

Version 2.0

# **Preterm Labour and Birth**

Appendices I & J

Clinical Guideline <...> Methods, evidence and recommendations 1 June 2015

Draft for Consultation

Commissioned by the National Institute for Health and Care Excellence

### Disclaimer

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## Appendices

## <sup>2</sup> Appendix A: Scope

3 The scope is presented in a separate document.

# **Appendix B: Stakeholders**

5 The stakeholders are presented in a separate document.

# **6** Appendix C: Declarations of interest

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# 8 Appendix D: Review protocols

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# **Appendix E: Search strategies**

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# 12 Appendix F:PRISMA flow diagrams

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## 14 Appendix G: Excluded studies

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# 16 Appendix H: Evidence tables

17 The evidence tables are presented in a separate document.

# 18 Appendix I: Forest plots

## ka Information and support

20 No forest plots were generated for this review question.

### Prophylactic vaginal progesterone and prophylactic **2**2 cervical cerclage 22

1.23 Prophylactic progesterone

### 1.2241 Vaginal progesterone versus no treatment in women with a previous history 25 spontaneous preterm birth

### Figure 1: Preterm birth less than 34 weeks



Test for subgroup differences: Not applicable

26

### Figure 2: Preterm birth less than 37 weeks



Test for subgroup differences: Not applicable

### 27

### Figure 3: Neonatal sepsis

			-							
•	Progeste	rone	N o treati	ment		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-H, Fixe	ed, 95% Cl	
1.5.2 Vaginal										
Akbari 2009	0	69	4	72	55.7%	0.12 [0.01, 2.11]			<u> </u>	
Majhi 2009	0	50	3	50	44.3%	0.14 [0.01, 2.70]		-	<u> </u>	
Subtotal (95% CI)		119		122	100.0%	0.13 [0.02, 1.01]				
Total events	0		7							
Heterogeneity: Chi <sup>2</sup> =	0.01, df = 1	(P = 0.9	92); I² = 0%	6						
Test for overall effect:	Z = 1.95 (P	= 0.05)								
								01 1		100
							Eavours n	U.I I	Favours no tre	atment
							i avouro pr	responsed of the	T Greate He the	SHOT SHEET

Test for subgroup differences: Not applicable

# I.282 Vaginal progesterone versus placebo in women with a previous history29 spontaneous preterm birth (singletons)

### Figure 4: Preterm birth less than 34 weeks



Favours progesterone Favours placebo

Test for subgroup differences: Not applicable

### 30

### Figure 5: Preterm birth less than 37 weeks

	Progeste	rone	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
2.6.2 Vaginal							
Cetingoz 2011	9	37	17	34	28.9%	0.49 [0.25, 0.94]	
da Fonseca 2003	10	72	20	70	28.2%	0.49 [0.25, 0.96]	
O'Brien 2007	129	309	123	302	42.9%	1.03 [0.85, 1.24]	_ +
Subtotal (95% CI)		418		406	100.0%	0.67 [0.37, 1.21]	
Total events	148		160				
Heterogeneity: Tau <sup>2</sup> =	= 0.21; Chi <b></b>	= 8.27,	df = 2 (P :	= 0.02)	; I <b>²</b> = 76%		
Test for overall effect:	Z = 1.32 (F	<sup>e</sup> = 0.19)	)				
						F	avours progesterone Favours placebo

Test for subgroup differences: Not applicable

## Figure 6: Preterm birth less than 37 weeks: sub group analysis of therapy started before and after 20 weeks

	Progeste	rone	Placeb	00		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
3.1.1 Therapy comme	ences befo	re 20 w	eeks				
O'Brien 2007 Subtotal (95% CI)	129	309 <b>309</b>	123	302 <b>302</b>	100.0% 1 <b>00.0%</b>	1.03 [0.85, 1.24] 1.03 [0.85, 1.24]	•
Total events	129		123				
Heterogeneity: Not app	plicable						
Test for overall effect:	Z = 0.26 (P	= 0.80)					
3.1.2 Therapy comme	ences after	20 wee	eks				
da Fonseca 2003	10	72	20	70	53.4%	0.49 [0.25, 0.96]	
Cetingoz 2011	9	37	17	34	46.6%	0.49 [0.25, 0.94]	
Subtotal (95% CI)		109		104	100.0%	0.49 [0.30, 0.78]	$\bullet$
Total events	19		37				
Heterogeneity: Chi <sup>2</sup> =	0.00, df = 1	(P = 1.0	00); l <sup>2</sup> = 0 <sup>4</sup>	%			
Test for overall effect:	Z = 2.96 (P	= 0.003	3)				
						Fa	0.1 0.2 0.5 1 2 5 10 Nours progesterone Favours placebo

Test for subgroup differences:  $Chi^2 = 8.09$ , df = 1 (P = 0.004), I<sup>2</sup> = 87.6%

## I.23 Prophylactic cervical cerclage

Figure 7: Prop	hylact	ic cel	rvical	cer	clage	versus no cerclag	e- perinatal death
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.1.1 History-indicate	ed cerclag	e vs no	cerclage	)			
Ezechi 2004	0	39	2	42	1.9%	0.21 [0.01, 4.34]	
Rush 1984	9	96	9	98	6.9%	1.02 [0.42, 2.46]	+
MRC/RCOG 1993	53	635	66	629	51.3%	0.80 [0.56, 1.12]	
Subtotal (95% CI)		770		769	60.0%	0.80 [0.58, 1.10]	•
Total events	62		77				
Heterogeneity: Chi <sup>2</sup> =	1.03, df = 3	2 (P = 0.	60); I <sup>z</sup> = I	0%			
Test for overall effect	Z=1.35 (F	P = 0.18)	)				
1.1.2 One-off ultraso	und-indica	ted cer	clage in l	high ris	sk for PTI	L vs no cerclage	
To 2004	2	26	3	30	2.2%	0.77 [0.14, 4.25]	
Subtotal (95% CI)		26		30	2.2%	0.77 [0.14, 4.25]	-
Total events	2		3				
Heterogeneity: Not ap	plicable						
Test for overall effect	Z = 0.30 (F	P = 0.76)	)				
1.1.3 Serial ultrasou	nd-indicate	ed cercl	age in hi	gh risk	for PTL	vs no cerclage	
Althuisius 2001	0	19	3	16	2.9%	0.12 [0.01, 2.19]	
Berghella 2004	4	25	4	22	3.3%	0.88 [0.25, 3.11]	
Rust 2000	7	61	5	66	3.7%	1.51 [0.51, 4.52]	
Owen 2009	13	148	25	152	19.1%	0.53 [0.28, 1.00]	
Subtotal (95% CI)		253		256	29.0%	0.66 [0.41, 1.06]	•
Total events	24		37				
Heterogeneity: Chi <sup>2</sup> =	4.17, df = 3	3 (P = 0.	24); I <sup>2</sup> = :	28%			
Test for overall effect	Z=1.72 (F	P = 0.09)	)				
1.1.4 One-off ultraso	und-indica	ted cer	clage in l	low/un	specified	risk for PTL vs no cerclage	
Berghella 2004	0	3	0	7		Not estimable	
Rust 2000	5	43	2	37	1.7%	2.15 [0.44, 10.44]	
To 2004	7	101	9	96	7.1%	0.74 [0.29, 1.91]	
Subtotal (95% CI)		147		140	8.8%	1.01 [0.46, 2.22]	<b>•</b>
Total events	12		11				
Heterogeneity: Chi <sup>2</sup> =	1.30, df = 1	1 (P = 0.	26); l <sup>a</sup> = ;	23%			
Test for overall effect	Z = 0.01 (F	P = 0.99)	)				
Total (95% CI)		1196		1195	100.0%	0.78 [0.61, 1.00]	•
Total events	100		128				
Heterogeneity: Chi <sup>2</sup> =	7.10, df = !	9 (P = 0.	63); I <sup>z</sup> = I	0%			0.002 0.1 1 10 500
Test for overall effect	Z = 1.99 (F	P = 0.05)	)				Favours experimental Favours control
Test for subgroup diff	ferences: C	hi <sup>2</sup> = 0.9	92, df = 3	(P = 0	.82), I <sup>z</sup> = (	1%	

Experimental         Control         Risk Ratio         Risk Ratio           Study or Subgroup         Events         Total         Events         Total         Weight         M-H, Fixed, 95% CI           1.2.2 One-off ultrasound-indicated cerclage         Image: cerclage         Image: cerclage         M-H, Fixed, 95% CI           To 2004         2         26         30         6.8%         0.77 [0.14, 4.25]           Subtotal (95% CI)         26         30         6.8%         0.77 [0.14, 4.25]           Total events         2         3         6.8%         0.77 [0.14, 4.25]           Total events         2         3         6.8%         0.77 [0.14, 4.25]           Total events         2         3         6.8%         0.77 [0.14, 4.25]           Test for overall effect: Z = 0.30 (P = 0.76)               L2.3 Serial ultrasound-indicate         cerclage                Owen 2009         16         148         18         153         43.0%         0.92 [0.49, 1.73]             Subtotal (95% CI)         234         241         72.5%         0.84 [0.51, 1.37]
Study or Subgroup         Events         Total         Events         Total         Weight         M-H, Fixed, 95% Cl         M-H, Fixed, 95% Cl           1.2.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage         Total events         2         26         3         30         6.8%         0.77 [0.14, 4.25]           Subtotal (95% Cl)         26         30         6.8%         0.77 [0.14, 4.25]         Image: Comparison of the comparis
1.2.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage         To 2004       2       26       3       30       6.8%       0.77 [0.14, 4.25]         Subtotal (95% Cl)       26       30       6.8%       0.77 [0.14, 4.25]         Total events       2       3         Heterogeneity: Not applicable       7
To 2004       2       26       3       30 $6.8\%$ $0.77 [0.14, 4.25]$ Subtotal (95% CI)       26       30 $6.8\%$ $0.77 [0.14, 4.25]$ Total events       2       3         Heterogeneity: Not applicable       Test for overall effect: $Z = 0.30$ (P = $0.76$ ) <b>1.2.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage</b> Berghella 2004 $6$ 25 $6$ 22 $15.5\%$ $0.88 [0.33, 2.33]$ Owen 2009       16       148       18       153 $43.0\%$ $0.92 [0.49, 1.73]$ Rust 2000       3       61       6       64 $14.0\%$ $0.54 [0.14, 2.07]$ Subtotal (95% CI)       234       241 $72.5\%$ $0.84 [0.51, 1.37]$ Total events       25       30         Heterogeneity: Chi <sup>2</sup> = 0.50, df = 2 (P = 0.78); I <sup>2</sup> = 0\%         Test for overall effect $Z = 0.70$ (P = $0.48$ ) <b>1.2.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004       1       3       2       7 $2.9\%$ $1.17 [0.16, 8.48]$ To 2001       4       43       3       37 $7.8\%$ $1.15 [0.27, 4.80]$
Subtotal (95% Cl)       26       30 $6.8\%$ $0.77 [0.14, 4.25]$ Total events       2       3         Heterogeneity: Not applicable       Test for overall effect $Z = 0.30$ (P = 0.76) <b>1.2.3 Serial ultrasound-indicated cerctage in high risk for PTL vs no cerctage</b> Berghella 2004       6       25       6       22       15.5%       0.88 [0.33, 2.33]         Owen 2009       16       148       18       153       43.0%       0.92 [0.49, 1.73]         Rust 2000       3       61       6       64       14.0%       0.54 [0.14, 2.07]         Subtotal (95% Cl)       234       241       72.5%       0.88 [0.51, 1.37]
Total events       2       3         Heterogeneity: Not applicable       Test for overall effect: $Z = 0.30$ (P = 0.76) <b>1.2.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage</b> Berghella 2004       6       25       6       22       15.5%       0.88 [0.33, 2.33]         Owen 2009       16       148       18       153       43.0%       0.92 [0.49, 1.73]         Rust 2000       3       61       6       64       14.0%       0.54 [0.14, 2.07]         Subtoal (95% Cl)       234       241       72.5%       0.84 [0.51, 1.37]         Total events       25       30         Heterogeneity: Chi <sup>P</sup> = 0.50, df = 2 (P = 0.78); I <sup>P</sup> = 0%         Test for overall effect: $Z = 0.70$ (P = 0.48) <b>1.2.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004       1       3       2       7       2.9%       1.17 [0.16, 8.48]
Heterogeneity: Not applicable Test for overall effect: $Z = 0.30$ (P = 0.76) <b>1.2.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage</b> Berghella 2004       6       25       6       22       15.5%       0.88 [0.33, 2.33]         Owen 2009       16       148       18       153       43.0%       0.92 [0.49, 1.73]         Rust 2000       3       61       6       66       14.0%       0.54 [0.14, 2.07]         Subtotal (95% CI)       234       241       72.5%       0.84 [0.51, 1.37]         Total events       25       30         Heterogeneity: Chi <sup>2</sup> = 0.50, df = 2 (P = 0.78); I <sup>2</sup> = 0%         Test for overall effect: Z = 0.70 (P = 0.48) <b>1.2.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004       1       3       2       7       2.9%       1.17 [0.16, 8.48]         Rust 2000       4       43       3       37       7.8%       1.15 [0.27, 4.80]
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Berghella 2004       6       25       6       22       15.5%       0.88 [0.33, 2.33]         Owen 2009       16       148       18       153       43.0%       0.92 [0.49, 1.73]         Rust 2000       3       61       6       66       14.0%       0.54 [0.14, 2.07]         Subtotal (95% Cl)       234       241       72.5%       0.84 [0.51, 1.37]         Total events       25       30         Heterogeneity: Chi² = 0.50, df = 2 (P = 0.78); I² = 0%         Test for overall effect: Z = 0.70 (P = 0.48)         1.2.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage         Berghella 2004       1       3       2       7       2.9%       1.17 [0.16, 8.48]         Rust 2000       4       43       3       37       7.8%       1.15 [0.27, 4.80]
Owen 2009       16       148       18       153       43.0%       0.92 [0.49, 1.73]         Rust 2000       3       61       6       66       14.0%       0.54 [0.14, 2.07]         Subtotal (95% Cl)       234       241       72.5%       0.84 [0.51, 1.37]         Total events       25       30         Heterogeneity: Chi <sup>2</sup> = 0.50, df = 2 (P = 0.78); I <sup>2</sup> = 0%         Test for overall effect: Z = 0.70 (P = 0.48)         1.2.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage         Berghella 2004       1       3       2       7       2.9%       1.17 [0.16, 8.48]         Rust 2000       4       43       3       37       7.8%       1.15 [0.27, 4.80]
Rust 2000       3       61       6       66       14.0%       0.54 [0.14, 2.07]         Subtotal (95% Cl)       234       241       72.5%       0.84 [0.51, 1.37]         Total events       25       30         Heterogeneity: Chi <sup>2</sup> = 0.50, df = 2 (P = 0.78); I <sup>2</sup> = 0%         Test for overall effect Z = 0.70 (P = 0.48)         1.2.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage         Berghella 2004       1       3       2       7       2.9%       1.17 [0.16, 8.48]         Rust 2000       4       43       3       37       7.8%       1.15 [0.27, 4.80]
Subtotal (95% Cl)       234       241       72.5%       0.84 [0.51, 1.37]         Total events       25       30         Heterogeneity: Chi² = 0.50, df = 2 (P = 0.78); I² = 0%         Test for overall effect Z = 0.70 (P = 0.48) <b>1.2.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004       1       3       2       7       2.9%       1.17 [0.16, 8.48]         Rust 2000       4       43       3       37       7.8%       1.15 [0.27, 4.80]
Total events         25         30           Heterogeneity: Chi² = 0.50, df = 2 (P = 0.78); I² = 0%         Test for overall effect Z = 0.70 (P = 0.48) <b>1.2.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004         1         3         2         7         2.9%         1.17 [0.16, 8.48]
Heterogeneity: Chi² = 0.50, df = 2 (P = 0.78); l² = 0%         Test for overall effect Z = 0.70 (P = 0.48) <b>1.2.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004       1       3       2       7       2.9%       1.17 [0.16, 8.48]         Rust 2000       4       43       3       37       7.8%       1.15 [0.27, 4.80]
Test for overall effect Z = 0.70 (P = 0.48) <b>1.2.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004         1         3         2         7         2.9%         1.17 [0.16, 8.48]           Rust 2000         4         43         3         37         7.8%         1.15 [0.27, 4.80]
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Rust 2000 4 43 3 37 7.8% 1.15 [0.27, 4.80]
10 2004 7 101 4 90 10.0% 1.66 [0.50, 5.50]
Subtotal (95% Cl) 147 140 20.7% 1.40 [0.61, 3.23]
Total events 12 9
Heterogeneity: Chi <sup>2</sup> = 0.19, df = 2 (P = 0.91); I <sup>2</sup> = 0%
Test for overall effect: Z = 0.79 (P = 0.43)
Total (95% Cl) 407 411 100.0% 0.95 [0.63, 1.43]
Total events 39 42
Heterogeneity: Chi <sup>2</sup> = 1.72, df = 6 (P = 0.94); l <sup>2</sup> = 0%
Test for overall effect: Z = 0.25 (P = 0.80)
Test for subgroup differences: Chi <sup>2</sup> = 1.13, df = 2 (P = 0.57), I <sup>2</sup> = 0%

