean Difference		Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixe	ed, 95% Cl	1	
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]					
Test for overall effect:	Z = 0.66	i (P =	0.51)						-100 Favours	-50 Restrictive	o b Favour:	50 s Libe	10 eral

#### Figure 118: Pulmonary oedema (children)



#### Figure 119: Infections (nosocomial infections) -children

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl		
Lacroix 2007	65	320	79	317	100.0%	0.82 [0.61, 1.09]	•		
Total (95% CI)		320		317	100.0%	0.82 [0.61, 1.09]	•		
Total events	65		79						
Heterogeneity: Not ap	plicable	0-04	71					10	
rest for overall effect.	Z= 1.39 (	,== 0.1	0				Favours Restrictive Favours Liber	ral	

### 1 K.3.3 Target haemoglobin concentrations for blood transfusion

Figure 120: Number of patients needing transfusions-adults												
	Restric	tive	Liber	al		Risk Ratio	Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl					
1.2.4 Peri-operative	surgical p	atients										
Hajjar 2010	118	249	198	253	22.5%	0.61 [0.52, 0.70]						
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: Tau <sup>2</sup> =	= 0.00; Chi	r = 0.31	, df = 1 (i	P = 0.5	8); I² = 0%							
Test for overall effect:	Z = 7.08 (	P < 0.0	0001)									
1.2.6 Critical care												
Hebert 1995	18	33	35	36	8.1%	0.56 [0.41, 0.77]						
Hebert 1999	280	418	420	420	36.5%	0.67 [0.63, 0.72]	•					
Subtotal (95% CI)		451		456	44.6%	0.66 [0.59, 0.73]	♦					
Total events	298		455									
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Chi	<b>²</b> = 1.18	3, df = 1 (8	P = 0.2	8); I <sup>z</sup> = 15 <sup>o</sup>	%						
Test for overall effect:	Z=7.42 (	(P < 0.0	0001)									
1.2.9 Acute blood los	s/trauma											
Villanueva 2013A	219	444	384	445	30.1%	0.57 [0.52, 0.63]	•					
Subtotal (95% CI)		444		445	30.1%	0.57 [0.52, 0.63]	•					
Total events	219		384									
Heterogeneity: Not ap	oplicable											
Test for overall effect:	Z=10.82	(P ≤ 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	oplicable											
Test for overall effect:	Not appli	cable										
Total (95% CI)		1169		1181	100.0%	0.61 [0.55, 0.67]	•					
Total events	644		1056									
Heterogeneity: Tau <sup>2</sup> =	= 0.01; Chi	<sup>2</sup> = 8.92	?, df = 4 (i	P = 0.0	6); I <sup>2</sup> = 55°	% -						
Test for overall effect:	Z= 9.71 (	P < 0.0	0001)				0.1 0.2 0.5 1 2 5 10 Eavoure Restrictive Eavoure Liberal					
Test for subgroup dif	ferences:	Chi <sup>2</sup> = 3	).33, df=	2 (P =	0.19), l² =	40.0%						

# 1 K.4 Target haemoglobin concentrations for blood transfusion

		n puti	cinto in	ccung	5 ci unisit				
	Restric	Restrictive Liberal				Risk Ratio		Risk Ra	tio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-F	l, Randon	n, 95% CI
1.2.4 Peri-operative	surgical pa	atients							
Hajjar 2010	118	249	198	253	23.5%	0.61 [0.52, 0.70]		•	
Subtotal (95% CI)		249		253	23.5%	0.61 [0.52, 0.70]		◆	
Total events	118		198						
Heterogeneity: Not ap	oplicable								
Test for overall effect	: Z = 6.73 (F	<b>&gt;</b> < 0.00	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]			
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	9 = 0.28	); l² = 15%				
Test for overall effect	: Z = 7.42 (F	<b>P</b> < 0.00	0001)						
120 Aguta blood la	~~#r~~~~~~								
1.2.9 Acute blood lo	ss/trauma							_	
Villanueva 2013A	219	444	384	445	30.9%	0.57 [0.52, 0.63]			
Tatal avanta	240		204	445	30.976	0.57 [0.52, 0.05]		•	
l otar events	219		384						
Test for everall offers			20004						
Test for overall effect	Z = 10.82	(P < 0.0	50001)						
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							
Total (95% CI)		1144		1154	100.0%	0.61 [0.55, 0.68]		•	
Total events	635		1037					.	
Heterogeneity: Tau <sup>2</sup> =	= 0.01; Chi²	= 8.31,	df = 3 (P	9 = 0.04	); I² = 64%				+ + + + 2 5 10
Test for overall effect	: Z = 9.19 (F	⊂ < 0.00	0001)			F	avours Rest	rictive F	∠ 5 Tu avours Libera
Test for subgroup diff	erences: Cl	hi² = 3.3	30, df = 2	(P = 0.	19), I <sup>2</sup> = 39	9.4%			

#### Figure 121: Number of patients needing transfusions-adults

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

	Res	strictiv	/e	Li	bera			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	IV, Random, 95% CI
Cooper 2011	1.6	2	24	2.5	1.3	21	25.3%	-0.90 [-1.87, 0.07]	
Hebert 1999	3.88	4.49	280	5.6	5.3	420	32.2%	-1.72 [-2.45, -0.99]	-
Villanueva 2013A	1.5	2.3	444	3.7	3.8	445	42.5%	-2.20 [-2.61, -1.79]	•
Total (95% CI)			748			886	100.0%	-1.72 [-2.41, -1.02]	•
Heterogeneity: Tau <sup>2</sup> =	0.25; Cł	$ni^2 = 6.$	25, df =	= 2 (P =	0.04	); I <sup>2</sup> = 6	8%		-10 -5 0 5 10
Test for overall effect:	Z = 4.82	: (P < 0	0.00001	1)					Favours Restrictive Favours Liberal

#### Figure 123: Length of hospital stay-adults

0	0		•		•								
	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]	I	-	-		
Hebert 1999	34.8	19.5	418	35.5	19.4	420	26.2%	-0.70 [-3.33, 1.93]	I				
Villanueva 2013A	9.6	8.7	444	11.5	12.8	445	48.9%	-1.90 [-3.34, -0.46]	I	_			
Total (95% CI)			886			886	100.0%	-2.16 [-3.81, -0.50]					
Heterogeneity: Tau <sup>2</sup> =	0.92; Cł	ni² = 3.	42, df =	= 2 (P =	0.18);	l² = 42	%		H		<u> </u>	<u> </u>	
Test for overall effect:	Z = 2.56	6(P = 0)	0.01)						-10	-5	0	5	10
			,						⊢avour	's Restric	tive Fav	ours Libe	erai

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

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Cooper 2011	2	24	1	21	0.8%	1.75 [0.17, 17.95]	
Hajjar 2010	15	249	13	253	8.7%	1.17 [0.57, 2.41]	<del>_</del>
Hebert 1995	8	33	9	36	6.6%	0.97 [0.42, 2.22]	<b>_</b>
Hebert 1999	78	418	98	420	64.7%	0.80 [0.61, 1.04]	
Markatou 2012	0	25	2	27	0.5%	0.22 [0.01, 4.28]	
Villanueva 2013A	23	444	41	445	18.6%	0.56 [0.34, 0.92]	
Total (95% CI)		1193		1202	100.0%	0.78 [0.63, 0.97]	•
Total events	126		164				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi	<sup>2</sup> = 4.40	), df = 5 (i	P = 0.49	9); I <sup>2</sup> = 0%		
Test for overall effect:	Z= 2.24 (	P = 0.0	3)				Favours Restrictive Favours Liberal

1

#### Figure 125: New cardiac events-adults



Test for subgroup differences:  $Chi^2 = 0.89$ , df = 1 (P = 0.35), I<sup>2</sup> = 0%

#### 3

#### Figure 126: Infection-adults

-	Restric	tive	Liber	al		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixe	d, 95% Cl	
5.1.1 Pneumonia										
Hebert 1999	87	418	86	420	89.9%	1.02 [0.78, 1.33]				
Markatou 2012 Subtotal (95% CI)	3	25 <b>443</b>	10	27 <b>447</b>	10.1% <b>100.0%</b>	0.32 [0.10, 1.04] <b>0.95 [0.73, 1.22]</b>				
Total events	90		96							
Heterogeneity: Chi <sup>2</sup> =	3.50, df =	1 (P =	0.06); l² =	:71%						
Test for overall effect:	Z=0.42 (	(P = 0.6	8)							
5.1.5 Infection (not s	pecified)									
Hajjar 2010 Subtotal (95% CI)	30	249 <mark>249</mark>	25	253 <b>253</b>	100.0% <b>100.0%</b>	1.22 [0.74, 2.01] <b>1.22 [0.74, 2.01]</b>				
Total events	30		25							
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 0.78 (	(P = 0.4	4)							
							0.01	0.1 1	10	10
To all for a selection of the		0.617			0.000 17	~~		Favours restrictive	Favours liberal	
lest for subgroup diff	erences:	Unif = l	J.78, dt =	1 (P = I	J.38), I* =	0%				

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

	Restric	tive	Liberal			Risk Ratio		R	lisk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		М-Н,	Fixed, 95% Cl	
5.1.1 Pneumonia										
Hebert 1999	87	418	86	420	100.0%	1.02 [0.78, 1.33]	1			
Subtotal (95% CI)		418		420	1 <b>00.0%</b>	1.02 [0.78, 1.33]			•	
Total events	87		86							
Heterogeneity: Not app	licable									
Test for overall effect: 2	Z = 0.12 (F	<b>P</b> = 0.90	D)							
5.1.5 Infection (not sp	ecified)									
Hajjar 2010	30	249	25	253	100.0%	1.22 [0.74, 2.01]	1		- <b>-</b>	
Subtotal (95% CI)		249		253	1 <b>00.0%</b>	1.22 [0.74, 2.01]			•	
Total events	30		25							
Heterogeneity: Not app	olicable									
Test for overall effect: 2	Z = 0.78 (F	⊃ = 0.44	4)							
							0.01	0.1	1 10	100
							Favour	s restrict	ive Favours li	beral

Test for subgroup differences:  $Chi^2 = 0.40$ , df = 1 (P = 0.53),  $I^2 = 0\%$ 

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

	Resrict	ive	Liber	al		<b>Risk Ratio</b>		Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	1	M-H, I	Fixe	ed, 95% C	I	
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]			•			
Total events	146		310									
Heterogeneity: Not app	licable											100
Tost for overall offect:	7 - 12 27	(P > 0)	00001)				0.01	0.1		1 10	)	100
Test for overall effect. 2	effect: Z = 12.37 (P < 0.00001)						Favours	s Restricti	ve	Favours I	_ibe	eral

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

	Resrictive Liberal					Mean Difference		Mea	n Diffe	erence			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	1	IV, F	ixed, s	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 ap	plicable								100		<u> </u>		100
Test for overall effect:	Z = 0.65	(P =	0.51)						Favour	-50 s Restrict	ive F	avours Libe	əral

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

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
Lacroix 2007	14	320	14	317	100.0%	0.99 [0.48, 2.04]	
Total (95% CI)		320		317	100.0%	0.99 [0.48, 2.04]	<b>•</b>
Total events	14		14				
Heterogeneity: Not app	olicable						
Test for overall effect:	Z = 0.03 (I	P = 0.98	B)				Favours restrictive Favours liberal

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

	Restrictive Liberal					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]					
Heterogeneity: Not app	olicable								100		<u> </u>		100
Test for overall effect:	Z = 0.66	(P =	0.51)						Favour	s Restrict	ive Fav	ours Libe	ral

#### Figure 132: Pulmonary oedema- children (critical care)

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
Lacroix 2007	0	320	5	317	100.0%	0.09 [0.01, 1.62]	
Total (95% CI)		320		317	100.0%	0.09 [0.01, 1.62]	
Total events	0		5				
Heterogeneity: Not app	licable						
Test for overall effect: 2	Z = 1.63 (I	licable Z = 1.63 (P = 0.10)					0.01 0.1 1 10 100 Favours Restrictive Favours Liberal

2

#### Figure 133: Nosocomial infections- children (critical care)

	Restrictive		Liberal		Risk Ratio		Risl	k Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	CI M-H, Fix	ced, 95% Cl	
Lacroix 2007	65	320	79	317	100.0%	0.82 [0.61, 1.09]	]		
Total (95% CI)		320		317	100.0%	0.82 [0.61, 1.09]	1	•	
Total events	65		79						
Heterogeneity: Not app	olicable							+ $+$ $+$	
Test for overall effect: $Z = 1.39 (P = 0.17)$			7)				0.01 0.1 Favours Restrictive	1 10 Favours Libr	100 eral

#### 3

# 4 K.5 Platelets

#### 5 K.5.1 Low dose versus medium dose

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

	Low dose			dose	Risk Ratio			Risk Ratio			
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-H, Fi	xed, 95%	∕₀ CI	
2009	30	58	30	61	9.0%	1.05 [0.74, 1.50]			<u>+</u>		
r 2010	296	417	292	423	89.7%	1.03 [0.94, 1.12]					
uth 2004	6	56	4	55	1.2%	1.47 [0.44, 4.94]				_	
95% CI)		531		539	100.0%	1.04 [0.95, 1.13]			•		
vents	332		326								
geneity: Chi² = 0.36, df = 2 (P = 0.84); l² = 0%							H		<u>+</u>		
r overall effect:	Z = 0.79 (	P = 0.4	3)				0.01 Fav	0.1 ours low dose	1 Favou	10 urs medii	100 um dose