## Figure 8: Prophylactic cervical cerclage versus no cerclage- Serious neonatal morbidity

## Figure 9: : Prophylactic cervical cerclage versus no cerclage- Preterm birth before 37+0 weeks

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl			
1.7.1 History-indicated cerclage vs no cerclage										
Ezechi 2004	3	39	15	42	1.8%	0.22 [0.07, 0.69]				
Lazar 1984	18	268	13	238	4.5%	1.23 [0.62, 2.46]				
MRC/RCOG 1993	161	635	190	629	19.5%	0.84 [0.70, 1.00]	-			
Rush 1984	33	96	31	98	9.9%	1.09 [0.73, 1.62]	+			
Subtotal (95% CI)		1038		1007	35.7%	0.86 [0.59, 1.27]	+			
Total events	215		249							
Heterogeneity: Tau <sup>2</sup> =	0.09; Chi <sup>a</sup>	= 7.89,	df = 3 (P	= 0.05)	; I <sup>2</sup> = 62%	6				
Test for overall effect	Z = 0.74 (F	P = 0.46)	)							
1.7.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage										
To 2004	9	26	19	30	5.7%	0.55 [0.30, 0.99]	-			
Subtotal (95% CI)		26		30	5.7%	0.55 [0.30, 0.99]	-			
Total events	9		19							
Heterogeneity: Not ap	plicable									
Test for overall effect	Z = 1.99 (F	P = 0.05	)							
1.7.3 Serial ultrasour	nd-indicate	ed cerci	age in hi	gh risk	for PTL	vs no cerclage				
Althuisius 2001	4	19	10	16	2.6%	0.34 [0.13, 0.87]				
Berghella 2004	13	25	14	22	7.6%	0.82 [0.50, 1.34]				
Owen 2009	66	148	91	153	17.3%	0.75 [0.60, 0.94]	•			
Rust 2000	27	61	29	66	10.2%	1.01 [0.68, 1.49]				
Subtotal (95% CI)		253		257	37.6%	0.78 [0.60, 1.02]	•			
Total events	110		144							
Heterogeneity: Tau <sup>2</sup> =	0.03; Chi <sup>2</sup>	= 4.80,	df= 3 (P	= 0.19	); I² = 38%	6				
Test for overall effect	Z = 1.82 (F	P = 0.07	)							
1750										
1.7.5 One-off ultraso	und-Indica	ted cer	clage in l	low/un	specified	risk for PTL vs no cerclage				
Berghella 2004	1	3	6	7	0.9%	0.39 [0.08, 1.98]				
Rust 2000	22	43	18	37	8.8%	1.05 [0.68, 1.64]				
To 2004	32	101	44	96	11.3%	0.69 [0.48, 0.99]	1			
Subtotal (95% CI)		147		140	21.0%	0.80 [0.55, 1.16]	•			
Total events	55		68		-					
Heterogeneity: Tau* =	0.03; Chi	= 2.90,	df = 2 (P	= 0.23)	); I* = 31%	b				
Test for overall effect	Z = 1.16 (F	<sup>o</sup> = 0.25)	)							
Total (95% CD		1464		1434	100.0%	0.80 (0.69, 0.95)	•			
Total events	200	1404	490	1404	100.070	and [mast meal	•			
Hotorogeneity Tou? -	0.03-02-	- 10 11	40U	/P = 0.	001-18-2	0%				
Test for overall effect	7=264/0	2 = 0.00	, or = 11 9)	(r. = 0.)	00), 1 = 3	2 //	0.01 0.1 1 10 100			
Test for cubarous diff	2 = 2.04 (r	bi7 = 1 4	0) 86 df= 2	/P = 0	66) R-0	196	Favours experimental Favours control			
restion subgroup diff	erences; c	/01" = 1.0	00, ui = 3	(P = 0)	00), r== (	170				

## Figure 10: Prophylactic cervical cerclage versus no cerclage- Preterm birth before 34+0 weeks

••	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
1.8.1 History-indicate	ed cerclag	e vs no o	cerclage	!			
Ezechi 2004	0	39	11	42	0.3%	0.05 [0.00, 0.77]	·
MRC/RCOG 1993	92	635	113	629	39.5%	0.81 [0.63, 1.04]	-
Rush 1984	14	96	14	98	5.4%	1.02 [0.51, 2.03]	-
Subtotal (95% Cl)		770		769	45.2%	0.76 [0.40, 1.46]	
Total events	106		138				
Heterogeneity: Tau <sup>2</sup> =	: 0.17; Chi	= 4.66,	df=2 (P	= 0.10)	); I² = 57%	6	
Test for overall effect	Z = 0.81 (	P = 0.42)					
1.8.2 One-off ultraso	und-indica	ted cerc	:lage in l	hiah ris	k for PTI	vs no cerclage	
To 2004	6	26	11	30	3 5%	0.63 (0.27, 1.46)	
Subtotal (95% Cl)	·	26		30	3.5%	0.63 [0.27, 1.46]	-
Total events	6		11				-
Heterogeneity: Not ar	policable						
Test for overall effect	Z = 1.07 (	P = 0.28					
		,					
1.8.3 Serial ultrasour	nd-indicate	ed cercla	age in hi	gh risk	for PTL	vs no cerclage	
Althuisius 2001	0	19	7	16	0.3%	0.06 [0.00, 0.92]	•
Berghella 2004	10	25	11	22	6.2%	0.80 [0.42, 1.51]	
Owen 2009	42	148	57	153	23.3%	0.76 [0.55, 1.06]	
Rust 2000	13	61	15	66	5.8%	0.94 [0.49, 1.81]	
Subtotal (95% CI)		253		257	35.7%	0.77 [0.55, 1.10]	•
Total events	65		90				
Heterogeneity: Tau* =	0.03; Chi	= 3.92, (	df = 3 (P	= 0.27)	); I* = 23%	b	
Test for overall effect	Z=1.42 (	P = 0.15)					
1.8.5 One-off ultraso	und-indica	ted cerc	lage in l	iow/un:	specified	risk for PTL vs no cerclag	e
Berghella 2004	0	3	1	7	0.3%	0.67 [0.03, 12.96]	
Rust 2000	11	43	12	37	5.3%	0.79 [0.40, 1.57]	-
To 2004	22	101	25	96	10.0%	0.84 [0.51, 1.38]	-
Subtotal (95% Cl)		147		140	15.6%	0.82 [0.55, 1.22]	•
Total events	33		38				
Heterogeneity: Tau <sup>2</sup> =	: 0.00; Chi	= 0.04,	df = 2 (P	= 0.98)	); I <sup>2</sup> = 0%		
Test for overall effect	Z = 0.99 (	P = 0.32)					
Total (95% CI)		1196		1196	100.0%	0.79 [0.68, 0.93]	•
Total events	210		277				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi	= 8.88.	df = 10 (8	P = 0.5	4); I <sup>2</sup> = 0%	6	
Test for overall effect	Z = 2.87 (	P = 0.004	() ()			-	0.01 0.1 1 10 100
Test for subgroup diff	ferences: (	Chi <sup>2</sup> = 0.3	0. df = 3	(P = 0.	.96), I² = 0	1%	ravours experimental ravours control

Experimental Study or Subgroup         Events         Total         Verints         Total         Verints         Math, Fixed, 95% CI           1.9.1 History-indicated cerclage vs no cerclage         so cerclage         so cerclage         M.H., Fixed, 95% CI         M.H., Fixed, 95% CI           20204         0         39         1         42         1.0%         0.36 [0.02, 8.54]           MRC/RCOG 1993         53         635         65         629         43.8%         0.81 [0.57, 1.14]           Rush 1984         7         96         4.9%         0.82 [0.59, 1.13]             Total events         60         73         Heterogeneity. Chi <sup>2</sup> = 0.45, df = 2 (P = 0.80); P = 0.%          Test for overall effect Z = 1.21 (P = 0.23)           1.9.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage          3         5           Heterogeneity. Not applicable         26         30         3.1%         0.69 [0.18, 2.62]           Total events         3         5         5         1.06 [0.01, 2.19]            Berghelia 2004         6         25         5         22         3.6%         1.02 [0.37, 2.99]           Own 2009         21         148         33         15         1.06 [0.	3070	WEEKS	>					
Study or Subgroup         Events         Total         Events         Total         Weight         M.H, Fixed, 95% Cl         M.H, Fixed, 95% Cl           1.9.1 History-indicated cerclage vs no cerclage         vs no cerclage <th></th> <th>Experime</th> <th>ental</th> <th>Contr</th> <th>ol</th> <th></th> <th>Risk Ratio</th> <th>Risk Ratio</th>		Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
<b>1.9.1 History-indicated cerclage vs no cerclage</b> Ezechi 2004       0       39       1       42       1.0%       0.36 [0.02, 8.54]         MRC/RC006 1993       53       635       65       629       43.8%       0.81 [0.57, 1.14]         Rush 1984       7       96       7       98       4.6%       1.02 [0.37, 2.80]         Subtotal (95% CI)       770       769       49.4%       0.82 [0.59, 1.13]       1.0%         Total events       60       73	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Ezechi 2004 0 39 1 42 1.0% 0.36 [0.02, 8.54] MRC/RCOG 1993 53 635 65 629 43.8% 0.81 [0.57, 1.14] Rush 1984 7 96 7 98 4.6% 1.02 [0.37, 2.80] Subtotal (95% CI) 770 769 49.4% 0.82 [0.59, 1.13] Total events 60 73 Heterogeneity. Ch <sup>2</sup> = 0.45, df = 2 (P = 0.80); $P = 0$ % Test for overall effect Z = 1.21 (P = 0.23) <b>1.9.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage</b> To 2004 3 26 5 30 3.1% 0.69 [0.18, 2.62] Subtotal (95% CI) 26 30 3.1% 0.69 [0.18, 2.62] Total events 3 5 Heterogeneity. Not applicable Test for overall effect Z = 0.54 (P = 0.59) <b>1.9.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage</b> Althuisius 2001 0 19 3 16 2.5% 0.12 [0.01, 2.19] Berghella 2004 6 25 5 22 3.6% 1.06 [0.37, 2.99] Owen 2009 21 148 33 153 21.8% 0.66 [0.40, 1.08] Rust 2000 9 61 11 66 7.1% 0.89 [0.39, 1.99] Subtotal (95% CI) 253 257 35.0% 0.71 [0.48, 1.04] Total events 36 52 Heterogeneity. Ch <sup>2</sup> = 2.38, df = 3 (P = 0.50); F = 0% Test for overall effect Z = 1.78 (P = 0.08) <b>1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004 0 3 1 7 0.7% 0.67 [0.03, 12.96] Rust 2000 7 43 5 37 3.6% 1.20 [0.42, 3.48] <b>1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004 0 3 1 7 0.7% 0.67 [0.03, 12.96] Rust 2000 7 43 5 37 3.6% 1.20 [0.42, 3.48] <b>1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004 0 3 1 7 0.7% 0.67 [0.03, 12.96] Rust 2000 7 43 5 37 3.6% 1.20 [0.42, 2.01] <b>1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004 0 3 1 7 0.7% 0.67 [0.03, 12.96] Rust 2000 7 4 43 5 37 3.6% 1.20 [0.42, 3.48] <b>1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004 0 3 1 7 0.7% 0.67 [0.03, 12.96] Rust 2000 7 4 43 5 37 3.6% 1.20 [0.42, 3.48] <b>1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs </b>	1.9.1 History-indicate	ed cerclage	e vs no	cerclage	1			
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Ezechi 2004	0	39	1	42	1.0%	0.36 [0.02, 8.54]	
Rush 1984       7       96       7       98       4.6%       1.02 [0.37, 2.80]         Subtotal (95% CI)       770       769       49.4%       0.82 [0.59, 1.13]         Total events       60       73         Heterogeneity: Chi <sup>P</sup> = 0.45, df = 2 (P = 0.80); P = 0%       769       49.4%       0.82 [0.59, 1.13]         1.9.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage       700       30       3.1%       0.69 [0.18, 2.62]         Subtotal (95% CI)       26       30       3.1%       0.69 [0.18, 2.62]       701       700         1.9.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage       710       769       98       0.69 [0.18, 2.62]         1.9.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage       1.06 [0.17, 2.19]       710       769       710<	MRC/RCOG 1993	53	635	65	629	43.8%	0.81 [0.57, 1.14]	-
Subtotal (95% Cl)       770       769       49.4%       0.82 [0.59, 1.13]         Total events       60       73         Heterogeneity: Chi <sup>2</sup> = 0.45, df = 2 (P = 0.80); I <sup>2</sup> = 0%         Test for overall effect Z = 1.21 (P = 0.23) <b>1.9.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage</b> To 2004       3       26       5       30       3.1%       0.69 [0.18, 2.62]         Subtotal (95% Cl)       26       30       3.1%       0.69 [0.18, 2.62]         Total events       3       5         Heterogeneity: Not applicable         Test for overall effect Z = 0.54 (P = 0.59) <b>1.9.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage</b> Althuisius 2001       0       19       3       16       2.5%       0.12 [0.01, 2.19]         Berghella 2004       6       25       5       22       3.6%       1.06 [0.37, 2.99] <b>(P = 0.50)</b> Subtotal (95% Cl)       253       257       35.0%       0.71 [0.48, 1.04] <b>(P = 0.50)</b> Subtotal (95% Cl)       253       257       35.0%       0.71 [0.48, 1.04] <b>(P = 0.50)</b> 1.55 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage       1.55 (0.42, 2.01]       1	Rush 1984	7	96	7	98	4.6%	1.02 [0.37, 2.80]	
Total events       60       73         Heterogeneity: Chi <sup>2</sup> = 0.45, df = 2 (P = 0.80); P = 0%       Test for overall effect Z = 1.21 (P = 0.23) <b>1.9.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage</b> Total events       3       26       5       30       3.1%       0.69 [0.18, 2.62]         Subtotal (95% Cl)       26       30       3.1%       0.69 [0.18, 2.62]         Total events       3       5         Heterogeneity: Not applicable       Test for overall effect Z = 0.54 (P = 0.59) <b>1.9.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage</b> Althuisius 2001       0       19       3       16       2.5%       0.12 [0.01, 2.19]         Berghella 2004       6       25       5       22       3.6%       1.06 [0.37, 2.99]         Owner 2009       21       14.8       33       153       21.8%       0.66 [0.40, 1.08]         Subtotal (95% Cl)       253       257       35.0%       0.71 [0.48, 1.04]       4         Total events       36       52       52       53       257       35.0%       0.71 [0.48, 1.04]       5         Total events       36       52       53       257       35.0%       0.71 [0.48, 1.04]	Subtotal (95% CI)		770		769	49.4%	0.82 [0.59, 1.13]	•
Heterogeneity: Chi <sup>2</sup> = 0.45, df = 2 (P = 0.80);   <sup>2</sup> = 0% Test for overall effect $Z = 1.21$ (P = 0.23) <b>1.9.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage</b> To 2004 3 26 5 30 3.1% 0.69 [0.18, 2.62] Subtotal (95% CI) 26 30 3.1% 0.69 [0.18, 2.62] Total events 3 5 Heterogeneity: Not applicable Test for overall effect $Z = 0.54$ (P = 0.59) <b>1.9.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage</b> Althuisius 2001 0 19 3 16 2.5% 0.12 [0.01, 2.19] Berghella 2004 6 25 5 22 3.6% 1.06 [0.37, 2.99] Owen 2009 21 148 33 153 21.8% 0.66 [0.40, 1.08] Rust 2000 9 61 11 66 7.1% 0.89 [0.39, 1.99] Subtotal (95% CI) 253 257 35.0% 0.71 [0.48, 1.04] Total events 36 52 Heterogeneity: Chi <sup>2</sup> = 2.38, df = 3 (P = 0.50);   <sup>2</sup> = 0% Test for overall effect $Z = 1.78$ (P = 0.08) <b>1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004 0 3 1 7 0.7% 0.67 [0.03, 12.96] Rust 2000 7 43 5 37 3.6% 1.20 [0.42, 3.48] To 2004 12 101 12 96 8.3% 0.95 [0.45, 2.01] <b>Subtotal (95% CI) 147</b> 140 12.5% 1.01 [0.55, 1.83]	Total events	60		73				
Test for overall effect: $Z = 1.21$ ( $P = 0.23$ ) <b>1.9.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage</b> To 2004       3       26       5       30       3.1%       0.69 [0.18, 2.62]         Subtotal (95% Cl)       26       30       3.1%       0.69 [0.18, 2.62]         Total events       3       5         Heterogeneity: Not applicable         Test for overall effect: $Z = 0.54$ ( $P = 0.59$ ) <b>1.9.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage</b> Althuisius 2001       0       19       3       16       2.5%       0.12 [0.01, 2.19]         Berghella 2004       6       25       5       22       3.6%       1.06 [0.37, 2.99]         Owen 2009       21       148       33       153       21.8%       0.66 [0.40, 1.08]         Rust 2000       9       61       11       66       7.1%       0.89 [0.39, 1.99]         Subtotal (95% Cl)       253       257       35.0%       0.71 [0.48, 1.04] <b>4</b> Total events       36       52 <b>5</b> Heterogeneity: Chi <sup>P</sup> = 2.38, df = 3 (P = 0.50); P = 0.% <b>5 5 5 104</b> alevents	Heterogeneity: Chi <sup>2</sup> =	0.45, df = 2	2 (P = 0.	80); I <sup>2</sup> = (	0%			
1.9.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage         To 2004       3       26       5       30 $3.1\%$ $0.69 [0.18, 2.62]$ Subtotal (95% CI)       26       30 $3.1\%$ $0.69 [0.18, 2.62]$ Total events       3       5         Heterogeneity: Not applicable       Test for overall effect: $Z = 0.54$ ( $P = 0.59$ )         1.9.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage         Althuisius 2001       0       19       3       16 $2.5\%$ $0.12 [0.01, 2.19]$ Berghella 2004       6       25       5       22 $3.6\%$ $1.06 [0.37, 2.99]$ Owen 2009       21       148       33       153 $21.8\%$ $0.89 [0.39, 1.99]$ Subtotal (95% CI)       263       257 $35.0\%$ $0.71 [0.48, 1.04]$ $\bullet$ Total events       36 $52$ Heterogeneity: Chi <sup>2</sup> = 2.38, df = 3 (P = 0.50); P = 0.6%       Test for overall effect: $Z = 1.78 (P = 0.08)$ $\bullet$ $\bullet$ 1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage $\bullet$ $\bullet$ $\bullet$ Berghella 2004       0       3       1       7 $0.7\%$ $0.67 [0$	Test for overall effect	Z = 1.21 (F	P = 0.23)	)				
To 2004 3 26 5 30 3.1% 0.69 [0.18, 2.62] To 2104 3 26 5 30 3.1% 0.69 [0.18, 2.62] Total events 3 5 Heterogeneity: Not applicable Test for overall effect: $Z = 0.54$ (P = 0.59) <b>1.9.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage</b> Althuisius 2001 0 19 3 16 2.5% 0.12 [0.01, 2.19] Berghella 2004 6 25 5 22 3.6% 1.06 [0.37, 2.99] Owen 2009 21 148 33 153 21.8% 0.66 [0.40, 1.08] Rust 2000 9 61 11 66 7.1% 0.89 [0.39, 1.99] Subtotal (95% CI) 253 257 35.0% 0.71 [0.48, 1.04] Total events 36 52 Heterogeneity: Chi <sup>P</sup> = 2.38, df = 3 (P = 0.50); P = 0% Test for overall effect: $Z = 1.78$ (P = 0.08) <b>1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004 0 3 1 7 0.7% 0.67 [0.03, 12.96] Rust 2000 7 43 5 37 3.6% 1.20 [0.42, 3.48] To 2004 12 101 12 96 8.3% 0.95 [0.45, 2.01] Subtotal (95% CI) 147 140 12.5% 1.01 [0.55, 1.83]	1 9 2 One off ultraso	und_indica	tod cor	clano in l	hiah ris	k for DTI	ve no corclago	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	To 2004	2 oru	26	ciage ii i	20	2.10	0 60 10 10 2 621	
Total events 3 5 Heterogeneity: Not applicable Test for overall effect $Z = 0.54$ (P = 0.59) <b>1.9.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage</b> Althuisius 2001 0 19 3 16 2.5% 0.12 [0.01, 2.19] Berghella 2004 6 25 5 22 3.6% 1.06 [0.37, 2.99] Owen 2009 21 148 33 153 21.8% 0.66 [0.40, 1.08] Rust 2000 9 61 11 66 7.1% 0.89 [0.39, 1.99] Subtotal (95% CI) 253 257 35.0% 0.71 [0.48, 1.04] Total events 36 52 Heterogeneity: Chi <sup>P</sup> = 2.38, df = 3 (P = 0.50); I <sup>P</sup> = 0% Test for overall effect $Z = 1.78$ (P = 0.08) <b>1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004 0 3 1 7 0.7% 0.67 [0.03, 12.96] Rust 2000 7 43 5 37 3.6% 1.20 [0.42, 3.48] To 2004 12 101 12 96 8.3% 0.95 [0.45, 2.01] Subtotal (95% CI) 147 140 12.5% 1.01 [0.55, 1.83]	Subtotal (95% Cl)	2	20	5	30	3.1%	0.69 [0.16, 2.62]	
Heterogeneity: Not applicable         Test for overall effect: $Z = 0.54$ (P = 0.59) <b>1.9.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage</b> Althuisius 2001       0       19       3       16       2.5%       0.12 [0.01, 2.19]         Berghella 2004       6       25       5       22       3.6%       1.06 [0.37, 2.99]         Owen 2009       21       148       33       153       21.8%       0.66 [0.40, 1.08]         Rust 2000       9       61       11       66       7.1%       0.89 [0.39, 1.99]         Subtotal (95% CI)       253       257       35.0%       0.71 [0.48, 1.04]         Total events       36       52         Heterogeneity: Chi <sup>#</sup> = 2.38, df = 3 (P = 0.50); P = 0%         Test for overall effect: $Z = 1.78$ (P = 0.08) <b>1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004       0       3       1       7       0.7%       0.67 [0.03, 12.96]       Image: Colored c	Total events	2	20	6	50	0.170	0.00 [0.10, 2.02]	
Test for overall effect $Z = 0.54$ (P = 0.59) <b>1.9.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage</b> Althuisius 2001 0 19 3 16 2.5% 0.12 [0.01, 2.19] Berghella 2004 6 25 5 22 3.6% 1.06 [0.37, 2.99] Owen 2009 21 148 33 153 21.8% 0.66 [0.40, 1.08] Rust 2000 9 61 11 66 7.1% 0.89 [0.39, 1.99] Subtotal (95% CI) 253 257 35.0% 0.71 [0.48, 1.04] Total events 36 52 Heterogeneity: Chi <sup>P</sup> = 2.38, df = 3 (P = 0.50); P = 0% Test for overall effect $Z = 1.78$ (P = 0.08) <b>1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004 0 3 1 7 0.7% 0.67 [0.03, 12.96] Rust 2000 7 43 5 37 3.6% 1.20 [0.42, 3.48] To 2004 12 101 12 96 8.3% 0.95 [0.45, 2.01] Subtotal (95% CI) 147 140 12.5% 1.01 [0.55, 1.83]	Heterogeneity Not an	olicable		5				
<b>1.9.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage</b> Althuisius 2001       0       19       3       16       2.5%       0.12 [0.01, 2.19]         Berghella 2004       6       25       5       22       3.6%       1.06 [0.37, 2.99]         Owen 2009       21       148       33       153       21.8%       0.66 [0.40, 1.08]         Rust 2000       9       61       11       66       7.1%       0.89 [0.39, 1.99]         Subtotal (95% CI)       253       257       35.0%       0.71 [0.48, 1.04]       •         Total events       36       52       •       •       •         Heterogeneity: Chi <sup>P</sup> = 2.38, df = 3 (P = 0.50); P = 0%       •       •       •         Test for overall effect Z = 1.78 (P = 0.08)       •       •       •       • <b>1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> •       •       •         Berghella 2004       0       3       1       7       0.7%       0.67 [0.03, 12.96]       •         Rust 2000       7       43       5       37       3.6%       1.20 [0.42, 3.48]       •       •         To 2004       12       101       12 <td>Tect for overall effect</td> <td>7 = 0.64/5</td> <td>- 0.60</td> <td>、 、</td> <td></td> <td></td> <td></td> <td></td>	Tect for overall effect	7 = 0.64/5	- 0.60	、 、				
1.9.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage         Althuisius 2001       0       19       3       16       2.5%       0.12 [0.01, 2.19]         Berghella 2004       6       25       5       22       3.6%       1.06 [0.37, 2.99]         Owen 2009       21       148       33       153       21.8%       0.66 [0.40, 1.08]         Rust 2000       9       61       11       66       7.1%       0.89 [0.39, 1.99]         Subtotal (95% CI)       253       257       35.0%       0.71 [0.48, 1.04]         Total events       36       52         Heterogeneity: Chi <sup>P</sup> = 2.38, df = 3 (P = 0.50); P = 0%       7       9.067 [0.03, 12.96]         Test for overall effect Z = 1.78 (P = 0.08)       9       0.67 [0.03, 12.96]         Rust 2000       7       43       5       37       3.6%       1.20 [0.42, 3.48]         To 2004       12       101       12       96       8.3%       0.95 [0.45, 2.01]       4         Subtotal (95% CI)       147       140       12.5%       1.01 [0.55, 1.83]       4	restion overall ellect	Z = 0.54 (r	- 0.55	,				
Althuisius 2001       0       19       3       16       2.5%       0.12 [0.01, 2.19]         Berghella 2004       6       25       5       22       3.6%       1.06 [0.37, 2.99]         Owen 2009       21       148       33       153       21.8%       0.66 [0.40, 1.08]         Rust 2000       9       61       11       66       7.1%       0.89 [0.39, 1.99]         Subtotal (95% CI)       253       257       35.0%       0.71 [0.48, 1.04]         Total events       36       52         Heterogeneity: Chi <sup>2</sup> = 2.38, df = 3 (P = 0.50); P = 0%         Test for overall effect Z = 1.78 (P = 0.08) <b>1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004       0       3       1       7       0.7%       0.67 [0.03, 12.96]         Rust 2000       7       43       5       37       3.6%       1.20 [0.42, 3.48]	1.9.3 Serial ultrasour	nd-indicate	d cercl	age in hi	gh risk	for PTL	vs no cerclage	
Berghella 2004       6       25       5       22       3.6%       1.06 [0.37, 2.99]         Owen 2009       21       148       33       153       21.8%       0.66 [0.40, 1.08]         Rust 2000       9       61       11       66       7.1%       0.89 [0.39, 1.99]         Subtotal (95% CI)       253       257       35.0%       0.71 [0.48, 1.04]         Total events       36       52         Heterogeneity: Chi <sup>2</sup> = 2.38, df = 3 (P = 0.50); P = 0%         Test for overall effect Z = 1.78 (P = 0.08) <b>1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004       0       3       1       7       0.7%       0.67 [0.03, 12.96]         Rust 2000       7       43       5       37       3.6%       1.20 [0.42, 3.48]       Image: Chi and the correlage in	Althuisius 2001	0	19	3	16	2.5%	0.12 [0.01, 2.19]	← <u></u>
Owen 2009       21       148       33       153       21.8%       0.66 [0.40, 1.08]         Rust 2000       9       61       11       66       7.1%       0.89 [0.39, 1.99]         Subtotal (95% CI)       253       257       35.0%       0.71 [0.48, 1.04]         Total events       36       52         Heterogeneity: Chi <sup>P</sup> = 2.38, df = 3 (P = 0.50); P = 0%       Test for overall effect Z = 1.78 (P = 0.08) <b>1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004       0       3       1       7       0.7%       0.67 [0.03, 12.96]         Rust 2000       7       43       5       37       3.6%       1.20 [0.42, 3.48] $\bullet$ To 2004       12       101       12       96       8.3%       0.95 [0.45, 2.01] $\bullet$ Subtotal (95% CI)       147       140       12.5%       1.01 [0.55, 1.83]	Berghella 2004	6	25	5	22	3.6%	1.06 [0.37, 2.99]	
Rust 2000       9       61       11       66       7.1%       0.89 [0.39, 1.99]         Subtotal (95% Cl)       253       257       35.0%       0.71 [0.48, 1.04]         Total events       36       52         Heterogeneity: Chi <sup>2</sup> = 2.38, df = 3 (P = 0.50); P = 0%       Test for overall effect Z = 1.78 (P = 0.08) <b>1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004       0       3       1       7       0.7%       0.67 [0.03, 12.96]         Rust 2000       7       43       5       37       3.6%       1.20 [0.42, 3.48]         To 2004       12       101       12       96       8.3%       0.95 [0.45, 2.01]         Subtotal (95% Cl)       147       140       12.5%       1.01 [0.55, 1.83]	Owen 2009	21	148	33	153	21.8%	0.66 [0.40, 1.08]	
Subtotal (95% Cl)       253       257       35.0%       0.71 [0.48, 1.04]         Total events       36       52         Heterogeneity: Chi <sup>2</sup> = 2.38, df = 3 (P = 0.50); P = 0%         Test for overall effect Z = 1.78 (P = 0.08) <b>1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004       0       3       1       7       0.7%       0.67 [0.03, 12.96]         Rust 2000       7       43       5       37       3.6%       1.20 [0.42, 3.48]         To 2004       12       101       12       96       8.3%       0.95 [0.45, 2.01]         Subtotal (95% Cl)       147       140       12.5%       1.01 [0.55, 1.83]       •	Rust 2000	9	61	11	66	7.1%	0.89 (0.39, 1.99)	-
Total events       36       52         Heterogeneity: Chi <sup>2</sup> = 2.38, df = 3 (P = 0.50); I <sup>2</sup> = 0%         Test for overall effect Z = 1.78 (P = 0.08) <b>1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004       0       3       1       7       0.7%       0.67 [0.03, 12.96]         Rust 2000       7       43       5       37       3.6%       1.20 [0.42, 3.48]         To 2004       12       101       12       96       8.3%       0.95 [0.45, 2.01]         Subtotal (95% Cl)       147       140       12.5%       1.01 [0.55, 1.83]       •	Subtotal (95% CI)		253		257	35.0%	0.71 [0.48, 1.04]	•
Heterogeneity: Chi <sup>2</sup> = 2.38, df = 3 (P = 0.50); P = 0%         Test for overall effect: Z = 1.78 (P = 0.08) <b>1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage</b> Berghella 2004       0       3       1       7       0.7%       0.67 [0.03, 12.96]         Rust 2000       7       43       5       37       3.6%       1.20 [0.42, 3.48]         To 2004       12       101       12       96       8.3%       0.95 [0.45, 2.01]         Subtotal (95% Cl)       147       140       12.5%       1.01 [0.55, 1.83]       •	Total events	36		52				
1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage         Berghella 2004       0       3       1       7       0.7%       0.67 [0.03, 12.96]         Rust 2000       7       43       5       37       3.6%       1.20 [0.42, 3.48]         To 2004       12       101       12       96       8.3%       0.95 [0.45, 2.01]         Subtotal (95% Cl)       147       140       12.5%       1.01 [0.55, 1.83]	Heterogeneity: Chi <sup>2</sup> =	2.38, df = 3	3 (P = 0.	.50); I <sup>2</sup> = (	0%			
1.9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage         Berghella 2004       0       3       1       7       0.7%       0.67 [0.03, 12.96]         Rust 2000       7       43       5       37       3.6%       1.20 [0.42, 3.48]         To 2004       12       101       12       96       8.3%       0.95 [0.45, 2.01]         Subtotal (95% Cl)       147       140       12.5%       1.01 [0.55, 1.83]       •••	Test for overall effect:	Z = 1.78 (F	P = 0.08	)				
Berghella 2004         0         3         1         7         0.7%         0.67 [0.03, 12.96]           Rust 2000         7         43         5         37         3.6%         1.20 [0.42, 3.48]           To 2004         12         101         12         96         8.3%         0.95 [0.45, 2.01]           Subtotal (95% Cl)         147         140         12.5%         1.01 [0.55, 1.83]         Image: Close 100 (0.00)	1.9.5 One-off ultraso	und-indica	ted cer	clage in l	ow/un:	specified	risk for PTL vs no cerclage	
Rust 2000         7         43         5         37         3.6%         1.20 [0.42, 3.48]           To 2004         12         101         12         96         8.3%         0.95 [0.45, 2.01]           Subtotal (95% Cl)         147         140         12.5%         1.01 [0.55, 1.83]         Image: the second se	Berghella 2004	0	3	1	7	0.7%	0.67 [0.03, 12.96]	
To 2004         12         101         12         96         8.3%         0.95 [0.45, 2.01]           Subtotal (95% Cl)         147         140         12.5%         1.01 [0.55, 1.83]	Rust 2000	7	43	5	37	3.6%	1.20 [0.42, 3.48]	
Subtotal (95% Cl) 147 140 12.5% 1.01 [0.55, 1.83]	To 2004	12	101	12	96	8.3%	0.95 [0.45, 2.01]	<u>+</u>
	Subtotal (95% CI)		147		140	12.5%	1.01 [0.55, 1.83]	<b>•</b>
Total events 19 18	Total events	19		18				
Heterogeneity: Chi <sup>2</sup> = 0.21, df = 2 (P = 0.90); l <sup>2</sup> = 0%	Heterogeneity: Chi <sup>2</sup> =	0.21, df = 2	2 (P = 0.	.90); I <sup>z</sup> = (	0%			
Test for overall effect Z = 0.03 (P = 0.98)	Test for overall effect	Z = 0.03 (F	P = 0.98	)				
Total (95% Cl) 1196 1196 100.0% 0.80 [0.64, 1.00]	Total (95% CI)		1196		1196	100.0%	0.80 [0.64, 1.00]	•
Total events 118 148	Total events	118		148				
Heterogeneity: Chi <sup>2</sup> = 3.87, df = 10 (P = 0.95); l <sup>2</sup> = 0%	Heterogeneity: Chi <sup>2</sup> =	3.87, df = 1	10 (P = I	0.95); I <sup>2</sup> =	0%			
Test for overall effect: Z = 1.95 (P = 0.05)	Test for overall effect	Z = 1.95 (F	P = 0.05	)				U.U1 U.1 1 10 100
Test for subgroup differences: Chi <sup>2</sup> = 1.05, df = 3 (P = 0.79), l <sup>2</sup> = 0%	Test for subgroup diff	erences: C	hi² = 1.0	05. df = 3	(P = 0.	79), I² = 0	3%	ravours experimental ravours control