#### Figure 135: All-cause mortality at 30 days

Low dose			Medium	dose	Risk Ratio			Risk Ratio			
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-H, F	ixed, 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]					
uth 2004	0	56	0	55		Not estimable					
95% CI)		531		539	100.0%	2.04 [0.70, 5.93]				►	
vents	10		5								
geneity: Chi² = 0.26, df = 1 (P = 0.61); l² = 0%							H		<u> </u>	-+	
r overall effect:	Z = 1.31 (	P = 0.1	9)				0.01 Fav	0.1 ours low dos	1 e Favo	10 ours mediu	100 um dose

1

#### Figure 136: Infections

Low dose			Medium	dose	Risk Ratio			Risk Ratio				
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		М-Н,	Fixed, 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]		-	$\blacklozenge$			
vents	5		5									
geneity: Not applicable						0.01	0.1	1	10	100		
r overall effect: $Z = 0.02$ (P = 0.98)						Fav	ours low do	ose Favo	urs mediu	ım dose		

2

#### Figure 137: Serious adverse event (any)

	Low do	ose	Medium	dose		Risk Ratio		Risk	Rat	io	
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed,	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]			$\blacklozenge$		
vents	35		27								
geneity: Not app	licable								+	10	100
r overall effect: $Z = 1.11$ (P = 0.27)							0.01 Fav	0.1 ours low dose	1 Fa	10 vours medi	100 um dose

#### 3

4

### K.5.2 High dose versus medium dose

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

	High d	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	
be 2004	3	48	2	48	0.7%	1.50 [0.26, 8.58]			<u> </u>	_	
r 2010	302	432	292	423	99.3%	1.01 [0.93, 1.11]					
95% CI)		480		471	100.0%	1.02 [0.93, 1.11]			•		
vents	305		294								
geneity: Chi <sup>2</sup> = 0	0.20, df =	1 (P = 0	0.66); l <sup>2</sup> = 0	0%						+	
r overall effect: 2	Z = 0.35 (	P = 0.73	3)				0.01 Favo	0.1 ours high dose	T Favours	10 3 mediu	100 Im dose

#### Figure 139: All-cause mortality at 30 days

High dose			Medium	dose	Risk Ratio			Risk Ratio			
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-H, F	ixed, 95	% CI	
ce 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]		-			
vents	7		4								
geneity: Not app	olicable						H		-		
r everell effects 7 0.86 (D 0.30)						0.01	0.1	1	10	100	
r overall effect: $Z = 0.86$ (P = 0.39		9)				Favo	ours high dose	e Favo	ours mediu	ım dose	

1

#### Figure 140: Infections

	High d	ose	Medium	dose	se Risk Ratio				io		
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H	, Fixed, 9	95% 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	licable							01	1	10	100
r overall effect: $Z = 0.54$ (P = 0.59)						Favo	o. i ours high d	ose Fa	vours med	ium dose	

2

#### Figure 141: Serious adverse events (any)

High dose			Medium	dose	Risk Ratio			Risk Ratio			
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-H, Fix	ed, 95%	∕₀ 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]					
vents	36		27								
geneity: Not app	olicable						H		!		
r overall effect: $Z = 1.09 (P = 0.28)$						0.01 Favo	0.1 ours high dose	1 Favor	10 urs mediu	100 Im dose	

3

### 4 K.5.3 Low dose versus high dose

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

	Low dose		High dose		Risk Ratio			Risk	Ratio		
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fix	ed, 95%	6 CI	
r 2010	71	417	70	432	100.0%	1.05 [0.78, 1.42]					
(95% CI)		417		432	100.0%	1.05 [0.78, 1.42]		•	•		
vents	71		70								
geneity: Not app	licable		_`				0.01	0.1	 1	10	100
or overall effect: $Z = 0.32$ (P = 0.75)					Favou	irs low dose	Favou	ırs higł	n dose		

#### Figure 143: All-cause mortality at 30 days

	Low do	ose	High d	ose	Risk Ratio			Risk Ratio			
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fiz	xed, s	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]		-	$\blacklozenge$		
vents	9		7								
geneity: Not app	licable								1	10	100
or overall effect: 2	2 = 0.57 (	P = 0.5	7)				Eavou	urs low dose	Fa	vours hial	n dose

1

#### Figure 144: Infections

	Low dose		High dose		Risk Ratio			Risk Ratio			
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		М-Н, І	Fixed, 9	5% CI	
r 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]					
vents	5		7								
geneity: Not app	licable							0.1	1	10	100
or overall effect: $Z = 0.52$ (P = 0.60)							Favo	urs low do:	se Fav	ours high	dose

2

#### Figure 145: Serious adverse events (any)

	Low do	ose	High d	ose		Risk Ratio		Ri	sk Rati	0	
or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, F	ixed, 9	5% CI	
er 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]			•		
⇒vents	35		36								
geneity: Not app or overall effect: 2	licable Z = 0.03 (I	P = 0.9	7)				0.01	0.1	1 1 50 Fax	10	100

#### 3

#### 4 K.5.4 Platelet thresholds and Targets

### 5 Prophylactic transfusion versus no prophylactic transfusion - adults who are 6 haematology patients (non-bleeding patients)

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

	Prophylactic trans	sfusion	No prophylactic trai	nsfusion		Risk Ratio		Ris	k Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fix	ed, 95% C	3	
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]		•			
Total events	193		278								
Heterogeneity: Chi <sup>2</sup> =	11.85, df = 1 (P = 0.	0006); I <sup>z</sup> =	92%					0.6			- <u>L</u>
Test for overall effect:	Z = 5.12 (P ≺ 0.000	D1)					Prophylactic	transfusior	No prop	ohylactic	transfus

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

	Prophylactic transfusion No prophylactic transfusion					Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% Cl		
Stanworth 2013	1	299	6	301	22.3%	0.17 [0.02, 1.39]	<				
Wandt 2012	7	194	21	197	77.7%	0.34 [0.15, 0.78]		-			
Total (95% CI)		493		498	100.0%	0.30 [0.14, 0.65]					
Total events	8		27								
Heterogeneity: Chi <sup>2</sup> =	0.37, df = 1 (P = 0.5)	4); I <sup>2</sup> = 0%						0.5	<u> </u>	<u>_</u>	10
Test for overall effect:	Z = 3.06 (P = 0.002)						Prophyla	ctic transfusion	No prophyla	actic trans	sfusion

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

	Prophylactic trans	sfusion	No prophylactic tran	sfusion		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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:	plicable Z = 0.36 (P = 0.72)						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)

0								
	Prophylactic trans	fusion	No prophylactic trans	sfusion		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 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:	oplicable : Z = 0.68 (P = 0.50)						0.01 0.1 1 10 10 Prophylactic transfusion No prophylactic transfus	00 ion

#### 3

#### Figure 150: Number of patients needing platelet transfusion

•		•		•••							
	Prophylactic tran	sfusion	No prophylactic tra	nsfusion		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixe	d, 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	plicable							0.5	<u> </u>		10
Test for overall effect: .	Z = 7.97 (P < 0.000	01)					Prophylac	tic transfusion	No prophy	o lactic trans	sfusion

4

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

	Prophylact	tic transfu	usion	No prophyla	ctic transf	usion		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 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: .	plicable Z = 4.61 (P ≺	0.00001)							-10 -5 0 5 10 Prophylactic transfusion No prophylactic transfusion

#### Figure 152: Mortality (all cause)

-							
	Prophylactic trans	fusion	No prophylactic trans	sfusion		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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	plicable						
lest for overall effect:	Z = 0.56 (P = 0.58)						Prophylactic transfusion No prophylactic transfusion

1

#### Figure 153: Side effects of transfusion (not specified)

				1 P							
	Prophylactic tran	sfusion	No prophylactic tra	nsfusion		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixe	d, 95% CI		
Wandt 2012	25	194	27	197	100.0%	0.94 [0.57, 1.56]					
Total (95% CI)		194		197	100.0%	0.94 [0.57, 1.56]					
Total events	25		27								
Heterogeneity: Not ap Test for overall effect:	oplicable Z = 0.24 (P = 0.81)						0.1 0.2 Prophylact	0.5 1 ic transfusion	2 No prophyl	5 actic tran	10 sfusion

2

# 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)

					. <b>.</b>				··· <b>·</b>		
	Prophyla	actic	No prophylactic trai	nsfusion		Risk Ratio		Ris	k Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fix	ed, 95% Cl		
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	plicable						<u> </u>		+ +	<u> </u>	
Toot for overall offect:	7 = 1 70 /	0 - 0 07	2				0.1	0.2 0.5	1 2	5	) 10
restion overall ellect.	Z = 1.79 (I	F - 0.07	)					Favours Prophylactic	Favours N	o prophyla	actic transfu

5

#### Figure 155: Mortality (all cause) 3 years

			, (an caase, c	,									
	Prophyla	actic	No prophylactic tran	sfusion		Risk Ratio			Ris	k Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl			M-H, Fi	xed, 95% Cl			
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 app Test for overall effect: 2	plicable Z = 0.07 (I	P = 0.94	)				⊢ 0.1	0.2 Favour	0.5 s Prophylacti	1 2 c Favours	No prophyla	5 actic tr	10 ansfi

6

#### Figure 156: Mortality from bleeding (3 years)

-	Prophyl	actic	No prophylactic tr	ansfusion		Risk Ratio			Risk	Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl			M-H, Fixe	ed, 95% CI			
Murphy 1982	1	35	2	21	100.0%	0.30 [0.03, 3.11]	4						
Total (95% CI)		35		21	100.0%	0.30 [0.03, 3.11]							
Total events	1		2										
Heterogeneity: Not ap Test for overall effect:	oplicable Z=1.01 (	P = 0.31	)				0.1	0.2 Favou	0.5 rs Prophylactic	1 2 Favours N	o prophyla	5 actic tra	10 ansfu

### 1 K.5.6 Low threshold versus high threshold - adults who are haematology patients (non-2 bleeding patients)

#### Figure 157: Mortality (all cause)

	Low platelet three	eshold	High platelet thre	shold		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
1.1.1 Patients under	going chemothera	ру					
Heckman 1997	25	37	29	41	37.0%	0.96 [0.71, 1.29]	
Rebulla 1997	18	135	9	120	12.8%	1.78 [0.83, 3.81]	
Subtotal (95% CI)		172		161	49.8%	1.17 [0.85, 1.60]	◆
Total events	43		38				
Heterogeneity: Chi <sup>2</sup> =	: 2.91, df = 1 (P = 0.)	09); I <b>²</b> = 6	6%				
Test for overall effect	Z = 0.96 (P = 0.34)	1					
1.1.2 Patients under	going stemcell trai	nsplant					
Diedrich 2005	32	79	34	87	43.5%	1.04 [0.71, 1.51]	<b>_</b>
Zumberg 2002	8	78	5	81	6.6%	1.66 [0.57, 4.86]	
Subtotal (95% CI)		157		168	50.2%	1.12 [0.78, 1.60]	-
Total events	40		39				
Heterogeneity: Chi <sup>z</sup> =	: 0.68, df = 1 (P = 0.4	41); I² = 0	%				
Test for overall effect	: Z = 0.62 (P = 0.54)	l i					
Total (95% CI)		329		329	100.0%	1.14 [0.90, 1.45]	-
Total events	83		77				
Heterogeneity: Chi <sup>2</sup> =	: 3.41, df = 3 (P = 0.3	33); I <sup>z</sup> = 1	2%				
Test for overall effect	: Z = 1.10 (P = 0.27)	1					Favours Low platelet threshold Favours High platelet threshold
Test for subgroup dif	ferences: Chi <sup>z</sup> = 0.0	03. df = 1	(P = 0.86), I <sup>2</sup> = 0%				· · · · · · · · · · · · · · · · · · ·

#### Figure 158:

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

Low platelet threshold		eshold	High platelet th	reshold		Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed	I, 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	2		10
Test for overall effect: Z = 0.87 (P = 0.38)		0					Favours Low platelet	hreshold	Favours High pla	telet thre	eshold

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

	Low platelet three	eshold	High platelet thr	eshold		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
1.3.1 Patients under	going chemothera	ру					
Heckman 1997	17	37	7	41	13.1%	2.69 [1.26, 5.75]	· · · · · · · · · · · · · · · · · · ·
Rebulla 1997	29	135	24	120	50.1%	1.07 [0.66, 1.74]	
Subtotal (95% CI)		172		161	63.2%	1.41 [0.95, 2.10]	$\bullet$
Total events	46		31				
Heterogeneity: Chi <sup>2</sup> =	4.01, df = 1 (P = 0.	05); I <sup>2</sup> = 7	5%				
Test for overall effect:	Z = 1.69 (P = 0.09)	1					
1.3.2 Patients under	going stemcell tra	nsplant					
Diedrich 2005	3	79	5	81	9.7%	0.62 [0.15, 2.49]	
Zumberg 2002	11	78	14	81	27.1%	0.82 [0.39, 1.69]	
Subtotal (95% CI)		157		162	36.8%	0.76 [0.40, 1.45]	
Total events	14		19				
Heterogeneity: Chi <sup>2</sup> =	0.12, df = 1 (P = 0.	72); I <sup>2</sup> = 0	%				
Test for overall effect:	Z = 0.82 (P = 0.41)	1					
Total (95% CI)		329		323	100.0%	1.17 [0.84, 1.64]	-
Total events	60		50				
Heterogeneity: Chi <sup>2</sup> =	6.50, df = 3 (P = 0.	09); I² = 5	4%				
Test for overall effect	Z = 0.92 (P = 0.36)	1					Favours Low platelet threshold Favours High platelet threshold
Test for subgroup dif	ferences: Chi² = 2.5	52, df = 1	(P = 0.11), I <sup>2</sup> = 60.	3%			