## Figure 11: prophylactic cervical cerclage versus no cerclage- Preterm birth before 38+0 weeks

<b>J</b>	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.17.1 History-indic	ated cercla	ge vs no	cerclag	e			
Lazar 1984	60	268	43	238	47.9%	1.24 [0.87, 1.76]	-
Rush 1984	11	96	4	98	29.7%	2.81 [0.93, 8.51]	
Subtotal (95% CI)		364		336	77.6%	1.57 [0.76, 3.24]	◆
Total events	71		47				
Heterogeneity: Tau <sup>2</sup>	= 0.16; Chi <sup>2</sup>	= 1.92, 0	df = 1 (P	= 0.17)	); I <sup>2</sup> = 48%	b	
Test for overall effect	t Z = 1.21 (F	P = 0.23)					
1.17.2 One-off ultra	sound-indic	ated cer	clage in	high r	isk for Pl	IL vs no cerclage	
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not a	applicable						
Test for overall effect	t: Not applic	able					
4 47 9 Cosial ultrage	armal indicat		lawa in h	interior		un un constano	
1.17.3 Serial uttras	ouna-indicat	tea cerc	iage in n	ign ris	KTOPPIL	. vs no cerciage	
Subtotal (95% Ci)		0		U		Notesumable	
l otal events	U		U				
Test for everall offer	applicable	abla					
rest for overall effec	E NOL applic	apie					
1.17.4 Physical exa	m-indicated	l cerclag	je in higt	h risk f	or PTL vs	s no cerclage	
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not a	applicable						
Test for overall effect	t Not applic	able					
1.17.5 One-off ultra	sound-indic	ated cer	clage in	low/u	nspecifie	d risk for PTL vs no cerclage	
To 2004	12	127	2	126	22.4%	5.95 [1.36, 26.06]	
Subtotal (95% CI)		127		126	22.4%	5.95 [1.36, 26.06]	
Total events	12		2				
Heterogeneity: Not a	applicable						
Test for overall effect	:t Z = 2.37 (F	P = 0.02)					
Total (95% CI)		491		462	100.0%	2 25 [0 89 5 69]	
Total (85% CI)	0.2	491	40	402	100.0%	2,20 [0,09, 0,09]	
Heterogeneity Tour	83 = 0.44- Chil	- 6 92 /	49 4f= 2 /D	- 0.05	· IZ = 669		
Test for overall effect	+ 7 = 1 70 /	= 0.03, t	u – 2 (P	- 0.05,	, 1 = 00 %	2	0.01 0.1 1 10 100
Test for subgroup d	ifferences: C	:hi²= 2.5	3 df=1	(P = 0	11) E = 6	30.4%	Favours experimental Favours control
restion subgroup a	merences. c	- 2.0				19.4 M	