#### Figure 160: Infections

-	Low platelet threshold		High platelet threshold		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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]	-
Total events	31		30				
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.63 (P = 0.53	)					0.1 0.2 0.5 1 2 5 10 Favours Low platelet threshold Favours High platelet threshold

1

#### Figure 161: Adverse events

	Low platelet thre	Low platelet threshold		reshold		Risk Ratio	Risk	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fix	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 a Test for overall effect	ipplicable t: Z = 1.90 (P = 0.06)						0.01 0.1 Favours Low platelet threshold	1 10 Favours High platelet ti	100 hreshold	

2

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



#### 3

# 4 K.6 Fresh frozen plasma

#### 5 K.6.1 Therapeutic FFP transfusion versus no FFP transfusion

## Figure 163: Mortality (all-cause)

	FFP transfusion		No FFP transfusion		Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fix	ed, 95% Cl	
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 applicable Test for overall effect: Z = 4.72 (P < 0.00001)							0.01	0.1 Favours FFF	1 10 P Favours no FFP	100



1

# 2 K.7 Prothrombin complex concentrates

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

Figure 165:	Mortality	,					
	Low de	ose	High d	ose		Risk Ratio	Risk Ratio
Study or Subgrou	p Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 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: No	t applicable						
Test for overall effe	ect: Z = 0.63	(P = 0.5	53)				Favours low dose Favours high dose

4

#### Figure 166: Patients with at least one adverse event

-	Low dose Subgroup Events Total		Low dose High dose			Risk Ratio	Risk Ratio			
Study or Subgroup			Events	Events Total		M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI			
Kerebel 2013	24	29	25	30	100.0%	0.99 [0.79, 1.25]	<b></b>			
Total (95% CI)		29		30	100.0%	0.99 [0.79, 1.25]	•			
Total events	24		25							
Heterogeneity: Not ap	plicable						0.01 0.1 1 10 10			
lest for overall effect:	2 = 0.06	(P = 0.9	15)				Favours low dose Favours high dose			

5



	Low dose		High dose			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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]	+
Total events	11		12				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z = 0.16	(P = 0.8	37)				Favours low dose Favours high dos

#### Figure 168: Patients with at least one thrombotic event



#### Figure 169: Target INR less than 1.2 achieved

-	Low dose		Low dose High dose			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 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	)2)				Image: Constraint of the second se	

2

3

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

Figure 170: Target INR reached

	-	-						Risk Ratio				
	fixed dose		ose	variable	dose		Risk Ratio					
_	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixe	d, 95% Cl		
	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									1	11	ר 1	
	Test for overall effect:	P = 0.6	3)				0.01 0	). I Since di de se s		ا ا بام ما جام	-	
				- /				Favours	fixed dose	Favours va	naple d	Ο

#### 4

Figure 171: Deep Vein Thrombosis (DVT)

0				•						
fixed dose		ose	variable	dose		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixe	ed, 95% Cl		
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: .	plicable Z = 0.48 (	(P = 0.6	i3)				0.01 0.1 Favours fixed dose	1 10 Favours variable /	10 do	

#### Figure 172: Mortality

	fixed dose		variable dose			Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 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 applicable Test for overall effect: Z = 2.18 (P = 0.03)			13)				0.01 0.1 1 10 10 Eavours fixed dose Eavours variable do:		

1

2

### 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 dose			Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	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]	<b>•</b>		
Total events	20		41						
Heterogeneity: Not applicable Test for overall effect: Z = 4.17 (P < 0.0001)			1)				0.01 0.1	1 10 10 Eavours standard dos	

3

Figure 174: Serious adverse events

0									
standard dose		Individualise	ed dose		Risk Ratio	Risk Ratio			
Study or Subgroup	ubgroup Events Total		Events	Total	Weight	M-H, Fixed, 95% Cl	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 a	pplicable								10
Test for overall effect: Z = 0.00 (P = 1.00)							Favours standard dose	Favours individ	lualised

#### 4

# 5 K.8 Cryoprecipitate

6 K.8.1 Cryoprecipitate versus no cryoprecipitate

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

	сгуо		No стуо		Risk Ratio		Risk Ratio
Study or Subgroup	Events Total		Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Holcomb 2013	95	359	163	879	100.0%	1.43 [1.14, 1.78]	
Total (95% CI)		359		879	100.0%	1.43 [1.14, 1.78]	•
Total events	95		163				
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.15 (P = 0.002)							Favours cryo Favours No cryo

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#### Appendix L: Network meta-analysis of 1 alternatives to blood transfusion in surgical 2 patients 3

# L.1 Introduction

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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.

15 To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was 16 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: 18

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

22 The analysis also provided estimates of effect (with 95% credible intervals) for each intervention 23 compared to one another and compared to a single baseline risk (in this case the baseline 24 treatment was standard treatment). These estimates provide a useful clinical summary of the 25 results and facilitate the formation of recommendations based on the best available evidence. 26 Furthermore, these estimates were used to parameterise treatment effectiveness in the de novo 27 cost-effectiveness modelling presented in appendix M.

- 28 Conventional fixed effects meta-analysis assumes that the relative effect of one treatment 29 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 30 common distribution and that this distribution is common across all sets of trials. 31
- 32 Network meta-analysis requires an additional assumption over conventional meta-analysis. The 33 additional assumption is that intervention A has the same effect on people in trials of intervention 34 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 35 intervention A has the same effect distribution across trials of A versus B, A versus C and so on. 36
- 37 This specific method is usually referred to as mixed-treatment comparisons analysis but the term 38 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.

# 3 L.2 Methods

### 4 L.2.1 Study selection and data collection

5 To estimate the relative risks, an NMA was performed that simultaneously used all the relevant 6 RCT evidence from the clinical evidence review. As with conventional meta-analyses, this type of 7 analysis does not break the randomisation of the evidence, nor does it make any assumptions 8 about adding the effects of different interventions. The effectiveness of a particular treatment 9 strategy combination will be derived only from randomised controlled trials that had that 10 particular combination in a trial arm.

- 11 From the outset, effeorts were made to minimise any clinical or methodological heterogeneity by 12 focusing the analysis on RCTs with comparable routes of administration of treatments, identifying 13 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). 14 All of the dosages of drugs in the included RCTs were within the therapeutic range as indicated by 15 16 the BNF. In consultation with the GDG, it was agreed that an NMA would be performed for 17 alternatives to blood transfusion including combinations of different types of cell salvage and/or 18 tranexamic acid. The evidence on these interventions included multiple comparisons and an NMA 19 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:

### 23 High risk group:

- 24 Network 1: Number of people receiving allogeneic transfusions
- 25 Network 2: Units of allogeneic blood transfused
- 26 Network 3: Length of stay in hospital

### 27 Moderate risk group:

- 28 Network 4: Number of people receiving allogeneic transfusions
- 29 Network 5: Units of allogeneic blood transfused

### 30 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.
#### Comparability of interventions 1 L.2.3

2 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 3 4 and in appendix H. If an intervention was evaluated in a study that met the inclusion criteria for 5 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, 6 otherwise it was excluded.

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

### 9 Table 1: Treatments included in network meta-analysis

High risk group			woderate 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			
ТХА	ICS	ТХА	ТХА	ТХА			
PCS	ТХА	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				

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

11 The details of these interventions can be found in the clinical evidence review in chapter 11 of the full guideline and evidence tables in appendix H. 12

#### L.2.4 **Baseline risk** 13

- 14 The baseline risk is defined here as the risk of achieving the outcome of interest in the standard 15 treatment group. This figure is useful because it allows the conversion of the results of the NMA 16 from odds ratios to relative risks.
- 17 Baseline odds were derived by the logistic regression in WinBUGS. This approach has the 18 advantage that baseline and relative effects are both modelled on the same log odds scale, and 19 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: 20
  - -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.2.1, Appendix M).

### 6 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.

- 11In order to be included in the analysis, a fundamental requirement is that each treatment is12connected directly or indirectly to every other intervention in the network. For each outcome13subgroup, a diagram of the evidence network is presented in section L.3.
- 14 The model used was a random effects logistic regression model, with parameters estimated by 15 Markov chain Monte Carlo simulation. As it was a Bayesian analysis, for each parameter the 16 evidence distribution is weighted by a distribution of prior beliefs. These were estimated from the 17 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>

20A non-informative prior distribution was used to maximise the weighting given to the data for21continuous outcomes. These priors were normally distributed with a mean of 0 and standard22deviation 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, θ, OR and p denote the baseline
   odds, treatment specific odds, treatment specific log odds ratio and absolute probability
   respectively. Then:

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

And:

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$$p=rac{e^{\widetilde{ heta}}}{1+e^{\widetilde{ heta}}}$$

2 Once the treatment specific probabilities for response were calculated, these were divided by the 3 baseline probability ( $p_b$ ) to get treatment specific relative risks ( $rr_b$ ):

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

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.

- 10Due to the skewness of the data, the NMA relative risks and rank results are reported as medians11rather than means (as in the direct comparisons) to give a more accurate representation of the12'most likely' value.
- 13A key assumption behind NMA is that the network is consistent. In other words, it is assumed that14the direct and indirect treatment effect estimates do not disagree with one another.15Discrepancies between direct and indirect estimates of effect may result from several possible16causes. First, there is chance and if this is the case then the network meta-analysis results are17likely to be more precise as they pool together more data than conventional meta-analysis18estimates alone. Second, there could be differences between the trials included in terms of their19clinical or methodological characteristics. Differences that could lead to inconsistency include:
- 20 Different populations

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- Different interventions
  - Difrent routes of administration

23 This heterogeneity is a problem for network meta-analysis but may be dealt with by subgroup 24 analysis, meta-regression or by carefully defining inclusion criteria. In this analysis, sub-group 25 analyses based on various factors such as haemoglobin status at baseline, different haemoglobin 26 thresholds for blood transfusion and different routes of administration was undertaken to 27 account for heterogeneity in the pair wise meta-analyses. Inconsistency in the network, caused by 28 heterogeneity, was assessed subjectively by comparing the odds ratios for binary outcomes and 29 mean differences for continuous outcomes from the direct evidence (from pair-wise meta-30 analysis) with the corresponding effects estimated from the combined direct and indirect 31 evidence (from NMA). We assumed the evidence to be inconsistent where the odds ratio or 32 mean difference from the NMA did not fit within the confidence interval of the odds ratio or 33 mean difference from the direct comparison. We further tested for inconsistency by developing 34 inconsistency models for networks of binary outcomes (number of patients transfused). We 35 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.

## 3 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.

### 8 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

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



### 1 L.3.2 Trial data

### 2 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.

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

Study	Treatment	Comparator	Treatmer	nt	Comparato	r
			Events	Ν	Events	Ν
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>	ТХА	ICS+TXA	13	29	12	24
Murphy2006 <sup>89</sup>	ICS+PCS	ICS+PCS+TXA	14	50	13	50
Klein2008 <sup>73</sup>	ТХА	ICS+PCS+TXA	33	111	31	102
Ahn2012 <sup>4</sup>	Standard treatment	ТХА	27	38	20	38
Andreasen2004 <sup>10</sup>	Standard treatment	ТХА	5	17	6	20
Baric2007 <sup>14</sup>	Standard	ТХА	51	96	51	97

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

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

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### Table 3: Study data for units of allogeneic blood transfused

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

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

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### 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	

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

<sup>1</sup> 

Study	Treatment	Comparator	Treatment		Comparato	or
	Standard					
Murphy2004 <sup>87</sup>	treatment	ICS+PCS	6.8	0.406	9.6	2.472393
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	ТХА	6.4	0.671	5.8	0.491935
Mehraein2007 <sup>83</sup>	Standard treatment	ТХА	4.8	0.157	4.8	0.069631
Wei2006 <sup>126</sup>	Standard treatment	ТХА	7.3	0.190	7.1	0.133333
Vermeijden2015 <sup>123</sup>	Standard treatment	ICS	11.8	0.72158	11.5	0.763763

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

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### 3 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	Treatmer	nt Comparator 1		Comparator 2		
				Events	Ν	Events	Ν	Events	Ν
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	Comparator 1		Comparator 2	
Abuzakuk2007 <sup>1</sup>	Standard treatment	PCS		12	52	13	52	NA	NA
Smith2007 <sup>111</sup>	Standard treatment	PCS		17	82	6	76	NA	NA
Moonen2007 <sup>86</sup>	Standard treatment	PCS		15	80	5	80	NA	NA
Tripkovic2008 <sup>120</sup>	Standard treatment	PCS		24	30	4	30	NA	NA
Amin2008 <sup>9</sup>	Standard treatment	PCS		13	86	12	92	NA	NA
Thomassen2014 <sup>118</sup>	Standard treatment	PCS		12	190	29	382	NA	NA
Horstmann2014 <sup>58</sup>	Standard treatment	PCS		11	56	6	59	NA	NA
Soosman2014 <sup>113</sup>	Standard treatment	PCS	ICS+PC S	54	658	33	321	23	321
Horstmann2014a <sup>59</sup>	Standard treatment	ICS+PCS		4	62	2	56	NA	NA
Wong2008 <sup>129</sup>	ICS	ICS+TXA		30	74	23	73	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
Thomassen2012 <sup>119</sup>	ТХА	ICS+PCS+ TXA		13	101	9	96	NA	NA
Aguilera2013 <sup>3</sup>	Standard treatment	ТХА		12	42	2	41	NA	NA
Benoni1996 <sup>15</sup>	Standard treatment	ТХА		24	43	8	43	NA	NA
Benoni2000 <sup>17</sup>	Standard treatment	ТХА		15	19	9	20	NA	NA
Benoni2001 <sup>16</sup>	Standard treatment	ТХА		8	20	4	18	NA	NA
Bidolegui2014 <sup>18</sup>	Standard treatment	ТХА		8	25	0	25	NA	NA
Dakir2014 <sup>33</sup>	Standard treatment	ТХА		2	6	0	6	NA	NA
Ellis2001 <sup>40</sup>	Standard treatment	ТХА		7	10	1	10	NA	NA
Engel2001 <sup>41</sup>	Standard treatment	ТХА		3	12	0	12	NA	NA
Hiipala1995 <sup>53</sup>	Standard treatment	ТХА		12	13	10	15	NA	NA
Hiipala1997 <sup>54</sup>	Standard treatment	ТХА		34	38	17	39	NA	NA

Study	Treatment	Compara tor 1	Compa rator 2	Treatme	nt	Comparator 1		Comparator 2	
Jansen 1999 <sup>62</sup>	Standard treatment	ТХА		13	21	2	21	NA	NA
Sorin1999 <sup>114</sup>	Standard treatment	ТХА		13	21	2	21	NA	NA
Tanaka2001 <sup>117</sup>	Standard treatment	ТХА		26	26	47	73	NA	NA
Alshryda2013 <sup>6</sup>	Standard treatment	ТХА		13	78	1	79	NA	NA
Bradshaw2012 <sup>21</sup>	Standard treatment	ТХА		1	20	0	26	NA	NA
Caglar2008 <sup>22</sup>	Standard treatment	ТХА		10	50	15	50	NA	NA
Charoeanch2012 <sup>25</sup>	Standard treatment	ТХА		102	120	57	120	NA	NA
Charoeanch2011 <sup>26</sup>	Standard treatment	ТХА		45	50	28	50	NA	NA
Claeys2007 <sup>29</sup>	Standard treatment	ТХА		6	20	1	20	NA	NA
Crescenti2011 <sup>32</sup>	Standard treatment	ТХА		55	100	34	100	NA	NA
Farrokhi2011 <sup>43</sup>	Standard treatment	ТХА		15	38	10	38	NA	NA
Garneti2004 <sup>45</sup>	Standard treatment	ТХА		14	25	16	25	NA	NA
Georgiadis2013 <sup>46</sup>	Standard treatment	ТХА		4	51	0	50	NA	NA
Gill2009 <sup>48</sup>	Standard treatment	ТХА		4	5	1	5	NA	NA
Good2003 <sup>50</sup>	Standard treatment	ТХА		14	24	3	27	NA	NA
Gungorduk2011 <sup>51</sup>	Standard treatment	ТХА		7	330	2	330	NA	NA
Husted2003 <sup>60</sup>	Standard treatment	ТХА		7	20	2	20	NA	NA
Ishida2011 <sup>61</sup>	Standard treatment	ТХА		1	50	0	50	NA	NA
Johansson2005 <sup>65</sup>	Standard treatment	ТХА		23	53	8	47	NA	NA
Karimi2012 <sup>66</sup>	Standard treatment	ТХА		1	16	0	16	NA	NA
Kazemi2010 <sup>70</sup>	Standard treatment	ТХА		11	32	4	32	NA	NA
Kim2014i <sup>71</sup>	Standard	TXA		6	90	1	90	NA	NA

Study	Treatment	Compara tor 1	Compa rator 2	Treatmer	nt	Comparator 1		Comparator 2	
	treatment								
Kim 2014ii <sup>71</sup>	Standard treatment	ТХА		20	73	5	73	NA	NA
Lee2013 <sup>77</sup>	Standard treatment	ТХА		20	34	9	34	NA	NA
Lemay2004 <sup>78</sup>	Standard treatment	ТХА		8	19	0	20	NA	NA
Macgillvray2010 <sup>80</sup>	Standard treatment	ТХА		10	20	13	40	NA	NA
Niskanen 2005 <sup>92</sup>	Standard treatment	ТХА		8	20	5	19	NA	NA
Orpen2006 <sup>95</sup>	Standard treatment	ТХА		3	14	1	15	NA	NA
Rajesparan2009 <sup>98</sup>	Standard treatment	ТХА		10	37	3	36	NA	NA
Raviraj2012 <sup>99</sup>	Standard treatment	ТХА		18	88	7	88	NA	NA
Roy2012 <sup>101</sup>	Standard treatment	ТХА		7	25	2	25	NA	NA
Sa- ngasoongsong2011 <sup>102</sup>	Standard treatment	ТХА		8	24	1	24	NA	NA
Sa- ngasoongsong2013	Standard treatment	ТХА		10	45	6	90	NA	NA
Sadeghi2007 <sup>104</sup>	Standard treatment	ТХА		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	ТХА		12	36	3	38	NA	NA
Vijay2013 <sup>124</sup>	Standard treatment	ТХА		18	45	7	45	NA	NA
Wong2010 <sup>128</sup>	Standard treatment	ТХА		9	35	5	64	NA	NA
Zohar2004 <sup>138</sup>	Standard treatment	ТХА		12	20	3	20	NA	NA
Yang2014 <sup>131</sup>	Standard treatment	ТХА		19	40	10	40	NA	NA
Yue2015 <sup>133</sup>	Standard treatment	ТХА		11	49	3	52	NA	NA

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

Study	Treatment	Comp arato r 1	Compara tor 2	Treatm	ent	Compara	tor 1	Compara	itor 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	ТХА	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	ТХА	NA	1.6	0.21	1.8	0.14	NA	NA
Charoench2011 <sup>26</sup>	Standard treatment	ТХА	NA	1.89	0.12	0.71	0.11	NA	NA
Charoench2012 <sup>25</sup>	Standard treatment	ТХА	NA	1.55	0.09	0.55	0.06	NA	NA
Hiipala1995 <sup>53</sup>	Standard treatment	ТХА	NA	3.58	0.45	2.25	0.28	NA	NA
Hiipala1997 <sup>54</sup>	Standard treatment	ТХА	NA	3.46	0.21	2.29	0.13	NA	NA
Jansen1999 <sup>62</sup>	Standard treatment	ТХА	NA	2.5	0.54	0.46	0.32	NA	NA
Kazemi2010 <sup>70</sup>	Standard treatment	ТХА	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> 0	Standard treatment	ТХА	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

### Table 6: Study data for units of allogeneic blood transfused

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

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

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.

group)				
Comparison		Odds ratio		
		Direct (mean)	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)	
ТХА	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 PCS	ICS vs. PCS	-	3.003 (1.191, 8.247)	
	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)	

# Table 7:Odds ratios for number of patients receiving allogeneic transfusions (Adults- high risk<br/>group)

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

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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.

<sup>4</sup> 5



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.

6 The random effects model used for the NMA is a relatively good fit, with a residual deviance of 7 125.8 reported. This corresponds fairly well to the total number of trial arms, 112. The between 8 study variance was 0.2149 (0.01189, 0.4721). No inconsistency was identified between the direct 9 and NMA results for any comparison. All the median odds ratios from the NMA lie within the 95% 10 confidence interval from the direct comparison of the same comparisons (see Table 42). The DiC 11 value from the network was 624.777 and the DiC value from the inconsistency model was 12 626.856.

#### 1 **Evidence statement:**

2 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 3 4 ranked fourth and standard treatment ranked least effective at reducing the number of adult 5 patients receiving allogeneic transfusions in the high risk group, but there was considerable 6 uncertainty.

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

8 Table 8 summarises the results of the conventional meta-analyses in terms of mean differences 9 generated from studies directly comparing different interventions, together with the results of 10 the NMA in terms of mean differences for every possible treatment comparison.

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#### 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)
ТХА	ICS+TXA vs. TXA	-	-1.309 (-2.589, 0.03418)
Versus	ICS+TXA vs. PCS	-	-1.141 (-2.965, 0.6136)

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

13 Figure 183 shows the rank of each intervention compared to the others. Figure 184 shows the

14 median of the mean differences of each intervention compared to the others. The rank is based

15 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. 16

## Figure 183: Rank order for treatments based Figure 184: Mean differences (median) for on units of allogeneic blood units of allogeneic blood transfused



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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.

### 1 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.

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### 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)

		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)	
ТХА	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	ICS+PCS vs. PCS	-	9.961 (4.498, 15.46)	
PCS	ICS+TXA vs. PCS	-	7.748 (4.834, 10.78)	
Versus ICS+PCS	ICS+TXA vs. ICS+PCS	-	-2.196 (-7.537, 3.248)	

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

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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.

4The random effects model used for the NMA is a relatively good fit, with a residual deviance of516.82 reported. This corresponds fairly well to the total number of trial arms, 20. The between6study variance was 0.261 (0.01098, 1.459). The DiC value for this network was 44.320. No7inconsistency was identified between the direct and NMA results for any comparison. All the8mean differences from the NMA lie within the 95% confidence interval from the direct9comparison of the same comparisons.

### 10 **Evidence statement**:

11 A network meta-analysis of 10 studies comparing six treatments suggested that PCS is ranked as 12 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.

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### Table 10: Risk ratios for number of patients receiving allogeneic transfusions (Adultsmoderate 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)	
ТХА	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)
Abbraviations: TVA Transvamic acid DCS Post operative call salvage JCS Intra operative call salvage			

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ranexamic acid, PCS-Post-operative cell salvage, ICS-Intra-operative cell salvage

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.



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8 Based on the direct comparisons (first results column Table 10), efficacy as assessed by number of 9 patients receiving allogeneic transfusions favours the use of post-operative cell salvage or 10 tranexamic acid over standard treatment. No other treatment effects reached statistical 11 significance.

The random effects model used for the NMA is a relatively good fit, with a residual deviance of 12 145.2 reported. This corresponds fairly well to the total number of trial arms, 147. The between 13

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.

### 7 **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.

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

14Table summarises the results of the conventional meta-analyses in terms of mean differences15generated from studies directly comparing different interventions, together with the results of16the 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 treatment	PCS vs. standard treatment	-0.82 (-1.31, -0.33)	-0.8217 (-1.364, -0.2834)
	ICS+PCS vs. standard treatment	0.81 (0.49, 1.13)	1.11(-0.1026, 2.313)
Versus TXA	PCS vs. TXA	-	0.0816(-0.6285, 0.8177)
	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)

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

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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.



1Based on the direct comparisons (first results column Table 46), efficacy as assessed by reduced2number of units of allogeneic transfusions received favours tranexamic acid and post-operative3cell salvage over standard treatment, and standard treatment over the combination of intra-4operative cell salvage and post-operative cell salvage. No other treatment effects reached5statistical significance.

6 The random effects model used for the NMA is a relatively good fit, with a residual deviance of 7 33.45 reported. This corresponds fairly well to the total number of trial arms, 33. The DiC value 8 of the network was 8.237. No inconsistency was identified between the direct and NMA results 9 for any comparison. All the mean differences from the NMA lie within the 95% confidence interval 10 from the direct comparison of the same comparisons.

11 Evidence statement:

12A network meta-analysis of 16 studies comparing four treatments suggested that PCS and TXA are13jointly ranked as the best treatment, standard treatment is ranked third and the combination of14ICS+PCS is ranked least effective at reducing the number of units of allogeneic blood transfusions15in adult patients in the moderate risk group, but there was some uncertainty.

## 2 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 metaanalysis of the direct evidence were performed.

- 8 Our analyses were divided into two risk groups- high and moderate risk groups (For details of 9 stratification, please refer section 6.4.2, chapter 6). 73 studies formed 3 networks, each for a 10 different outcome, in the high risk group; 56 studies were included in a network for one outcome 11 in the moderate risk group. Four treatment interventions were evaluated alone or in combination 12 with one another in these analyses.
- 13The findings from the NMA were used to facilitate the GDG in decision making when developing14recommendations 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+TXA, ICS+PCS; ICS+PCS+TXA was found to be superior to ICS, ICS+PCS; ICS+PCS was found
   to be superior to ICS alone.
- 20 In the ranking of treatments PCS was ranked as the best treatment although there is considerable 21 uncertainty about this estimate as the credible intervals are quite wide; the GDG also discussed 22 concerns regarding the applicability of this evidence and highlighted that it may not be an 23 appropriate intervention in all high risk surgeries (for details, please refer the full cost-24 effectiveness analysis in Appendix M and the LETR). ICS+TXA was ranked second and the GDG 25 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 26 27 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 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.