## Figure 12: prophylactic cervical cerclage versus no cerclage- maternal side effects

	Experim	ental	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.19.1 History-indicat	ted vs. no	cerclag	e				
MRC/RCOG 1993	23	407	11	391	69.4%	2.01 [0.99, 4.07]	
Rush 1984	11	96	4	98	24.5%	2.81 [0.93, 8.51]	
Subtotal (95% CI)		503		489	93.9%	2.22 [1.22, 4.01]	◆
Total events	34		15				
Heterogeneity: Chi <sup>2</sup> =	0.25, df=	1 (P = 0.	62); I <sup>2</sup> =	0%			
Test for overall effect:	Z = 2.63 (	P = 0.009	9)				
1.19.2 One-off ultras	ound-indic	ated ce	rclage ir	n high r	isk for Pi	fL vs no cerclage	
To 2004	1	26	0	30	2.9%	3.44 [0.15, 81.09]	
Subtotal (95% CI)		26		30	2.9%	3.44 [0.15, 81.09]	
Total events	1		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.77 (	P = 0.44	)				
1 10 3 One off ultrac	ound indic	atod co	relago ir	a low in	nenocifio	d riek for DTL ve no corcla	40
To 2004	ounu-muic	ateu ce	r ciage ii	110974	nspecifie 2.2%		96
10 2004 Subtotal (05% CD	3	101	0	90	3.2%	6.66 (0.35, 127.20) 6.66 (0.35, 127.20)	
Subtotal (95% Ci)	2	101		30	J.278	0.00 [0.33, 127.20]	
Total events	J		0				
Heterogeneity: Not ap	plicable	- 0.241					
rest for overall effect.	2 = 1.26 (	° = 0.21)	,				
Total (95% CI)		630		615	100.0%	2.39 [1.35, 4.23]	◆
Total events	38		15				-
Heterogeneity: Chi#=	0.83, df=	3 (P = 0.	84); I <sup>2</sup> =	0%			
Test for overall effect:	Z = 3.00 (	P = 0.003	3)				U.UT U.T T 10 100
Test for subgroup diff	erences: (	chi² = 0.5	57, df = 2	2 (P = 0	75), l <sup>2</sup> = 0	)%	Favours experimental Favours control

## Figure 13: Prophylactic cervical cerclage versus no cerclage- pyrexia

# biagnosing preterm prelabour rupture of membranes (P PROM)



Figure 14: Positive likelihood ratio for diagnosing preterm pre-labour rupture of membranes



Figure 15: Negative likelihood ratio for diagnosing preterm pre-labour rupture of membranes



Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful

## 44 Antenatal prophylactic antibiotics for women with P-PROM

### I.461 Any antibiotic versus placebo

### I.4.471 Neonatal outcomes



### Control **Risk Ratio** Treatment **Risk Ratio** Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI 1.5.1 Any antibiotic versus placebo Cox 1995 31 11.00 [0.63, 190.79] 5 0 31 3.1% Fuhr 2006 1 47 3 58 4.8% 0.41 [0.04, 3.83] Grable 1996 31 29 3.3% 0.94 [0.06, 14.27] 1 1 Johnston 1990 2 40 3 45 7.2% 0.75 [0.13, 4.26] 3.13 [1.35, 7.26] Kenvon 2001 3584 1225 19.2% 55 6 Lockwood 1993a 37 2 0 35 2.8% 4.74 [0.24, 95.33] McGregor 1991 2 26 4 27 8.2% 0.52 [0.10, 2.60] Mercer 1992 8 106 12 114 18.9% 0.72 [0.31, 1.69] Mercer 1997 24 299 27 312 27.6% 0.93 [0.55, 1.57] 42 2.5% Ovalle Salas 1997 0 1 43 0.34 [0.01, 8.14] Svare 1997a 30 37 2.5% 0.41 [0.02, 9.68] 0 1 4273 1.09 [0.65, 1.83] Subtotal (95% CI) 1956 100.0% Total events 100 58 Heterogeneity: Tau<sup>2</sup> = 0.18; Chi<sup>2</sup> = 13.98, df = 10 (P = 0.17); I<sup>2</sup> = 28% Test for overall effect: Z = 0.32 (P = 0.75) 1.5.2 All penicillin (excluding co-amoxiclav) versus placebo Fuhr 2006 1 47 3 58 31.3% 0.41 [0.04, 3.83] Johnston 1990 2 40 3 45 51.5% 0.75 [0.13, 4.26] Lockwood 1993a 37 0 35 17.3% 4.74 [0.24, 95.33] 2 138 100.0% 0.85 [0.25, 2.97] Subtotal (95% CI) 124 Total events 6 Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 1.71, df = 2 (P = 0.43); I<sup>2</sup> = 0% Test for overall effect: Z = 0.25 (P = 0.80) 1.5.3 Beta lactum (including co-amoxiclav) versus placebo Cox 1995 0 31 15.0% 31 11.00 [0.63, 190.79] 5 Kenyon 2001 24 1205 3 613 85.0% 4.07 [1.23, 13.46] Subtotal (95% CI) 1236 644 100.0% 4.72 [1.57, 14.23] Total events 29 3 Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 0.40, df = 1 (P = 0.53); I<sup>2</sup> = 0% Test for overall effect: Z = 2.76 (P = 0.006) 1.5.4 Macrolide (including erythromycin) versus placebo Kenyon 2001 11 1190 3 613 26.3% 1.89 [0.53, 6.75] 26 4 27 McGregor 1991 2 16.5% 0.52 [0.10, 2.60] 57.2% Mercer 1992 8 106 12 114 0.72 [0.31, 1.69] Subtotal (95% CI) 1322 754 100.0% 0.88 [0.45, 1.69] Total events 21 19 Heterogeneity: Tau<sup>2</sup> = 0.01; Chi<sup>2</sup> = 2.03, df = 2 (P = 0.36); I<sup>2</sup> = 2% Test for overall effect: Z = 0.39 (P = 0.70) 1.5.5 Other antibiotic versus placebo Grable 1996 1 31 1 29 3.4% 0.94 [0.06, 14.27] Mercer 1997 24 299 27 312 91.5% 0.93 [0.55, 1.57] 0.34 [0.01, 8.14] Ovalle Salas 1997 0 42 43 2.5% 1 Svare 1997a 30 37 2.5% 0.41 [0.02. 9.68] 0 1 Subtotal (95% CI) 402 421 100.0% 0.89 [0.54, 1.47] Total events 25 30 Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 0.61, df = 3 (P = 0.89); I<sup>2</sup> = 0% Test for overall effect: Z = 0.47 (P = 0.64) 0.001 0.1 10 1000 1

### Figure 17: Neonatal necrotising enterocolitis

### Control **Risk Ratio** Treatment **Risk Ratio** Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI 1.5.1 Any antibiotic versus placebo Cox 1995 31 11.00 [0.63, 190.79] 5 0 31 3.1% Fuhr 2006 1 47 3 58 4.8% 0.41 [0.04, 3.83] Grable 1996 31 29 3.3% 0.94 [0.06, 14.27] 1 1 Johnston 1990 2 40 3 45 7.2% 0.75 [0.13, 4.26] 3.13 [1.35, 7.26] Kenvon 2001 55 3584 1225 19.2% 6 Lockwood 1993a 2 37 0 35 2.8% 4.74 [0.24, 95.33] McGregor 1991 2 26 4 27 8.2% 0.52 [0.10, 2.60] Mercer 1992 8 106 12 114 18.9% 0.72 [0.31, 1.69] Mercer 1997 24 299 27 312 27.6% 0.93 [0.55, 1.57] 42 2.5% 0.34 [0.01, 8.14] Ovalle Salas 1997 0 1 43 30 0.41 [0.02, 9.68] Svare 1997a 0 37 2.5% 1 4273 1.09 [0.65, 1.83] Subtotal (95% CI) 1956 100.0% Total events 100 58 Heterogeneity: Tau<sup>2</sup> = 0.18; Chi<sup>2</sup> = 13.98, df = 10 (P = 0.17); I<sup>2</sup> = 28% Test for overall effect: Z = 0.32 (P = 0.75) 1.5.2 All penicillin (excluding co-amoxiclav) versus placebo Fuhr 2006 1 47 3 58 31.3% 0.41 [0.04, 3.83] Johnston 1990 2 40 3 45 51.5% 0.75 [0.13, 4.26] 4.74 [0.24, 95.33] Lockwood 1993a 37 0 35 17.3% 2 Subtotal (95% CI) 138 100.0% 0.85 [0.25, 2.97] 124 Total events 6 Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 1.71, df = 2 (P = 0.43); I<sup>2</sup> = 0% Test for overall effect: Z = 0.25 (P = 0.80) 1.5.3 Beta lactum (including co-amoxiclav) versus placebo 5 31 Cox 1995 0 31 15.0% 11.00 [0.63, 190.79] Kenyon 2001 24 1205 3 613 85.0% 4.07 [1.23, 13.46] Subtotal (95% CI) 1236 644 100.0% 4.72 [1.57, 14.23] Total events 29 3 Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 0.40, df = 1 (P = 0.53); I<sup>2</sup> = 0% Test for overall effect: Z = 2.76 (P = 0.006) 1.5.4 Macrolide (including erythromycin) versus placebo 11 1190 Kenyon 2001 3 613 26.3% 1.89 [0.53, 6.75] McGregor 1991 2 26 4 27 0.52 [0.10, 2.60] 16.5% Mercer 1992 106 114 57.2% 0.72 [0.31, 1.69] 8 12 Subtotal (95% CI) 1322 754 100.0% 0.88 [0.45, 1.69] Total events 21 19 Heterogeneity: Tau<sup>2</sup> = 0.01; Chi<sup>2</sup> = 2.03, df = 2 (P = 0.36); I<sup>2</sup> = 2% Test for overall effect: Z = 0.39 (P = 0.70) 1.5.5 Other antibiotic versus placebo Grable 1996 1 31 1 29 3.4% 0.94 [0.06, 14.27] Mercer 1997 299 312 91.5% 0.93 [0.55, 1.57] 24 27 42 Ovalle Salas 1997 0 1 43 2.5% 0.34 [0.01, 8.14] Svare 1997a 0 30 37 2.5% 0.41 [0.02, 9.68] 1 Subtotal (95% CI) 402 421 100.0% 0.89 [0.54, 1.47] Total events 25 30 Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 0.61, df = 3 (P = 0.89); I<sup>2</sup> = 0% Test for overall effect: Z = 0.47 (P = 0.64) 0.001 0.1 1 10 1000

### Figure 18: Neonatal necrotising enterocolitis

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### Figure 19: Birth before 37 weeks' gestation

ge					- 3			
-	Treatm	nent	Cont	rol	-	Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
Kenyon 2001	3049	3584	1041	1225	84.3%	1.00 [0.97, 1.03]		
McGregor 1991	28	28	27	27	13.0%	1.00 [0.93, 1.07]	+	
Svare 1997a	27	30	34	37	2.7%	0.98 [0.84, 1.14]	+	
Total (95% CI)		3642		1289	100.0%	1.00 [0.98, 1.03]		
Total events	3104		1102					
Heterogeneity: Tau <sup>2</sup> =	0.00; Cł	$hi^2 = 0.$	08, df =	2 (P =	0.96); l <sup>2</sup>	= 0%		
Test for overall effect:	Z = 0.03	B (P = 0)	.98)				0.1 0.5 1 2 5 10	

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				-			
	Treatm	ient	Cont	Control Risk Ratio		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Fuhr 2006	17	47	32	58	5.4%	0.66 [0.42, 1.02]	
Grable 1996	17	31	21	29	6.6%	0.76 [0.51, 1.12]	
Johnston 1990	22	40	37	45	9.2%	0.67 [0.49, 0.91]	
Kenyon 2001	2067	3584	775	1225	27.4%	0.91 [0.87, 0.96]	-
Lockwood 1993a	22	38	33	37	9.9%	0.65 [0.48, 0.87]	
Mercer 1992	77	106	94	114	19.8%	0.88 [0.76, 1.02]	-
Mercer 1997	166	299	229	312	21.8%	0.76 [0.67, 0.85]	-
Total (95% CI)		4145		1820	100.0%	0.79 [0.71, 0.89]	•
Total events	2388		1221				
Heterogeneity: Tau <sup>2</sup> =	= 0.01; Cł	$hi^2 = 16$	5.94, df :	= 6 (P =	= 0.010);	$I^2 = 65\%$	
Test for overall effect	: Z = 3.99	$\Theta (P < 0)$	).0001)				0.1 0.5 1 2 5 10

## Figure 20: Birth within 7 days of randomisation

## I.4.12 Maternal outcomes

iqure 21:	Materr	nal d	eath							
5	Treatm	nent	Cont	rol		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M	-H, Ran	dom, 959	% CI
1.1.1 Any antibiotic	versus pl	lacebo								
Johnston 1990	0	40	0	45		Not estimable				
Mercer 1997	0	299	0	312		Not estimable				
Svare 1997a	0	30	0	37		Not estimable				
Subtotal (95% CI)		369		394		Not estimable				
Total events	0		0							
Heterogeneity: Not a	pplicable									
Test for overall effect	t: Not appl	licable								
1.1.2 All penicillin (	excluding	co-am	oxiclav)	versus	placebo					
Johnston 1990	0	40	0	45		Not estimable				
Subtotal (95% CI)		40		45		Not estimable				
Total events	0		0							
Heterogeneity: Not a	pplicable								1	
Test for overall effect	t: Not appl	licable								
1.1.5 Other antibiot	tic versus	placeb	0							
Mercer 1997	0	299	0	312		Not estimable				
Svare 1997a	ŏ	30	õ	37		Not estimable			1	
Subtotal (95% CI)	•	329		349		Not estimable				
Total events	0		0							
Heterogeneity: Not a	pplicable		-							
Test for overall effect	t: Not appl	licable								
							0.102	015	1 1	
							0.10.2	0.5	1 2	2

Favours treatment Favours control

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## Figure 22: Maternal infection after delivery prior to discharge

	Treatm	nent	Cont	Control		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Garcia 1995	8	30	7	30	1.9%	1.14 [0.47, 2.75]	<u>+</u>
Kenyon 2001	686	3584	262	1225	90.5%	0.89 [0.79, 1.02]	
Mercer 1997	33	299	36	312	7.3%	0.96 [0.61, 1.49]	+
Svare 1997a	2	30	1	37	0.3%	2.47 [0.23, 25.91]	<u> </u>
Total (95% CI)		3943		1604	100.0%	0.91 [0.80, 1.02]	
Total events	729		306				
Heterogeneity: Tau2 =	0.00; Cł	$1i^2 = 1.5$	06, df =	3 (P =	0.79); I <sup>2</sup>	= 0%	0.001 01 10 1000
Test for overall effect:	Z = 1.61	(P = 0)	.11)				0.001 0.1 1 10 1000

### Figure 23: Chorioamnionitis

•	Treatment		Control			Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI			
Ernest 1994	3	77	9	67	6.4%	0.29 [0.08, 1.03]				
Garcia 1995	3	30	1	30	2.5%	3.00 [0.33, 27.23]				
Grable 1996	4	31	8	29	7.9%	0.47 [0.16, 1.39]				
Johnston 1990	3	40	16	45	7.2%	0.21 [0.07, 0.67]				
Kurki 1992	1	50	7	51	2.9%	0.15 [0.02, 1.14]				
Lockwood 1993a	10	35	10	37	12.4%	1.06 [0.50, 2.23]	_ <b>+</b> _			
McGregor 1991	7	28	6	27	9.4%	1.13 [0.43, 2.92]				
Mercer 1992	18	105	22	112	15.9%	0.87 [0.50, 1.53]	-			
Mercer 1997	69	299	101	312	22.3%	0.71 [0.55, 0.93]	-			
Ovalle Salas 1997	2	42	11	45	5.2%	0.19 [0.05, 0.83]				
Svare 1997a	6	30	5	37	7.9%	1.48 [0.50, 4.38]	- <del>-</del>			
Total (95% CI)		767		792	100.0%	0.66 [0.46, 0.96]	•			
Total events	126		196							
Heterogeneity: Tau <sup>2</sup> =	0.14; Cł	$1i^2 = 18$	.29, df =	= 10 (P	= 0.05);	$l^2 = 45\%$				
Test for overall effect:	Z = 2.18	S(P = 0)	.03)				0.01 0.1 1 10 100			

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### Figure 24: Major adverse drug reaction

-	Treatm	nent	Cont	rol		Risk Ratio		Risk	Ratio	D		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M	-H, Rano	iom,	95% (	CI	
Kenyon 2001	0	3584	0	1225		Not estimable						
Mercer 1997	0	299	0	312		Not estimable						
Svare 1997a	0	30	0	37		Not estimable						
Total (95% CI)		3913		1574		Not estimable						
Total events	0		0									
Heterogeneity: Not ap	plicable						<u>b</u> 1+	0.5	-	<del>\</del>	Ŧ	10
Test for overall effect:	Not appl	icable					0.1	0.5	*	6	3	10

	Treatn	nent	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
4.1.1 New Subgroup							
Amon 1988a	2	43	6	39	1.5%	0.30 [0.06, 1.41]	
Camli 1997	3	15	4	16	2.1%	0.80 [0.21, 3.00]	
Christmas 1992	1	48	3	46	0.7%	0.32 [0.03, 2.96]	
Cox 1995	1	31	5	31	0.8%	0.20 [0.02, 1.61]	
Garcia 1995	2	30	5	30	1.5%	0.40 [0.08, 1.90]	
Grable 1996	0	31	2	29	0.4%	0.19 [0.01, 3.75]	
Johnston 1990	3	40	4	45	1.8%	0.84 [0.20, 3.54]	
Kenyon 2001	226	3584	82	1225	61.2%	0.94 [0.74, 1.20]	
Kurki 1992	1	57	1	58	0.5%	1.02 [0.07, 15.88]	
Lockwood 1993a	3	37	3	35	1.6%	0.95 [0.20, 4.38]	
Magwali 1999	8	82	11	86	4.9%	0.76 [0.32, 1.80]	-
McGregor 1991	6	28	0	27	0.5%	12.55 [0.74, 212.52]	
Mercer 1992	6	106	10	114	3.8%	0.65 [0.24, 1.71]	
Mercer 1997	19	299	18	312	9.4%	1.10 [0.59, 2.06]	+
Morales 1989	5	42	3	37	2.0%	1.47 [0.38, 5.73]	
Ovalle Salas 1997	7	42	6	43	3.6%	1.19 [0.44, 3.26]	
Owen 1993a	4	59	7	58	2.7%	0.56 [0.17, 1.82]	
Svare 1997a	2	30	2	37	1.0%	1.23 [0.18, 8.25]	
Subtotal (95% CI)		4604		2268	100.0%	0.89 [0.74, 1.08]	•
Total events	299		172				
Heterogeneity: Tau <sup>2</sup> =	: 0.00; Cl	$hi^2 = 12$	2.87, df :	= 17 (P	= 0.75);	$l^2 = 0\%$	
Test for overall effect:	Z = 1.18	8 (P = 0)	).24)				
4.1.2 Antibiotics ver	sus no tr	reatmei	nt (no pl	acebo)			
Amon 1988a	2	43	6	39	11.0%	0.30 [0.06, 1.41]	
Camli 1997	3	15	4	16	15.0%	0.80 [0.21, 3.00]	
Christmas 1992	1	48	3	46	5.3%	0.32 [0.03, 2.96]	
Magwali 1999	8	82	11	86	35.5%	0.76 [0.32, 1.80]	
Morales 1989	5	42	3	37	14.1%	1.47 [0.38, 5.73]	
Owen 1993a	4	59	7	58	19.0%	0.56 [0.17, 1.82]	
Subtotal (95% CI)		289		282	100.0%	0.69 [0.41, 1.14]	•
Total events	23		34				
Heterogeneity: Tau <sup>2</sup> =	0.00; C	hi² = 2.	97, df =	5 (P =	0.70); I <sup>2</sup>	= 0%	
Test for overall effect:	Z = 1.45	5 (P = 0)	).15)				
							0.001 01 10 1000
							0.001 0.1 1 10 1000

## Figure 25:Antibiotics therapy versus either placebo or no antibiotics therapy

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## Figure 26: Intraventricular haemorrhage

-	Treatm	nent	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Amon 1988a	4	42	6	36	6.2%	0.57 [0.17, 1.87]	
Christmas 1992	2	48	3	45	3.0%	0.63 [0.11, 3.57]	
Fuhr 2006	0	47	2	58	2.2%	0.25 [0.01, 5.00]	
Johnston 1990	5	40	14	45	12.7%	0.40 [0.16, 1.02]	
Lockwood 1993a	5	37	7	36	6.8%	0.69 [0.24, 1.99]	
Mercer 1992	57	299	68	312	64.2%	0.87 [0.64, 1.20]	<b>#</b>
Owen 1993a	1	59	5	58	4.9%	0.20 [0.02, 1.63]	
Total (95% CI)		572		590	100.0%	0.73 [0.56, 0.95]	◆
Total events	74		105				
Heterogeneity: Chi <sup>2</sup> =	5.05, df	= 6 (P)	= 0.54);	$I^2 = 0\%$	6		
Test for overall effect:	Z = 2.30	0 (P = 0)	0.02)			F	avours experimental Favours control

Figure 27:	Sepsis	5					
0	Treatm	ient	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M–H, Fixed, 95% CI
Amon 1988a	1	42	6	38	7.7%	0.15 [0.02, 1.20	1
Christmas 1992	2	48	0	45	0.6%	4.69 [0.23, 95.19	1
Lockwood 1993a	2	37	3	36	3.7%	0.65 [0.12, 3.66	]
Mercer 1997	46	299	67	312	80.5%	0.72 [0.51, 1.01	] 📕
Owen 1993a	2	59	6	58	7.4%	0.33 [0.07, 1.56	1 <del></del>
Total (95% CI)		485		489	100.0%	0.67 [0.49, 0.91	1 🔶
Total events	53		82				
Heterogeneity: Chi <sup>2</sup>	= 4.57, df	= 4 (P)	= 0.33);	$I^2 = 12$	1%		
Test for overall effect	tt Z = 2.52	2 (P = 0)	0.01)				Favours experimental Favours control

Figure 28:	Delive	ry de	elayed	1≥7	days		
•	Treatm	ient	Cont	rol	•	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Amon 1988a	20	43	11	39	8.6%	1.65 [0.91, 2.99]	
Christmas 1992	20	48	7	46	5.3%	2.74 [1.28, 5.85]	
Fuhr 2006	30	47	26	58	17.3%	1.42 [1.00, 2.04]	<b>+</b> -
Johnston 1990	18	40	8	45	5.6%	2.53 [1.24, 5.18]	
Lockwood 1993a	16	38	4	37	3.0%	3.89 [1.44, 10.56]	
Mercer 1997	133	299	83	312	60.3%	1.67 [1.34, 2.09]	•
Total (95% CI)		515		537	100.0%	1.80 [1.52, 2.13]	⊢  •
Total events	237		139				
Heterogeneity: Chi <sup>2</sup>	= 6.49, df	= 5 (P	= 0.26);	$l^2 = 23$	:%		
Test for overall effect	t Z = 6.76	5 (P < 0	0.00001)			1	Favours experimental Favours control

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### Identifying infection in women with P-PROM 6**5**

Figure 29: Predictive value of monitoring women with preterm pre-labour rupture of membranes – Positive likelihood ratio for C-reactive protein



Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful





Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful





Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful





Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful

Figure 33: Predictive value of monitoring women with preterm pre-labour rupture of membranes – Positive likelihood ratio for fetal heart rate



Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful

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### Figure 34: Predictive value of monitoring women with preterm pre-labour rupture of membranes - Negative likelihood ratio for fetal heart rate



Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful

66

### 'Rescue' cervical cerclage **6***i*

68 No forest plots were generated for this review question.

### Diagnosing preterm labour for women with intact **67** membranes 70





Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful

## Figure 36: Negative likelihood ratio of Bishop score to diagnose pre-term birth within 48 hours



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Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful





Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful





Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful











Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful





Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful

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Figure 43: Positive likelihood ratio of fetal fibronectin to diagnose pre-term birth within 48 hours



Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful





Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful





Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful





Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful

## Figure 47: Positive likelihood ratio of fetal fibronectin and digital examination to diagnose pre-term birth within 7 days



Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful

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Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful





Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful

Figure 50: Negative likelihood ratio of cervical length (measured by transvaginal ultrasound) to diagnose pre-term birth within 48 hours



Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful

85





Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful




Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful

# Figure 53: Positive likelihood ratio of cervical length (measured by transvaginal ultrasound) to diagnose pre-term birth within 48 hours in women with a Bishop score of 4-7



Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful

88





Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful

89

Figure 55: Positive likelihood ratio of cervical length (measured by transvaginal ultrasound) to diagnose pre-term birth within 7 days in women with a Bishop score of 4-7







Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful





Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful

92





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Figure 59: Positive likelihood ratio for fetal fibronectin score and Bishop score to diagnose pre-term birth within 7 days



Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful

## Figure 60: Negative likelihood ratio for fetal fibronectin score and Bishop score to diagnose pre-term birth within 7 days



Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful

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Figure 61: Positive likelihood ratio for pIGFBP-1 to diagnose pre-term birth within 7 days in women with different cervical lengths



Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful

## Figure 62: Negative likelihood ratio for pIGFBP-1 to diagnose pre-term birth within 7 days in women with different cervical lengths



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Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful





Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful

## Figure 64: Negative likelihood ratio for fetal fibronectin to diagnose pre-term birth within 48 hours in women with different cervical lengths



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Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful

## Figure 66: Negative likelihood ratio for fetal fibronectin to diagnose pre-term birth within 7 days in women with different cervical lengths



Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful

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## 1b8 A.8 Maternal corticosteroids