1In the ranking of treatments PCS was ranked as the best treatment with very precise credible2intervals. However, the GDG noted that this was based on data from one study where the3baseline group had a very high length of stay. ICS and TXA were jointly ranked as the second best4interventions having reduced length of stay, with identical credible intervals. Standard treatment5was ranked as the third best intervention over ICS+TXA and ICS+PCS, but all three had very wide6credible 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.

13In the ranking of treatments PCS+TXA was ranked first and ICS+PCS+TXA was ranked second,14although both rankings had very wide credible intervals spanning greater than five treatment15ranking interventions. TXA was ranked third, but with much smaller credible intervals only16spanning three ranking positions. ICS +TXA and ICS+PCS were jointly ranked fifth with very wide17credible intervals spanning greater than six treatment ranking interventions. PCS was also ranked18fifth, but had smaller credible intervals spanning four treatment ranking interventions. ICs was19ranked 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.

29Overall, the GDG agreed that results of the four networks in the high and moderate risk groups30were not conclusive. It was acknowledged that the combination of intra-operative cell salvage and31tranexamic acid and, tranexamic acid alone were likely to be the most effective blood saving32interventions and therefore appropriate as alternatives to blood transfusion in adult surgical33patients.

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).

## 1 L.6 WinBUGS codes

2 3	L.6.1 WinBUGS code for assessment of baseline risk of receiving allogeneic to (High risk group)	ansfusions
4		
5	# Baseline random effects model	
6	model{	
7	for (i in 1:ns){ # LOOP THROUGH STUDIES	
8	r[i] ~ dbin(p[i],n[i]) # Likelihood	
9	logit(p[i]) <- mu[i] # Log-odds of response	
10	mu[i] ~ dnorm(m,tau.m)  # Random effects model	
11	}	
12	mu.new ~ dnorm(m,tau.m) # predictive dist. (log-odds)	
13	m ~ dnorm(0,.0001) # vague prior for mean	
14	var.m <- 1/tau.m # between-trial variance	
15	tau.m <- pow(sd.m,-2) # between-trial precision = (1/between-trial variance)	
16	sd.m ~ dunif(0,5) # vague prior for between-trial SD	
17	#tau.m ~ dgamma(0.001,0.001)	
18	#sd.m <- sqrt(var.m)	
19	logit(R) <- m # posterior probability of response	
20	logit(R.new) <- mu.new  # predictive probability of response	
21	}	
22		
23	Data	
24	list(ns=48) # ns=number of studies	
25		
26	r[] n[]	
27	31 41	
28	7 31	
29	21 29	

1	8	25
2	1	33
3	30	30
4	3	24
5	19	49
6	64	102
7	10	15
8	27	38
9	5	17
10	51	96
11	10	43
12	23	50
13	7	25
14	41	165
15	12	20
16	8	33
17	21	40
18	8	39
19	12	31
20	221	278
21	54	59
22	27	50
23	6	30
24	54	115
25	8	40
26	17	108
27	63	140
28	9	14
29	4	20

1	8	14
2	12	20
3	37	40
4	4	20
5	13	19
6	27	44
7	16	44
8	10	31
9	27	106
10	9	14
11	18	24
12	11	15
13	43	75
14	22	50
15	74	100
16	108	177
17	END	
18		
19	Inits	
20 21	list(mu 0,0,0,0	=c( 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,
22 23	list(mu -1,-1,-1	= c(1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-1,-1,-1,-1,-1,-1,-1,-1,-1,-1,-1,-
24 25	list(mu 1,1,1,1	= c(1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,
26 27	L.6.2 Win risk	nBUGS code for number of adult patients receiving allogeneic transfusions (High group)
28		
29	NUMB	ER TRANSFUSED HIGH RISK
30	# Binor	nial likelihood, logit link

1	# Random effects model for multi-arm trials
2	model{
3	for(i in 1:ns){ # LOOP THROUGH STUDIES
4	w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
5	delta[i,1] <- 0 # treatment effect is zero for control arm
6	mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
7	for (k in 1:na[i]) { # LOOP THROUGH ARMS
8	r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
9	logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
10	<pre>rhat[i,k] &lt;- p[i,k] * n[i,k] # expected value of the numerators</pre>
11	#Deviance contribution
12	dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
13	+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k]))) }
14	# summed residual deviance contribution for this trial
15	resdev[i] <- sum(dev[i,1:na[i]])
16	for (k in 2:na[i]) {
17	# trial-specific LOR distributions
18	delta[i,k] ~ dnorm(md[i,k],taud[i,k])
19	# mean of LOR distributions (with multi-arm trial correction)
20	md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
21	# precision of LOR distributions (with multi-arm trial correction)
22	taud[i,k] <- tau *2*(k-1)/k
23	# adjustment for multi-arm RCTs
24	w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
25	# cumulative adjustment for multi-arm trials
26	sw[i,k] <- sum(w[i,1:k-1])/(k-1)
27	}
28	}
29	totresdev <- sum(resdev[]) # Total Residual Deviance

1	d[1]<-0 # treatment effect is zero for reference treatment
2	# vague priors for treatment effects
3	for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
4	sd ~ dunif(0,5) # vague prior for between-trial SD
5	tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
6	# Provide estimates of treatment effects T[k] on the natural (probability) scale
7	# Given a Mean Effect, meanA, for 'standard' treatment A,
8	# with precision (1/variance) precA
9	A ~ dnorm(meanA,precA)
10	for (k in 1:nt) { logit(T[k]) <- A + d[k] }
11	rr [1] < -1
12	for (k in 2:nt) {rr[k]<-T[k]/T[1] }
13	for (c in 1:(nt-1))
14	{ for (k in (c+1):nt)
15	{ lor[c,k] <- d[k] - d[c]
16	log(or[c,k]) <- lor[c,k]
17	<pre>Irr[c,k] &lt;- log(rr[k]) - log(rr[c])</pre>
18	log(rrisk[c,k]) <- lrr[c,k] }}
19	for (k in 1:nt) {
20	rk[k]<-rank(rr[],k)
21	best[k]<-equals(rank(rr[],k),1)}
22	
23	} # *** PROGRAM ENDS
24	
25	Data
26	<pre># ns= number of studies; nt=number of treatments</pre>
27	list(ns=56, nt=7, meanA=-0.07213, precA=0.708544479588251)
28	
29	r[,1] r[,2] n[,1] n[,2] t[,1] t[,2] na[]

1	31	21	41	40	1	4	2
2	7	4	31	30	1	4	2
3	21	17	29	30	1	4	2
4	8	7	25	25	1	4	2
5	1	2	33	32	1	3	2
6	30	19	30	30	1	3	2
7	3	1	24	23	1	3	2
8	19	6	49	41	1	3	2
9	64	41	102	98	1	5	2
10	10	8	15	15	1	5	2
11	13	9	50	52	4	6	2
12	27	20	60	60	4	6	2
13	19	9	26	24	4	6	2
14	12	5	20	20	4	6	2
15	73	57	103	99	4	6	2
16	13	12	29	24	2	6	2
17	14	13	50	50	5	7	2
18	33	31	111	102	2	7	2
19	27	20	38	38	1	2	2
20	5	6	17	20	1	2	2
21	51	51	96	97	1	2	2
22	10	8	43	44	1	2	2
23	23	15	50	50	1	2	2
24	7	2	25	22	1	2	2
25	41	24	165	147	1	2	2
26	12	7	20	20	1	2	2
27	8	5	33	33	1	2	2
28	21	15	40	40	1	2	2
29	8	7	39	40	1	2	2

1	12	7	31	29	1	2	2
2	221	166	278	274	1	2	2
3	54	42	59	58	1	2	2
4	27	8	50	50	1	2	2
5	6	3	30	32	1	2	2
6	54	37	115	116	1	2	2
7	8	3	40	36	1	2	2
8	17	0	108	106	1	2	2
9	63	35	140	143	1	2	2
10	9	7	14	15	1	2	2
11	4	2	20	20	1	2	2
12	8	9	14	16	1	2	2
13	12	15	20	41	1	2	2
14	37	29	40	42	1	2	2
15	4	3	20	20	1	2	2
16	13	14	19	19	1	2	2
17	27	28	44	42	1	2	2
18	16	12	44	37	1	2	2
19	10	7	31	62	1	2	2
20	27	11	106	104	1	2	2
21	9	2	14	16	1	2	2
22	18	12	24	24	1	2	2
23	11	13	15	15	1	2	2
24	43	22	75	75	1	2	2
25	22	15	50	50	1	2	2
26	74	60	100	100	1	2	2
27	108	98	177	189	1	4	2
28							
29	END						

1		Initial Values	
2		list(	
3		d=c(NA,0,0,0,0,0,0	)),
4		sd=.2,	
5 6		mu=c(2,0,3,0,2,-2, 2,2,2,0,1,2,0,0,-2,1	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,- l,-2,-2,-3,-2,1,2,1,2))
7		list(	
8		d=c(NA,1,1,1,1,1,1,1	.),
9		sd=.1,	
10 11		mu=c(2,1,3,1,2,0,2 3,2,1,3,0,2,2,1,1,2,	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,- ,1,1,0,1,0,0,-3,0,1,2,1,2))
12		list(	
13		d=c(NA,0.5,0.5,0.5	,0.5,0.5,0.5),
14		sd=.15,	
15 16		mu=c(2,0.5,3,0.5,2 3,2,1,3,1,2,2,0.5,1,	?,-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,- ,2,0.5,0.5,1,1,1,1,-3,-2,1,2,1,2))
17 18	L.6.3	WinBUGS code f allogeneic transf	or inconsistency model for number of adult patients receiving fusions (High risk group)
19		High risk number t	ransfused
20		56 trials	
21		7 treatments	
22			
23		# Binomial likeliho	od, logit link, inconsistency model
24		# Random effects	model
25		model{	# *** PROGRAM STARTS
26		for(i in 1:ns){	# LOOP THROUGH STUDIES
27		delta[i,1]<-0	# treatment effect is zero in control arm
28		mu[i] ~ dnorm(0	),.0001) # vague priors for trial baselines
29		for (k in 1:na[i])	{ # LOOP THROUGH ARMS
		ft i 1 er dirt dat	[i k] n[i k]) # hinomial likelihood

1	logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor						
2	#Deviance contribution						
3	<pre>rhat[i,k] &lt;- p[i,k] * n[i,k] # expected value of the numerators</pre>						
4	dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))						
5	+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))						
6	}						
7	# summed residual deviance contribution for this trial						
8	resdev[i] <- sum(dev[i,1:na[i]])						
9	for (k in 2:na[i]) { # LOOP THROUGH ARMS						
10	# trial-specific LOR distributions						
11	delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)						
12	}						
13	}						
14	totresdev <- sum(resdev[]) # Total Residual Deviance						
15	for (c in 1:(nt-1)) { # priors for all mean treatment effects						
16	for (k in (c+1):nt) { d[c,k] ~ dnorm(0,.0001) }						
17	}						
18	sd ~ dunif(0,5) # vague prior for between-trial standard deviation						
19	var <- pow(sd,2) # between-trial variance						
20	tau <- 1/var # between-trial precision						
21	} # *** PROGRAM ENDS						
22							
23							
24	Data						
25	# High risk number transfused						
26	# nt=no. treatments, ns=no. studies						
27	list(nt=7,ns=56 )						
28							
29	r[,1] r[,2] n[,1] n[,2] t[,1] t[,2] na[]						
1	31	21	41	40	1	4	2
----	----	----	-----	-----	---	---	---
2	7	4	31	30	1	4	2
3	21	17	29	30	1	4	2
4	8	7	25	25	1	4	2
5	1	2	33	32	1	3	2
6	30	19	30	30	1	3	2
7	3	1	24	23	1	3	2
8	19	6	49	41	1	3	2
9	64	41	102	98	1	5	2
10	10	8	15	15	1	5	2
11	13	9	50	52	4	6	2
12	27	20	60	60	4	6	2
13	19	9	26	24	4	6	2
14	12	5	20	20	4	6	2
15	73	57	103	99	4	6	2
16	13	12	29	24	2	6	2
17	14	13	50	50	5	7	2
18	33	31	111	102	2	7	2
19	27	20	38	38	1	2	2
20	5	6	17	20	1	2	2
21	51	51	96	97	1	2	2
22	10	8	43	44	1	2	2
23	23	15	50	50	1	2	2
24	7	2	25	22	1	2	2
25	41	24	165	147	1	2	2
26	12	7	20	20	1	2	2
27	8	5	33	33	1	2	2
28	21	15	40	40	1	2	2
29	8	7	39	40	1	2	2

1	12	7	31	29	1	2	2
2	221	166	278	274	1	2	2
3	54	42	59	58	1	2	2
4	27	8	50	50	1	2	2
5	6	3	30	32	1	2	2
6	54	37	115	116	1	2	2
7	8	3	40	36	1	2	2
8	17	0	108	106	1	2	2
9	63	35	140	143	1	2	2
10	9	7	14	15	1	2	2
11	4	2	20	20	1	2	2
12	8	9	14	16	1	2	2
13	12	15	20	41	1	2	2
14	37	29	40	42	1	2	2
15	4	3	20	20	1	2	2
16	13	14	19	19	1	2	2
17	27	28	44	42	1	2	2
18	16	12	44	37	1	2	2
19	10	7	31	62	1	2	2
20	27	11	106	104	1	2	2
21	9	2	14	16	1	2	2
22	18	12	24	24	1	2	2
23	11	13	15	15	1	2	2
24	43	22	75	75	1	2	2
25	22	15	50	50	1	2	2
26	74	60	100	100	1	2	2
27	108	98	177	189	1	4	2
28							
29	END						

1	
2	
3	
4	INITS
5	
6	# chain 1
7 8	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),
9	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,0,0,0,
10	NA,NA,NA,NA,NA,0,0, NA,NA,NA,NA,NA,NA,0), .Dim = c(6,7)))
11	
12	# chain 2
13 14	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),
15 16	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,0.5,2,0,
17	NA,NA,NA,NA,NA,2,0, NA,NA,NA,NA,NA,NA,1 ), .Dim = c(6,7)))
18	
19	# chain 3
20 21	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),
22 23	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,NA,0,1,2,
24	NA,NA,NA,NA,NA,1,1, NA,NA,NA,NA,NA,-1), .Dim = c(6,7)))
25	
26 27	L.6.4 WinBUGS code for number of units of receiving allogeneic blood transfusions (High risk group)
28	
29	UNITS TRANSFUSED - HIGH RISK
30	# Normal likelihood, identity link
31	# Random effects model for multi-arm trials

1	model{
2	for(i in 1:ns){ # LOOP THROUGH STUDIES
3	w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
4	delta[i,1] <- 0 # treatment effect is zero for control arm
5	mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
6	for (k in 1:na[i]) { # LOOP THROUGH ARMS
7	<pre>var[i,k] &lt;- pow(se[i,k],2) # calculate variances</pre>
8	prec[i,k] <- 1/var[i,k] # set precisions
9	y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
10	theta[i,k] <- mu[i] + delta[i,k] # model for linear predictor
11	#Deviance contribution
12	dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
13	}
14	# summed residual deviance contribution for this trial
15	resdev[i] <- sum(dev[i,1:na[i]])
16	for (k in 2:na[i]) { # LOOP THROUGH ARMS
17	# trial-specific LOR distributions
18	delta[i,k] ~ dnorm(md[i,k],taud[i,k])
19	# mean of LOR distributions, with multi-arm trial correction
20	md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
21	# precision of LOR distributions (with multi-arm trial correction)
22	taud[i,k] <- tau *2*(k-1)/k
23	# adjustment, multi-arm RCTs
24	w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
25	# cumulative adjustment for multi-arm trials
26	sw[i,k] <- sum(w[i,1:k-1])/(k-1)
27	}
28	}
29	totresdev <- sum(resdev[]) #Total Residual Deviance

1	d[1]<-0	d[1]<-0 # treatment effect is zero for control arm							
2	# vague	# vague priors for treatment effects							
3	for (k iı	n 2:nt){	d[k] ~ dı	norm(0,.	0001)}				
4	sd ~ du	ınif(0,5)	# vagı	ue prior	for betw	veen-tria	I SD		
5	tau <- p	pow(sd,-	2) # be	tween-t	rial prec	ision = (	1/betwe	een-trial	variance)
6	# Provi	de estin	nates of	treatme	nt effect	ts T[k] oi	n the na	tural sca	le
7	# Giver	n a Mear	n Effect,	meanA,	for 'star	ndard' tr	eatmen	t A,	
8	# with	precisio	n (1/vari	iance) pr	ecA				
9	A ~ dno	orm(mea	anA,prec	cA)					
10	for (k iı	n 1:nt) {	T[k] <- A	A + d[k]	}				
11	for (k iı	n 1:nt) {							
12	rk[k]<-rank(d[],k)								
13	best[k]<-equals(rank(d[],k),1)}								
14	for (c in 1:(nt-1))								
15	{ for (k in (c+1):nt)								
16	{        D[c,k	] <- d[k]	- d[c]}}						
17	}		#	*** PRC	) GRAM I	ENDS			
18	Data								
19	# ns= n	umber o	of studie	s; nt=nu	mber of	treatme	ents		
20	list(ns=	23, nt=5	5, meanA	4=-1, pre	ecA=1)				
21									
22									
23	t[,1]	t[,2]	y[,1]	y[,2]	se[,1]	se[,2]	na[]		
24	1	2	11.17	6.47	1.2635	97349	1.1216	539956	2
25	1	2	1.38	0.53	0.2071	29187	0.1027	74024	2
26	1	2	2.4	1.54	0.258	0.2245	3656	2	
27	1	2	0.7	0.4	0.2	0.16	2		
28	1	4	2.22	1.2	0.0730	29674	0.0492	29503	2
29	2	5	1.68	0.87	0.4531	39052	0.1962	231156	2

1		2	5	3.21	1.58	0.1078638	874	0.100020831	2
2		1	3	0.87	0.41	0.1098700	053	0.077770507	2
3		1	3	1.57	0.8	0.4008918	863	0.278854801	2
4		1	3	1.7	0.8	0.4024922	236	0.171791138	2
5		1	3	7.75	5.33	0.9961174	463	0.890330329	2
6		1	3	0.76	0.92	0.2414953	342	0.188561808	2
7		1	3	3.03	1.42	0.8207962	23	0.347980348	2
8		1	3	3.13	2.87	0.8520563	336	0.490577891	2
9		1	3	9.16	4.1	2.694438	717	0.910393688	2
10		1	3	12.4	7.9	2.5298222	128	1.043551628	2
11		1	3	1.68	0.52	0.2 0.	.18	2	
12		1	3	1.4	0.8	0.194665	705	0.129777137	2
13		1	3	3.17	2.03	0.0920683	326	0.074034324	2
14		1	3	6.51	3.93	0.4396243	185	0.281520895	2
15		1	3	9.36	4.84	1.4854554	474	0.768142632	2
16		1	3	1.62	0.91	0.239653	736	0.147627794	2
17		1	3	1.65	1.25	0.053 0.	.055	2	
18		END							
19		Initial V	Values						
20		#chain	1						
21		list(d=c	( NA, 0,0	),0,0), sd	l=1, mu=	=c(0,0,0,0,0	),0,0,0	,0,0,0,1,1,1, 0, 0	, 0, 0, 0, 1,1,1,0))
22		#chain	2						
23		list(d=c	( NA, -1,	-3,1,-1),	sd=4, m	u=c(0,3,0,-	-1,0,2,	1,0,-3,0,-2,1,1,1	, 2, 0, 0, 1, 1,1,1,2,0))
24		#chain	3						
25		list(d=c	( NA, 2,2	2,2,2), sd	l=2, mu=	=c(2,3,1,-1,	1,2,0,0	0,-3,0,2,1,-1,1,-2	, 0, 0,-1,-1,1,1,-1,0))
26									
27	L.6.5	5 Wir	BUGS	ode for	· length	of stay in	n hosp	oital (High risk ;	group)
28									

29 LENGTH OF STAY - HIGH RISK

1	# Normal likelihood, identity link
2	# Random effects model for multi-arm trials
3	model{
4	for(i in 1:ns){ # LOOP THROUGH STUDIES
5	w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
6	delta[i,1] <- 0 # treatment effect is zero for control arm
7	mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
8	for (k in 1:na[i]) { # LOOP THROUGH ARMS
9	<pre>var[i,k] &lt;- pow(se[i,k],2) # calculate variances</pre>
10	<pre>prec[i,k] &lt;- 1/var[i,k] # set precisions</pre>
11	y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
12	theta[i,k] <- mu[i] + delta[i,k] # model for linear predictor
13	#Deviance contribution
14	dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
15	}
16	# summed residual deviance contribution for this trial
17	resdev[i] <- sum(dev[i,1:na[i]])
18	for (k in 2:na[i]) { # LOOP THROUGH ARMS
19	# trial-specific LOR distributions
20	delta[i,k] ~ dnorm(md[i,k],taud[i,k])
21	# mean of LOR distributions, with multi-arm trial correction
22	md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
23	# precision of LOR distributions (with multi-arm trial correction)
24	taud[i,k] <- tau *2*(k-1)/k
25	# adjustment, multi-arm RCTs
26	w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
27	# cumulative adjustment for multi-arm trials
28	sw[i,k] <- sum(w[i,1:k-1])/(k-1)
29	}

1	}								
2	totreso	dev <- su	ım(resde	ev[])	#Tota	l Residu	al Deviance		
3	d[1]<-(	d[1]<-0 # treatment effect is zero for control arm							
4	# vagu	# vague priors for treatment effects							
5	for (k i	n 2:nt){	d[k] ~ d	norm(0,	.0001)}				
6	sd ~ dı	unif(0,5)	# vag	ue prior	for betw	veen-tria	al SD		
7	tau <-	pow(sd,-	-2) # be	etween-t	trial prec	ision = (	1/between-trial	variance)	
8	# Provi	ide estin	nates of	treatme	ent effect	ts T[k] o	n the natural sca	ale	
9	# Give	n a Meai	n Effect,	meanA,	for 'star	ndard' tr	eatment A,		
10	# with	# with precision (1/variance) precA							
11	A ~ dn	A ~ dnorm(meanA,precA)							
12	for (k i	for (k in 1:nt) { T[k] <- A + d[k] }							
13	for (k i	for (k in 1:nt) {							
14	rk[k]<-	rk[k]<-rank(d[],k)							
15	best[k]	best[k]<-equals(rank(d[],k),1)}							
16	for (c i	for (c in 1:(nt-1))							
17	{ for (I	k in (c+1)	):nt)						
18	{ D[c,k	<] <- d[k]	- d[c]}}						
19	}		#	*** PR(	DGRAM I	ENDS			
20									
21	Data								
22	# ns= r	number o	of studie	es; nt=nı	umber of	treatme	ents		
23	list(ns=	=10, nt=6	6, mean/	4=-1, pre	ecA=1)				
24									
25	t[,1]	t[,2]	y[,1]	y[,2]	se[,1]	se[,2]	na[]		
26	1	3	7.85	7.65	0.4190	0179	0.341525987	2	
27	1	4	16.45	9.32	0.9314	28571	0.398243093	2	
28	1	5	6.8	9.6	0.4061	38466	2.472393026	2	
29	3	6	4	4.5	0.7275	90861	0.724640716	2	

1	3	6	8.5	9.4	0.729143666	0.864332521	2	
2	2	6	12.1	14.2	1.355575969	2.435279909	2	
3	1	2	6.4	5.8	0.670820393	0.491934955	2	
4	1	2	4.8	4.8	0.15666989	0.069631062	2	
5	1	2	7.3	7.1	0.18973666	0.133333333	2	
6	1	3	11.8	11.5	0.721580187	0.763762616	2	
7								
8	END							
9	Initial	Values	i					
10	#chair	n 1						
11	list(d=c( NA, 0,0,0,0,0), sd=1, mu=c(1,0, 0, 0, 0, 0, 1,1,0,2))							
12	#chain 2							
13	list(d=c( NA, -3,1,-1,-3,-1), sd=4, mu=c(1, 2, 0, 0, 1, 1,1,1,0,1))							
14	#chain 3							
15	list(d=	c( NA, 2	2,2,2,2,2),	sd=2, n	nu=c(-2, 1, 0, 0,-1	L,-1,1,1,0,1))		
16								
17 18	L.6.6 Wi (M	nBUGS oderat	S code for te risk gro	r asses oup)	sment of basel	ine risk of rece	iving allogeneic transfusions	
19								
20	# Bino	mial lik	elihood, k	ogit link				
21	# Base	eline rar	ndom effe	cts moo	del			
22	model	{ 	#	*** PR	OGRAM STARTS			
23	for (i i	n 1:ns){		\$ LOOP	THROUGH STUD	IES		
24	r[i] ^	~ dbin(p	o[i],n[i])		# Likelihood			
25	logi	t(p[i]) <	- mu[i]		# Log	-odds of respon	se	
26	mu[	i] ~ dnc	orm(m,tau	.m) #	# Random effects	s model		
27	}							
28	mu.ne	w ~ dn	orm(m,taı	u.m)	# predictiv	e dist. (log-odds	)	
29	m ~ dr	norm(0,	,.0001)	# v	ague prior for m	ean		

1	var.m «	- 1/tau.m # between-t	rial variance
2	tau.m ·	<- pow(sd.m,-2) # between-tria	al precision = (1/between-trial variance)
3	sd.m ~	dunif(0,5) # vague prior	r for between-trial SD
4	#tau.m	~ dgamma(0.001,0.001)	
5	#sd.m	<- sqrt(var.m)	
6	logit(R)	<- m # posterior pro	bability of response
7	logit(R.	new) <- mu.new  # predict	ive probability of response
8	}		
9			
10	Data		
11	list(ns=	69) # ns=number of studies	
12			
13	r[]	n[]	
14	16	20	
15	23	70	
16	9	102	
17	15	19	
18	8	21	
19	13	34	
20	10	17	
21	10	22	
22	10	30	
23	12	52	
24	17	82	
25	15	80	
26	24	30	
27	13	86	
28	12	190	
29	11	56	

1	54	658
2	4	62
3	12	42
4	24	43
5	15	19
6	8	20
7	8	25
8	2	6
9	7	10
10	3	12
11	12	13
12	34	38
13	13	21
14	13	21
15	26	26
16	13	78
17	1	20
18	10	50
19	102	120
20	45	50
21	6	20
22	55	100
23	15	38
24	14	25
25	4	51
26	4	5
27	14	24
28	7	330
29	7	20