### h851 Different gestations

106 Single-course corticosteroids versus placebo or expectant management

### Figure 67: Fetal and neonatal mortality

Study or Subgroup	Treatm Events	total	Contr Events	ol Total	Weight	Risk Ratio M.H. Fixed, 95% CI	Risk Ratio M-H, Foord, 95% CI
1.1.1 in all babies							
Amorien 1999 Block 1977	24	110	36	108	10.5%	0.65 (0.42, 1.02) 0.60 (0.16, 2.01)	
Collaborative 1991	47	378	47	379	12.6%	1.00 (0.69, 1.46)	-
Dexiprom 1999	4	105	10	103	29%	0.39 (0.13, 1.21)	
Gamsu 1999	15	131	22	197	6.2%	0.20 (0.11, 0.23) 0.71 (0.39, 1.31)	
Ounte 1992	12	36	12	41	3.3%	1.14 (0.59, 2.21)	
Karl 1994		95	. 6	94	1.7%	0.82 (0.26, 2.81)	
Diggins 1972a Parsons 1988	108	23	122	22	0.4%	0.91 (0.72, 1.15) 0.32 (0.01, 7.45)	
Porto 2011	1	144	3	131	0.9%	0.30 (0.03, 2.66)	•
Qublish 2001	21	72	41	87	12.3%	0.48 (0.32, 0.72)	
Tabulch 1990	10	65	12	71	3.7%	0.45 (0.18, 1.11) 1.06 (0.49, 2.27)	
Subtotal (95% CI)		1957	- 13	1945	100.0%	0.77 [0.66, 0.88]	•
Total events Heterogeneity: Chif's Test for overall affert	262 19.66, df	= 13 (P)	344	*= 351			
							S 1 2 1 1
1.1.2 In babies born Designors 1999	trom prog	105	10	103	11.7%	0.39 I0.53 1.20	
Liggins 1972a	30	168	36	173	39.8%	0.86 (0.56, 1.33)	
Parsons 1988	0	23	1	22	1.7%	0.32 (0.01, 7.45)	
Subtotal (95% CI)	25	368	41	365	100.0%	0.62 (0.65, 0.62)	•
Total events	55		88				
Heterogeneity: Chi# = Test for overall effect	4.53, df = Z= 3.32 (	3 (P = 0 P = 0.00	(25); P+ (09)	34%			
1.1.3 in babies born	< 28 week	15					
Donan 1980	3	11	10	18	15.3%	0.49 (0.17, 1.40)	
Liggins 1972a Subtotal (95% Ct)	26	49	43	51	100.0%	0.87 (0.71, 1.07) 0.81 (0.65, 1.01)	
Total events	39	120	52	100		and broad traid	
Heterogenety: Chi# = Test for overall effect	1.32, df= Z=1.05 (	1 (P = 0 P = 0.06	125); (** 0	24%			
1.1.4 in babies born	< 30 week						
Lippins 1972a	59	99	71	102	100.0%	0.8630.70, 1.053	
Subtotal (95% CI)		- 99	1	102	100.0%	0.86 [0.70, 1.05]	· · · •
Heterogeneity Not a	policable		11				
Test for overall effect	Z=1.47(	P=0.14	0				
115 is balance born							
Block 1977	- 34 0000	14	- 5	- 19	3.8%	0.54 (0.12.2.40)	
Doran 1980	4	37	14	36	12.6%	0 20 00 10, 0 760	
Liggins 1972a	76	179	.91	168	83.6%	0.76 (0.63, 0.96)	
Seblotal (95% Ci) Total events	97	2.50	110	225	100.0%	0.24 [0.57, 0.86]	
Heterogeneity: Chi# = Test for overall effect	4.19, df= Z= 3.12 (	2 (P = 0 P = 0.00	(12); (** (2)	52%			
1.1.6 in babies born	< 34 week	is.					2010
Liggins 1972a	90	312	113	296	100.0%	0.73 (0.58, 0.91)	
Subtotal (95% CI)		312		206	100.0%	0.73 [0.58, 0.91]	•
Total events Heterogeneity: Not ap	90 pplicable		513				
restror overall effect	202101	P = 0.04	89.				
1.1.7 in babies born	< 36 week	18		0.2		1.11.11.11.11.11.1	30
Doran 1980	4	58	14	48	11.0%	0.24 (0.08, 0.67)	
Subtotal (95% Ci)	103	498	121	471	100.0%	0.02 [0.05, 1 0.0] 0.75 [0.01, 0.94]	
Total events	107		135				
Heterogeneity: Chi#=	5.25, df=	1 (P = 0	(02); P=	81%			
Test for overall effect	Z=2.524	P=0.01	3				
1.1.8 in babies < 26 v	weeks' pe	station	at fist de	944			
Liggins 1972a	15	23	17	26	100.0%	1.00 (0.66, 1.50)	
Subtonal (95% CI)	24	23	1.00	26	100.0%	1.00 [0.66, 1.50]	-
Heterogeneitic Not ac	pelicable		.17				
Test for overall effect	Z= 0.01 (	P×0.95	0				
1.1.0 in habins hotes		4 10-		antatio		losa	
Lioping 1972a	50	140	64	125	100.0%	0 80 10 59 1 061	-
Subtotal (95% CI)	5	140	- 77	121	100.0%	0.80 [0.59, 1.08]	-
Total events	50		54				
Heterogenety: Not ap Text for overall effect	7=147J	P=0.14	÷				
TABLES STREET	a - 1.44 1		ð				
1.1.10 is babies bety	veen 30 a	nd < 33	weeks'	gestat	ion at 1st	dose of the second	
Liggins 1972a Subtotal (95% CB	19	165	30	154	100.0%	0.59 (0.35, 1.01) 0.59 (0.35, 1.05)	
Total events	19		30			and find and	
Heterogeneity: Not ap	pplicable						
Testfor overall effect	Z=1.941	P=0.05	0				
1.1.11 in babies betw	ween 33 a	nd < 35	weeks'	gestat	ion at 1st	dose	1.00
Liggins 1972a	18	168	18	185	100.0%	1.10.00.59, 2.05]	
Subtonal (VSN-LI)	10	108	10	185	100.0%	a to farait's not	
Heterogenetiv Not a	ppicable		10				
Test for overall effect	Z= 0.31	P=0.76	6				
1.1.12 in babies bet	vees 15 a	nd + 37	weeks'	anatari	ion at 1+1	dose	
Lippins 1972a	3	87	3	107	100.0%	1 23 (0.25, 5.94)	
Subtotal (95% Ci)		87		107	100.0%	1.23 [0.25, 5.94]	
Total events	3		3				
Test for overall effect	Z=0.264	P×0.80	0				
1.1.13 In Dables > 36	weeks' g	estation	at 1st	eose Ar	+10.00	A 71 ID 81 107 07	
Subtotal (95% Ci)		10	0	24	100.0%	9.21 [0.51, 167.82]	
Total events	3	1	Ð	1000	10.00	1949 1949 25 19 25	
Heterogeneity: Not as	pplicable						
reactor overall effect	2=1.50(	F=0.13	×				
							0102 05 1 2 5 10
							Encaded delaborant Encader salarit

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### Figure 68: Cerebroventricular haemorrhage

Study or Subaroup	Treatm Events	Total	Contr Events	Total	Weight	Risk Ratio M.H. Fixed, 955 CI	Risk Ratio M.H. Fixed, 95% CI
1.2.1 in all babies	Litenta	T-S-Las	C.Perica	1 Vian	Troger	and room as a co	
Amorim 1999	6	100	17	100	10.7%	0.35 (0.15, 0.06)	
Doran 1980	1	80	4	60	2.9%	0.19 [0.02, 1.63]	• • • •
Fekih 2002	5	63	14	68	0.5%	0.39 (0.15, 1.01)	
Gamsu 1989 Garda 1992	2	130	4	132	2.5%	0.51 [0.09, 2.72]	
Kari 1994	8	77	18	66	12.3%	0.38 [0.18, 0.82]	
Lewis 1996	0	38	3	39	2.2%	0.15 [0.01, 2.74]	•
Liggins 1972a Morales 1999	16	554	27	567	10.9%	0.61 (0.30, 1.11) 0.58 (0.31, 1.09)	
Qublan 2001	2	70	8	65	5.2%	0.23 [0.05, 1.05]	• • • • • • • • • • • • • • • • • • • •
Silver 1996	25	54	17	42	12.1%	1.14 (0.72, 1.02)	
Subtotal (95% CI)	0	1445	•	1427	100.0%	0.54 [0.43, 0.69]	•
Total events	00		155				-
Heterogeneity: Chi# = Test for overall effect	18.25, df ( Z = 5.06.0	i 11 (P P < 0.0	= 0.13); / 0001\	*= 329	6		
1.2.2 In babies born 1	rom preg	nancie	s comple	cated	by prema	ture rupture of membranes at 1st dose	•
Lewis 1996	ŏ	38	3	39	8.7%	0.15[0.01, 2.74]	•
Liggins 1972a	4	154	7	158	17.4%	0.59 [0.18, 1.96]	
Morales 1989 Oublas 2001	13	87	20	78	53.1%	0.58 [0.31, 1.09]	
Subtotal (95% CI)	-	454	Ŷ	441	100.0%	0.47 [0.28, 0.79]	•
Total events	19		30				
Heterogenety: Chr = Test for overall effect	2.01, df = Z = 2.88 /	30°=0 P=0.0	1.57); P= 040	0%			
1.2.3 In babies born +	28 week	5			***	0.31011.000	
Subtotal (95% CI)		34	12	28	100.0%	0.34 [0.14, 0.86]	
Total events	5		12				
Heterogeneity: Not ap	plicable	0-00	94.				
restor overall enect	7 = 7.790	r = 0.0.	4				
1.2.4 In babies born +	30 week	8					
Liggins 1972a Sabtotal (95% CB	11	76	19	74	100.0%	0.56 (0.29, 1.10)	
Total events	11		19			acta farrai icial	
Heterogeneity: Not ap	plicable	_					
Test for overall effect	Z=1.68 ()	P = 0.0	90				
1.2.5 In babies born	32 week	5					_
Liggins 1972a	13	144	23	133	100.0%	0.52 (0.28, 0.99)	
Total events	13	144	23	133	100.018	0.52 [0.20, 0.30]	
Heterogeneity: Not ap	plicable						
Test for overall effect	Z= 2.00 (	P = 0.0	5)				
1.2.6 In babies born	34 week	8					_
Liggins 1972a	16	273	27	242	100.0%	0.53 (0.29, 0.95)	
Subtotal (95% CI)	16	2/3	27	242	100.0%	0.53 [0.29, 0.95]	-
Heterogeneity: Not ap	plicable						
Test for overall effect	Z=2.13 (	P = 0.0	3)				
1.2.7 In babies born	36 week	5					
Liggins 1972a	16	394	27	373	100.0%	0.56 (0.31, 1.02)	
Subtotal (95% CI)		394	3.7	373	100.0%	0.56 [0.31, 1.02]	-
Heterogeneity: Not ap	olicable		21				
Test for overall effect	Z=1.00 (	P = 0.0	6)				
1.2.8 In babies < 26 v	veeks' oe	station	at 1st de	ose.			
Liggins 1972a	3	15	2	12	100.0%	1.20 [0.24, 6.06]	
Subtotal (95% CI)		15		12	100.0%	1.20 [0.24, 6.06]	
Total events Heteropeneity: Not ap	3 olicable		2				
Test for overall effect	Z=0.22 (	P = 0.8	3)				
1.2.9 In babies betwe	en 26 and	I < 30 y	veeks' o	estatio	e at 1st d	lose	
Amorim 1999	0	1	0	1		Not estimable	_
Liggins 1972a	9	120	10	107	100.0%	0.45 (0.21, 0.95)	
Sebtotal (95% CI) Total events		121	18	108	100.0%	0.45 [0.21, 0.95]	
Heterogeneity: Not ap	plicable		10				
Test for overall effect	Z= 2.09 (	P = 0.0	4)				
1.2.10 In babies betw	veen 30 ar	id < 33	weeks'	pestati	ion at 1st	dose	
Liggins 1972a	1	155	4	140	100.0%	0.23 [0.03, 2.00]	•
Subtotal (95% CI)		155		140	100.0%	0.23 [0.03, 2.00]	
Heterogeneity: Not ap	plicable						
Test for overall effect	Z=1.34 (	P = 0.1	8)				
1.2.11 In babies betw	reen 33 ar	id < 35	weeks'	oestati	ion at 1st	dose	
Liggins 1972a	3	161	3	178	100.0%	1.11 (0.23, 5.40)	
Subtotal (95% CI)		161		178	100.0%	1.11 [0.23, 5.40]	
Heteropeneity: Not an	glicable		3				
Test for overall effect	Z=0.12 (	P = 0.9	0)				
1.2.12 In babies betw	rees 35 ar	id < 37	weeks'	pestat	on at 1st	dose	
Liggins 1972a	0	85	0	106		Not estimable	
Subtotal (95% CI)	-	85	-	106		Not estimable	
Heterogeneity: Not an	0 olicable		ġ				
Test for overall effect.	Not applic	able					
1.2.13 in babies 2.36	weeks' a	estatio	at fat i	fose			
Liggins 1972a	0	18	0	24		Not estimable	
Subtotal (95% CI)	_	18	_	24		Not estimable	
Total events Hateroperaily: Not an	0 olicable		0				
Test for overall effect	Not applic	able					
							0.1 0.2 0.5 1 2 5 10
							Favours realment. Pavours control

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### Figure 69: Intraventricular haemorrhage – grades 3 or 4