1	1	50
2	23	53
3	1	16
4	11	32
5	6	90
6	20	73
7	20	34
8	8	19
9	10	20
10	8	20
11	3	14
12	10	37
13	18	88
14	7	25
15	8	24
16	10	45
17	20	35
18	47	50
19	12	36
20	18	45
21	9	35
22	12	20
23	19	40
24	11	49
25		
26	END	
27	Inits	

1	
2 3 4	list(mu = c(1,-1,-1,-1,-1, -1,-1,-1,-1, -1,-1,-1,-1,-1,-1, -1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-1,-1,-1,-1,-1,-1,-1,-1,-1,-1,-1,-
5	
6 7	list(mu = c(1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,
8 9	L.6.7 WinBUGS code for number of adult patients receiving allogeneic transfusions (Moderate risk group)
10	
11	NUMBER TRANSFUSED MODERATE RISK
12	# Binomial likelihood, logit link
13	# Random effects model for multi-arm trials
14	model{
15	for(i in 1:ns){ # LOOP THROUGH STUDIES
16	w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
17	delta[i,1] <- 0 # treatment effect is zero for control arm
18	mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
19	for (k in 1:na[i]) { # LOOP THROUGH ARMS
20	r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
21	<pre>logit(p[i,k]) &lt;- mu[i] + delta[i,k] # model for linear predictor</pre>
22	<pre>rhat[i,k] &lt;- p[i,k] * n[i,k] # expected value of the numerators</pre>
23	#Deviance contribution
24	dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
25	+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
26	# summed residual deviance contribution for this trial
27	resdev[i] <- sum(dev[i,1:na[i]])
28	for (k in 2:na[i]) { # LOOP THROUGH ARMS
29	# trial-specific LOR distributions
30	delta[i,k] ~ dnorm(md[i,k],taud[i,k])

1	# mean of LOR distributions (with multi-arm trial correction)
2	md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
3	# precision of LOR distributions (with multi-arm trial correction)
4	taud[i,k] <- tau *2*(k-1)/k
5	# adjustment for multi-arm RCTs
6	w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
7	# cumulative adjustment for multi-arm trials
8	sw[i,k] <- sum(w[i,1:k-1])/(k-1)
9	}
10	}
11	totresdev <- sum(resdev[])  # Total Residual Deviance
12	d[1]<-0 # treatment effect is zero for reference treatment
13	# vague priors for treatment effects
14	for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
15	sd ~ dunif(0,5) # vague prior for between-trial SD
16	tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
17	# Provide estimates of treatment effects T[k] on the natural (probability) scale
18	# Given a Mean Effect, meanA, for 'standard' treatment A,
19	# with precision (1/variance) precA
20	A ~ dnorm(meanA,precA)
21	for (k in 1:nt) { logit(T[k]) <- A + d[k] }
22	rr [1] < -1
23	for (k in 2:nt) {rr[k]<-T[k]/T[1] }
24	for (c in 1:(nt-1))
25	{ for (k in (c+1):nt)
26	{ lor[c,k] <- d[k] - d[c]
27	log(or[c,k]) <- lor[c,k]
28	<pre>Irr[c,k] &lt;- log(rr[k]) - log(rr[c])</pre>
29	log(rrisk[c,k]) <- lrr[c,k] }}

1	for (k	for (k in 1:nt) {										
2	rk[k]<	rk[k]<-rank(rr[],k)										
3	best[k	best[k]<-equals(rank(rr[],k),1)}										
4												
5	}	# *** PROGRAM ENDS										
6	Data											
7	# ns=	number	of studi	es; nt=nı	umber o	f treatm	ents					
8	list(ns	=73, nt=	8, mean	A=-0.51	85, prec	A=0.479	585024	669854)				
9	r[,1]	r[,2]	r[,3]	n[,1]	n[,2]	n[,3]	t[,1]	t[,2]	t[,3]	na[]		
10	16	10	NA	20	20	NA	1	4	NA	2		
11	23	23	NA	70	70	NA	1	4	NA	2		
12	9	8	NA	102	102	NA	1	4	NA	2		
13	15	9	NA	19	17	NA	1	3	NA	2		
14	8	1	NA	21	20	NA	1	3	NA	2		
15	13	4	NA	34	26	NA	1	3	NA	2		
16	10	3	NA	17	32	NA	1	3	NA	2		
17	10	22	NA	22	47	NA	1	3	NA	2		
18	10	5	NA	30	30	NA	1	3	NA	2		
19	12	13	NA	52	52	NA	1	3	NA	2		
20	17	6	NA	82	76	NA	1	3	NA	2		
21	15	5	NA	80	80	NA	1	3	NA	2		
22	24	4	NA	30	30	NA	1	3	NA	2		
23	13	12	NA	86	92	NA	1	3	NA	2		
24	12	29	NA	190	382	NA	1	3	NA	2		
25	11	6	NA	56	59	NA	1	3	NA	2		
26	54	33	23	658	321	321	1	3	5	3		
27	4	2	NA	62	56	NA	1	5	NA	2		
28	30	23	NA	74	73	NA	4	8	NA	2		
29	6	1	NA	49	46	NA	3	7	NA	2		

1	5	3	NA	49	49	NA	3	7	NA	2
2	13	9	NA	101	96	NA	2	6	NA	2
3	12	2	NA	42	41	NA	1	2	NA	2
4	24	8	NA	43	43	NA	1	2	NA	2
5	15	9	NA	19	20	NA	1	2	NA	2
6	8	4	NA	20	18	NA	1	2	NA	2
7	8	0	NA	25	25	NA	1	2	NA	2
8	2	0	NA	6	6	NA	1	2	NA	2
9	7	1	NA	10	10	NA	1	2	NA	2
10	3	0	NA	12	12	NA	1	2	NA	2
11	12	10	NA	13	15	NA	1	2	NA	2
12	34	17	NA	38	39	NA	1	2	NA	2
13	13	2	NA	21	21	NA	1	2	NA	2
14	13	2	NA	21	21	NA	1	2	NA	2
15	26	47	NA	26	73	NA	1	2	NA	2
16	13	1	NA	78	79	NA	1	2	NA	2
17	1	0	NA	20	26	NA	1	2	NA	2
18	10	15	NA	50	50	NA	1	2	NA	2
19	102	57	NA	120	120	NA	1	2	NA	2
20	45	28	NA	50	50	NA	1	2	NA	2
21	6	1	NA	20	20	NA	1	2	NA	2
22	55	34	NA	100	100	NA	1	2	NA	2
23	15	10	NA	38	38	NA	1	2	NA	2
24	14	16	NA	25	25	NA	1	2	NA	2
25	4	0	NA	51	50	NA	1	2	NA	2
26	4	1	NA	5	5	NA	1	2	NA	2
27	14	3	NA	24	27	NA	1	2	NA	2
28	7	2	NA	330	330	NA	1	2	NA	2
29	7	2	NA	20	20	NA	1	2	NA	2

1	1	0	NA	50	50	NA	1	2	NA	2
2	23	8	NA	53	47	NA	1	2	NA	2
3	1	0	NA	16	16	NA	1	2	NA	2
4	11	4	NA	32	32	NA	1	2	NA	2
5	6	1	NA	90	90	NA	1	2	NA	2
6	20	5	NA	73	73	NA	1	2	NA	2
7	20	9	NA	34	34	NA	1	2	NA	2
8	8	0	NA	19	20	NA	1	2	NA	2
9	10	13	NA	20	40	NA	1	2	NA	2
10	8	5	NA	20	19	NA	1	2	NA	2
11	3	1	NA	14	15	NA	1	2	NA	2
12	10	3	NA	37	36	NA	1	2	NA	2
13	18	7	NA	88	88	NA	1	2	NA	2
14	7	2	NA	25	25	NA	1	2	NA	2
15	8	1	NA	24	24	NA	1	2	NA	2
16	10	6	NA	45	90	NA	1	2	NA	2
17	20	12	NA	35	32	NA	1	2	NA	2
18	47	10	NA	50	50	NA	1	2	NA	2
19	12	3	NA	36	38	NA	1	2	NA	2
20	18	7	NA	45	45	NA	1	2	NA	2
21	9	5	NA	35	64	NA	1	2	NA	2
22	12	3	NA	20	20	NA	1	2	NA	2
23	19	10	NA	40	40	NA	1	2	NA	2
24	11	3	NA	49	52	NA	1	2	NA	2
25										

- 26
- 27
- 28 Initial Values

END

list(

29

1		d=c(NA,0,0,0,0,0,0),
2		sd=.2,
3 4		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, -3,1,-2,1,2, 2,0,1,2,0, 0,-1,2,0,-1, 1,1,1,1,1, 2,2,3))
5		list(
6		d=c(NA,1,1,1,1,1,1),
7		sd=.1,
8 9		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,-1,3, 2,0,3,0,2, -2,1,2))
10		list(
11		d=c(NA,0.5,0.5,0.5,0.5,0.5,0.5),
12		sd=.15,
13 14		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))
15		
16		
17 18	L.6.8	WinBUGS code for inconsistency model for number of adult patients receiving allogeneic transfusions (Moderate risk group)
19		Moderate risk number transfused
20		73 trials (including one 3-arm-trial),
21		8 treatments
22		
23		
24		
		# Binomial likelihood, logit link, inconsistency model
25		# Binomial likelihood, logit link, inconsistency model # Random effects model
25 26		<pre># Binomial likelihood, logit link, inconsistency model # Random effects model model{</pre>
25 26 27		# Binomial likelihood, logit link, inconsistency model         # Random effects model         model{       # *** PROGRAM STARTS         for(i in 1:ns){       # LOOP THROUGH STUDIES
25 26 27 28		# Binomial likelihood, logit link, inconsistency model         # Random effects model         model{       # *** PROGRAM STARTS         for(i in 1:ns){       # LOOP THROUGH STUDIES         delta[i,1]<0
25 26 27 28 29		<pre># Binomial likelihod, logit link, inconsistency model # Random effects wodel model{</pre>

1	r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
2	logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
3	#Deviance contribution
4	rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
5	dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
6	+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
7	}
8	# summed residual deviance contribution for this trial
9	resdev[i] <- sum(dev[i,1:na[i]])
10	for (k in 2:na[i]) { # LOOP THROUGH ARMS
11	# trial-specific LOR distributions
12	delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
13	}
14	}
15	totresdev <- sum(resdev[]) # Total Residual Deviance
16	for (c in 1:(nt-1)) { # priors for all mean treatment effects
17	for (k in (c+1):nt) { d[c,k] ~ dnorm(0,.0001) }
18	}
19	sd ~ dunif(0,5) # vague prior for between-trial standard deviation
20	var <- pow(sd,2) # between-trial variance
21	tau <- 1/var # between-trial precision
22	} # *** PROGRAM ENDS
23	
24	
25	Data
26	# Moderate risk number transfused
27	# nt=no. treatments, ns=no. studies
28	list(nt=8,ns=73 )
29	

1	r[,1]	r[,2]	r[,3]	n[,1]	n[,2]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
2	16	10	NA	20	20	NA	1	4	NA	2
3	23	23	NA	70	70	NA	1	4	NA	2
4	9	8	NA	102	102	NA	1	4	NA	2
5	15	9	NA	19	17	NA	1	3	NA	2
6	8	1	NA	21	20	NA	1	3	NA	2
7	13	4	NA	34	26	NA	1	3	NA	2
8	10	3	NA	17	32	NA	1	3	NA	2
9	10	22	NA	22	47	NA	1	3	NA	2
10	10	5	NA	30	30	NA	1	3	NA	2
11	12	13	NA	52	52	NA	1	3	NA	2
12	17	6	NA	82	76	NA	1	3	NA	2
13	15	5	NA	80	80	NA	1	3	NA	2
14	24	4	NA	30	30	NA	1	3	NA	2
15	13	12	NA	86	92	NA	1	3	NA	2
16	12	29	NA	190	382	NA	1	3	NA	2
17	11	6	NA	56	59	NA	1	3	NA	2
18	54	33	23	658	321	321	1	3	5	3
19	4	2	NA	62	56	NA	1	5	NA	2
20	30	23	NA	74	73	NA	4	8	NA	2
21	6	1	NA	49	46	NA	3	7	NA	2
22	5	3	NA	49	49	NA	3	7	NA	2
23	13	9	NA	101	96	NA	2	6	NA	2
24	12	2	NA	42	41	NA	1	2	NA	2
25	24	8	NA	43	43	NA	1	2	NA	2
26	15	9	NA	19	20	NA	1	2	NA	2
27	8	4	NA	20	18	NA	1	2	NA	2
28	8	0	NA	25	25	NA	1	2	NA	2
29	2	0	NA	6	6	NA	1	2	NA	2

1	7	1	NA	10	10	NA	1	2	NA	2
2	3	0	NA	12	12	NA	1	2	NA	2
3	12	10	NA	13	15	NA	1	2	NA	2
4	34	17	NA	38	39	NA	1	2	NA	2
5	13	2	NA	21	21	NA	1	2	NA	2
6	13	2	NA	21	21	NA	1	2	NA	2
7	26	47	NA	26	73	NA	1	2	NA	2
8	13	1	NA	78	79	NA	1	2	NA	2
9	1	0	NA	20	26	NA	1	2	NA	2
10	10	15	NA	50	50	NA	1	2	NA	2
11	102	57	NA	120	120	NA	1	2	NA	2
12	45	28	NA	50	50	NA	1	2	NA	2
13	6	1	NA	20	20	NA	1	2	NA	2
14	55	34	NA	100	100	NA	1	2	NA	2
15	15	10	NA	38	38	NA	1	2	NA	2
16	14	16	NA	25	25	NA	1	2	NA	2
17	4	0	NA	51	50	NA	1	2	NA	2
18	4	1	NA	5	5	NA	1	2	NA	2
19	14	3	NA	24	27	NA	1	2	NA	2
20	7	2	NA	330	330	NA	1	2	NA	2
21	7	2	NA	20	20	NA	1	2	NA	2
22	1	0	NA	50	50	NA	1	2	NA	2
23	23	8	NA	53	47	NA	1	2	NA	2
24	1	0	NA	16	16	NA	1	2	NA	2
25	11	4	NA	32	32	NA	1	2	NA	2
26	6	1	NA	90	90	NA	1	2	NA	2
27	20	5	NA	73	73	NA	1	2	NA	2
28	20	9	NA	34	34	NA	1	2	NA	2
29	8	0	NA	19	20	NA	1	2	NA	2

1	10	13	NA	20	40	NA	1	2	NA	2	
2	8	5	NA	20	19	NA	1	2	NA	2	
3	3	1	NA	14	15	NA	1	2	NA	2	
4	10	3	NA	37	36	NA	1	2	NA	2	
5	18	7	NA	88	88	NA	1	2	NA	2	
6	7	2	NA	25	25	NA	1	2	NA	2	
7	8	1	NA	24	24	NA	1	2	NA	2	
8	10	6	NA	45	90	NA	1	2	NA	2	
9	20	12	NA	35	32	NA	1	2	NA	2	
10	47	10	NA	50	50	NA	1	2	NA	2	
11	12	3	NA	36	38	NA	1	2	NA	2	
12	18	7	NA	45	45	NA	1	2	NA	2	
13	9	5	NA	35	64	NA	1	2	NA	2	
14	12	3	NA	20	20	NA	1	2	NA	2	
15	19	10	NA	40	40	NA	1	2	NA	2	
16	11	3	NA	49	52	NA	1	2	NA	2	
17											
18	END										
19	INITS										
20											
21	# chai	n 1									
22 23	list(sd 3,0,-1	=1, mu ,-3, 2,1	=c(2,0,3) .,3,-2,2,	,0,2, -2 2,0,1,2	,2,-2,-1, ,0, 0,-2,	3, 2,-2, <u>2</u> 1,-2,-2,	1,3,1, -3,1,-2,	1,2,-3,2, 1,2, 2,0	-2, -2,1, ,1,2,0, 0	0,-3,3, 0,-3,-2,-3,-2, 3,- 1,2,0,-1, 1,1,1,1,1, 2,2,3	5),
24 25	d=stru NA,NA	ucture(.l NA,NA	Data=c(N A,0,0,0,0,0	NA,0,1,0 ,	,0,-2,0,0	), NA,N	A,0,0,2	,0,0,-2,	NA,NA,N	IA,0,0,0,0,0,0,	
26	NA,NA	A,NA,NA	A,NA,0,0,	1, NA,	NA,NA,I	NA,NA,N	A,0,0,	NA,N/	A,NA,NA,	NA,NA,NA,0), .Dim = c(7,8	;)))
27											
28	# chai	n 2									
29 30	list(sd 3, 2,	=1.5, m 1,3,0,2,	u=c(2,1, 2,1,1,2	,3,1,2, 2,1, 1,0	0,2,0,-1, 0,1,0,0,	3, 2,0,1 -3,0,1,2	1,3,1, 1 2,0, 2,0	1,2,-3,2,0 0,3,0,2,	), 0,1,1,- -2,2,-2,-1	3,3, 1,-3,0,-3,0, 3,-3,1,- 1,3, 2,0,3,0,2, -2,1,2),	1,-

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,2,1,1,0,0, NA,NA,NA,NA,NA,0.5,2,0,1,
3		NA,NA,NA,NA,NA,2,0,1, NA,NA,NA,NA,NA,NA,1,0, NA,NA,NA,NA,NA,NA,NA,1), .Dim = c(7,8)))
4		
5		# chain 3
6 7 8		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),
9 10		d = structure(.Data =c(NA,0,1,0,0,-2,0,0, NA,NA,0,1,-2,0,-1,0, NA,NA,NA,2,0,1,0,2, NA,NA,NA,NA,0,1,2,0,
11 12		NA,NA,NA,NA,NA,1,1,1, NA,NA,NA,NA,NA,NA,-1,2, NA,NA,NA,NA,NA,NA,NA,2), .Dim = c(7,8)))
13		
14 15	L.6.9	WinBUGS code for number of units of receiving allogeneic blood transfusions (Moderate risk group)
16		Units Transfused - Moderate risk
17		
18		# Normal likelihood, identity link
19		# Random effects model for multi-arm trials
20		model{
21		for(i in 1:ns){ # LOOP THROUGH STUDIES
22		w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
23		delta[i,1] <- 0 # treatment effect is zero for control arm
24		mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
25		for (k in 1:na[i]) {
26		<pre>var[i,k] &lt;- pow(se[i,k],2) # calculate variances</pre>
27		prec[i,k] <- 1/var[i,k] # set precisions
28		y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
29		theta[i,k] <- mu[i] + delta[i,k] # model for linear predictor
30		#Deviance contribution
31		dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]

1	}
2	# summed residual deviance contribution for this trial
3	resdev[i] <- sum(dev[i,1:na[i]])
4	for (k in 2:na[i]) { # LOOP THROUGH ARMS
5	# trial-specific LOR distributions
6	delta[i,k] ~ dnorm(md[i,k],taud[i,k])
7	# mean of LOR distributions, with multi-arm trial correction
8	md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
9	# precision of LOR distributions (with multi-arm trial correction)
10	taud[i,k] <- tau *2*(k-1)/k
11	# adjustment, multi-arm RCTs
12	w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
13	# cumulative adjustment for multi-arm trials
14	sw[i,k] <- sum(w[i,1:k-1])/(k-1)
15	}
16	}
17	totresdev <- sum(resdev[]) #Total Residual Deviance
18	d[1]<-0 # treatment effect is zero for control arm
19	# vague priors for treatment effects
20	for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
21	sd ~ dunif(0,5) # vague prior for between-trial SD
22	tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
23	# Provide estimates of treatment effects T[k] on the natural scale
24	# Given a Mean Effect, meanA, for 'standard' treatment A,
25	# with precision (1/variance) precA
26	A ~ dnorm(meanA,precA)
27	for (k in 1:nt) { T[k] <- A + d[k] }
28	for (k in 1:nt) {
29	rk[k]<-rank(d[],k)

1	best[k]<-equals(rank(d[],k),1)}										
2	for (c in 1:(nt-1))										
3	{ for (k in (c+1):nt)										
4	{ D[c,k] <- d[k] - d[c]}}										
5	}		#	# *** PR	OGRAM	ENDS					
6											
7											
8	Data										
9	# ns=	number	of studi	es; nt=n	umber o	of treatm	ents				
10	list(ns	=16, nt=	4, mean	A=-1, pr	ecA=1)						
11											
12	t[,1]	t[,2]	t[,3]	y[,1]	y[,2]	y[,3]	se[,1] se[,2]	se[,3] na[]			
13	1	3	NA	1.68	0.82	NA	0.330358657	0.259513119	NA	2	
14	1	3	NA	0.71	0.05	NA	0.209489175	0.049193496	NA	2	
15	1	3	NA	1.9	2.36	NA	0.221359436	0.189748638	NA	2	
16	1	3	NA	1.06	0.54	NA	0.133789717	0.097375825	NA	2	
17	1	3	NA	2.29	1.02	NA	0.305 0.28	NA 2			
18	1	3	NA	1.74	0.22	NA	0.209960314	0.178922702	NA	2	
19	1	3	4	2.68	1.26	3.49	0.122474487	0.121854359	0.104	257207	3
20	1	2	NA	3.58	2.25	NA	0.453219961	0.275118156	NA	2	
21	1	2	NA	3.46	2.29	NA	0.214373231	0.126118525	NA	2	
22	1	2	NA	2.5	0.46	NA	0.538998189	0.316415941	NA	2	
23	1	2	NA	1.6	1.8	NA	0.208710326	0.1394274	NA	2	
24	1	2	NA	1.89	0.71	NA	0.12303658	0.110308658	NA	2	
25	1	2	NA	1.55	0.55	NA	0.089461351	0.056597998	NA	2	
26	1	2	NA	0.84	0.31	NA	0.159099026	0.113137085	NA	2	
27	1	2	NA	1.11	0.76	NA	0.216898594	0.118585412	NA	2	
28	1	2	NA	2.2	0.8	NA	0.223606798	0.178885438	NA	2	
29											

1	
2	
3	
4	END
5	
6	
7	
8	Initial Values
9	#chain 1
10	list(d=c( NA, 0,0,0), sd=1, mu=c(0,0,0,0,0, 0,0,0,0,0, 0,1,1,1,0, 0))
11	#chain 2
12	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))
13	#chain 3
14	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))
15 16	<i>L.6.10</i> WinBUGS code for assessment of baseline risk of mortality (High risk group)- <i>for use in economic model</i>
17	
18	# Binomial likelihood, logit link
19	# Baseline random effects model
20	model{
21	for (i in 1:ns){ # LOOP THROUGH STUDIES
22	r[i] ~ dbin(p[i],n[i]) # Likelihood
23	logit(p[i]) <- mu[i] # Log-odds of response
24	mu[i] ~ dnorm(m,tau.m) # Random effects model
25	}
26	mu.new ~ dnorm(m,tau.m) # predictive dist. (log-odds)
27	m ~ dnorm(0,.0001) # vague prior for mean
28	var.m <- 1/tau.m # between-trial variance
29	tau.m <- pow(sd.m,-2) # between-trial precision = (1/between-trial variance)

1	sd.m ′	~ dunif(0,5)	# vague prior for between-trial SD			
2	#tau.r	#tau.m ~ dgamma(0.001,0.001)				
3	#sd.m	<- sqrt(var.m)				
4	logit(F	R) <- m	# posterior probability of response			
5	logit(F	R.new) <- mu.ne	ew # predictive probability of response			
6	}					
7	Data					
8	list(ns	=24)	iber of studies			
9						
10	r[]	n[]				
11	1	41				
12	15	23				
13	1	40				
14	2	29				
15	0	25				
16	3	97				
17	4	50				
18	0	23				
19	3	96				
20	1	165				
21	2	31				
22	3	278				
23	1	59				
24	3	150				
25	3	20				
26	1	14				
27	4	40				
28	4	19				
29	0	16				

1	0	31	
2	2	106	
3	2	45	
4	2	75	
5	5	177	
6	END		
7	Inits		
8	list(mu	=c( 0,0,0,0,0, 0,0	0,0,0,0, 0,0,0,0,0, 0,0,0,0,0,0,0,0,0,0
9	list(mu	= c(1,-1,-1,-1,-1,	-1,-1,-1,-1,-1, -1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-1,-1), sd.m=2, m= -1)
10	list(mu	= c(1,1,1,1,1, 1,	,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1,1,1), sd.m = 0.5, m = 1)
11			
12 13 14	L.6.11 Wi for	nBUGS code for use in economi	assessment of baseline risk of mortality (Moderate risk group)- ic model
15	# Bino	mial likelihood, lo	ogit link
16	# Base	line random effe	cts model
17	model	{ #	*** PROGRAM STARTS
18	for (i ir	1:ns){ #	LOOP THROUGH STUDIES
19	r[i] ^	<sup>,</sup> dbin(p[i],n[i])	# Likelihood
20	logit	(p[i]) <- mu[i]	# Log-odds of response
21	mu[i	] ~ dnorm(m,tau.	.m) # Random effects model
22	}		
23	mu.ne	w ~ dnorm(m,tau	n.m) # predictive dist. (log-odds)
24	m ~ dr	orm(0,.0001)	# vague prior for mean
25	var.m	<- 1/tau.m	# between-trial variance
26	tau.m	<- pow(sd.m,-2)	<pre># between-trial precision = (1/between-trial variance)</pre>
27	sd.m ~	dunif(0,5)	# vague prior for between-trial SD
28	#tau.m	n ~ dgamma(0.00	1,0.001)
29	#sd.m	<- sqrt(var.m)	

1	logit(	R) <- m # p	oosterior probability of response
2	logit(	R.new) <- mu.new	# predictive probability of response
3	}		
4	Data		
5	list(ns	s=10) # ns=number	of studies
6			
7	r[]	n[]	
8	0	62	
9	1	38	
10	0	78	
11	0	100	
12	0	42	
13	1	35	
14	0	50	
15	0	35	
16	0	86	
17	0	57	
18			
19	END		
20	Inits		
21	list(m	u=c( 0,0,0,0,0, 0,0,	0,0,0), sd.m=1, m=0)
22	list(m	u = c(1,-1,-1,-1,-1, -	·1,-1,-1,-1,-1), sd.m=2, m= -1)
23	list(m	u = c(1,1,1,1,1, 1,1,	,1,1,1), sd.m = 0.5, m = 1)

1

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2

3

4

5

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