0					<u> </u>	<u> </u>	
	Treatm	ent	Contr	lo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
Doran 1980	1	80	4	60	0.0%	0.19 [0.02, 1.63	1
Gamsu 1989	2	130	4	132	0.0%	0.51 [0.09, 2.72	1
Garite 1992	1	33	9	40	27.1%	0.13 (0.02, 1.01	]
Lewis 1996	0	38	3	39	11.5%	0.15 [0.01, 2.74	] <b></b>
Morales 1989	3	87	12	78	42.1%	0.22 [0.07, 0.77	
Silver 1996	2	28	6	30	19.3%	0.36 (0.08, 1.63	ı —•+
Total (95% CI)		186		187	100.0%	0.22 [0.10, 0.49]	•
Total events	6		30				
Heterogeneity: Chi <sup>2</sup> =	0.70, df=	3 (P =	0.87); l² =	:0%			
Test for overall effect.	Z= 3.64 (	(P = 0.0	003)				Favours experimental Favours control

<Insert Note here>

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### Figure 70: Chronic lung disease

	Treatm	ent	Contr	ol		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 In all babies							
Amorim 1999	1	100	5	100	9.6%	0.20 [0.02, 1.68]	← ■ ───────────────────────────────────
Garite 1992	9	33	9	40	15.6%	1.21 [0.54, 2.70]	
Kari 1994	6	85	1	76	2.0%	5.36 [0.66, 43.56]	
Morales 1989	8	87	19	78	38.4%	0.38 [0.18, 0.81]	
Silver 1996	24	54	16	42	34.5%	1.17 [0.72, 1.90]	
Taeusch 1979 Subtotal (95% CI)	0	54 413	0	69 405	100.0%	Not estimable 0.86 [0.61, 1.22]	•
Total events	48		50				-
Heterogeneity: Chi <sup>2</sup> =	11.35, df	= 4 (P =	= 0.02); P	= 65%			
Test for overall effect:	Z=0.84 (	(P = 0.4	0)				
1.3.2 In babies born f	rom preg	nancie	s compli	icated I	by prema	ture rupture of membranes at 1st dos	e
Morales 1989 Subtotal (95% CI)	23	87 87	41	78 78	100.0% 100.0%	0.50 [0.33, 0.76] 0.50 [0.33, 0.76]	
Total events	23		41				•
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 3.29 (	(P = 0.0	010)				
							0.1 0.2 0.5 1 2 5 10
							Favours treatment Favours control

Figure 71:	Need for	mechanical	intervention
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Favours treatment Favours control

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### Figure 72: Neonatal sepsis (systemic infection in first 48 hours of life)

		Treatment		Control			Risk Ratio	Risk Ratio		
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl		
	1.5.1 In all babies									
	Amorim 1999	13	100	28	100	42.6%	0.46 [0.26, 0.84]			
	Collaborative 1981	4	307	10	299	15.4%	0.39 [0.12, 1.23]			
	Dexiprom 1999	11	105	11	101	17.1%	0.96 [0.44, 2.12]			
	Gamsu 1989	4	130	7	132	10.6%	0.58 [0.17, 1.93]			
	Parsons 1988	0	23	0	22		Not estimable			
	Porto 2011 Subtotal (95% CI)	6	144 809	9	131 785	14.3% 100.0%	0.61 [0.22, 1.66] 0.57 [0.39, 0.83]	•		
	Total events	38		65						
	Heterogeneity: Chi <sup>2</sup> =	2.58, df=	4 (P =	0.63); P=	0%					
	Test for overall effect	Z = 2.91 (	(P = 0.0	004)						
	1.5.2 In babies born	from preg	nancie	es compl	cated	by prema	ture rupture of membranes at 1st de	ose		
	Dexiprom 1999	11	105	11	101	100.0%	0.96 [0.44, 2.12]			
	Parsons 1988	0	23	0	22		Not estimable	T		
	Subtotal (95% CI)		128		123	100.0%	0.96 [0.44, 2.12]	-		
	Total events	11		11						
	Heterogeneity: Not a	pplicable								
	Test for overall effect	Z=0.10 (	P = 0.9	32)						

0.1 0.2 0.5 1 2 5 10 Favours treatment Favours control

. 7								
		Treatm	ent	Contr	ol		Risk Ratio	Risk Ratio
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
	1.6.1 In all babies							
	Amorim 1999	1	60	2	34	8.4%	0.28 [0.03, 3.01]	• • •
	Collaborative 1981	9	200	15	206	48.6%	0.62 [0.28, 1.38]	
	Kari 1994	5	50	7	32	28.1%	0.46 [0.16, 1.32]	
	Liggins 1972a	3	129	2	107	7.2%	1.24 [0.21, 7.31]	
	Schutte 1980	2	51	2	35	7.8%	0.69 [0.10, 4.64]	
	Subtotal (95% CI)		490		414	100.0%	0.60 [0.34, 1.03]	-
	Total events	20		28				
	Heterogeneity: Chi <sup>2</sup> =	1.31, df=	4 (P =	0.86); l² =	: 0%			
	Test for overall effect:	Z = 1.85 (	P = 0.0	7)				
								0.1 0.2 0.5 1 2 5 10

### Figure 73: Cerebral palsy in childhood

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### Figure 74: Visual impairment in childhood



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Favours treatment Favours control

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#### Figure 75: Hearing impairment in childhood Control Treatment Risk Ratio **Risk Ratio** Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% CI 1.8.1 In all babies Kari 1994 50 32 100.0% 0.64 [0.04, 9.87] 1 1 Schutte 1980 0 50 34 Not estimable 0 100.0% Subtotal (95% CI) 100 66 0.64 [0.04, 9.87] Total events 1 1 Heterogeneity: Not applicable Test for overall effect: Z = 0.32 (P = 0.75) 0.1 0.2 0.5 ż 5 10

Favours treatment Favours control

### Figure 76: Neurodevelopment delay in childhood



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### Figure 77: Developmental delay in childhood

-	Treatm	ent	Contr	ol		Risk Ratio	Risk F	latio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed	I, 95% CI
1.10.1 In all babies								
Amorim 1999	4	60	7	34	43.4%	0.32 [0.10, 1.03]		
Collaborative 1981	7	206	12	218	56.6%	0.62 [0.25, 1.54]		_
Subtotal (95% CI)		266		252	100.0%	0.49 [0.24, 1.00]		
Total events	11		19					
Heterogeneity: Chi <sup>2</sup> =	0.74, df=	1 (P =	0.39); l² =	= 0%				
Test for overall effect:	Z=1.97 (	(P = 0.0)	5)					
								2 5 10

Favours treatment Favours control

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### Figure 78: Intellectual impairment in childhood

	Treatm	ent	Contr	ol		Risk Ratio		Risk Ra	tio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed,	95% CI		
1.11.1 In all babies											_
Collaborative 1981	8	211	13	219	71.6%	0.64 [0.27, 1.51]	-		-		
Liggins 1972a	5	144	4	114	25.1%	0.99 [0.27, 3.60]	-				
Schutte 1980	3	54	0	36	3.4%	4.71 [0.25, 88.52]	-			•	<b>→</b>
Subtotal (95% CI)		409		369	100.0%	0.86 [0.44, 1.69]					
Total events	16		17								
Heterogeneity: Chi <sup>2</sup> =	: 1.80, df =	2 (P =	0.41); l <sup>2</sup> =	= 0%							
Test for overall effect	Z= 0.43 (	P = 0.6	7)								
									<u> </u>	+	1
							0.1 0.2	0.5 1	2	5	10

Favours treatment Favours control

#### Treatment Control Risk Ratio Risk Ratio Events Total Events Total Weight M-H, Fixed, 95% CI Study or Subgroup M-H, Fixed, 95% CI 1.12.1 In all babies Schutte 1980 0.86 [0.35, 2.09] 9 54 7 36 100.0% Subtotal (95% CI) 54 36 100.0% 0.86 [0.35, 2.09] Total events 9 7 Heterogeneity: Not applicable Test for overall effect: Z = 0.34 (P = 0.74) 0.1 0.2 0.5 5 10 ż Favours treatment Favours control

### Figure 79: Behavioural/learning difficulties in childhood

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#### Figure 80: Maternal mortality Treatment Control **Risk Ratio** Risk Ratio Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI Study or Subgroup 1.13.1 In all women Amorim 1999 110 1 108 100.0% 0.98 [0.06, 15.50] 4 1 Dexiprom 1999 0 28 0 18 Not estimable Schutte 1980 0 50 0 51 Not estimable Subtotal (95% CI) 100.0% 0.98 [0.06, 15.50] 188 177 Total events 1 1 Heterogeneity: Not applicable Test for overall effect: Z = 0.01 (P = 0.99) 0.1 0.2 0.5 5 10

0.1 0.2 0.5 1 2 5 10 Favours treatment Favours control

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### Figure 81: Side-effects of therapy in women

	Treatm	nent	Contr	ol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
1.14.1 In all women								
Schutte 1980 Subtotal (95% CI)	0	50 50	0	51 51		Not estimable Not estimable		
Total events Heterogeneity: Not ar Test for overall effect:	0 oplicable Not appli	cable	0					
							0.1 0.2 0.5 1 2 5 Favours treatment Favours control	10

Figure 82:	Puerp	eral	sepsi	s			
-	Treatm	ent	Contr	ol		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 In all women							
Amorim 1999	9	110	13	108	30.4%	0.68 [0.30, 1.52]	
Dexiprom 1999	4	102	7	102	16.2%	0.57 [0.17, 1.89]	
Garite 1992	10	33	5	38	10.8%	2.30 [0.88, 6.06]	
Lewis 1996	2	38	4	39	9.2%	0.51 [0.10, 2.64]	· · · · · ·
Qublan 2001	9	72	2	67	4.8%	4.19 [0.94, 18.68]	<b>↓</b> →
Schutte 1980	1	50	1	51	2.3%	1.02 [0.07, 15.86]	$\leftarrow$
Silver 1996	11	39	5	36	12.1%	2.03 [0.78, 5.28]	
Taeusch 1979	11	52	7	66	14.3%	1.99 [0.83, 4.79]	
Subtotal (95% CI)		496		507	100.0%	1.35 [0.93, 1.95]	
Total events	57		44				
Heterogeneity: Chi <sup>2</sup> =	: 10.97, df	= 7 (P =	= 0.14); l <sup>a</sup>	= 36%			
Test for overall effect	: Z = 1.59 (	(P = 0.1	1)				
1.3.4 In women with	pregnanc	ies co	mplicate	d by pr	emature	rupture of membranes at 1st dose	
Dexiprom 1999	4	102	7	102	49.7%	0.57 [0.17, 1.89]	
Lewis 1996	2	38	4	39	28.1%	0.51 [0.10, 2.64]	• • • • • • • • • • • • • • • • • • •
Qublan 2001	9	72	2	67	14.7%	4.19 [0.94, 18.68]	<b>→</b>
Schutte 1980	1	30	1	27	7.5%	0.90 [0.06, 13.70]	$\leftarrow \rightarrow$
Subtotal (95% CI)		242		235	100.0%	1.11 [0.55, 2.25]	-
Total events	16		14				
Heterogeneity: Chi <sup>2</sup> =	= 5.09, df =	3 (P =	0.17); l² =	: 41%			
Test for overall effect	: Z = 0.30 (	(P = 0.7	7)				
							0102 05 1 2 5 10
							Favours treatment Favours control

### h832 Repeat courses

#### Figure 83: Fetal and neonatal mortality Repeat Single **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 In all babies Aghajafari 2002 Not estimable 0 9 0 7 Crowther 2006 27 568 29 578 27.9% 0.95 [0.57, 1.58] Garite 2009 289 288 5 7 6.8% 0.71 [0.23, 2.22] Guinn 2002 5 256 9 246 8.9% 0.53 [0.18, 1.57] 38 Mazumder 2008 4 8 38 7.8% 0.50 [0.16, 1.52] 0.5% McEvoy 2010 1 56 0 56 3.00 [0.12, 72.10] Murphy 2008 1164 40 1140 39.3% 1.05 [0.69, 1.61] 43 Peltoniemi 2007 8 159 167 2.8% 2.80 [0.76, 10.37] 3 Wapner 2006 3 252 6 243 5.9% 0.48 [0.12, 1.91] Subtotal (95% CI) 2791 2763 100.0% 0.94 [0.71, 1.23] Total events 96 102 Heterogeneity: Chi<sup>2</sup> = 6.89, df = 7 (P = 0.44); l<sup>2</sup> = 0% Test for overall effect: Z = 0.48 (P = 0.63) 1.3.2 In babies where pregnancy complicated by preterm prelabour rupture of membranes Guinn 2002 3 81 6 79 100.0% 0.49 [0.13, 1.88] Subtotal (95% CI) 81 79 100.0% 0.49 [0.13, 1.88] Total events 3 6 Heterogeneity: Not applicable Test for overall effect: Z = 1.04 (P = 0.30) 1.3.3 In babies exposed to one repeat course of prenatal corticosteroids Garite 2009 5 289 7 288 67.2% 0.71 [0.23, 2.22] McEvoy 2010 56 56 4.8% 3.00 [0.12, 72.10] Û 1 Peltoniemi 2007 8 159 3 167 28.0% 2.80 [0.76, 10.37] Subtotal (95% CI) 504 511 100.0% 1.41 [0.64, 3.08] Total events 14 10 Heterogeneity: Chi2 = 2.66, df = 2 (P = 0.26); I2 = 25% Test for overall effect: Z = 0.86 (P = 0.39) 0.1 0.2 0.5 ż 5 10 Favours repeat Favours single

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### Figure 84: Use of mechanical ventilation

•	Repe	at	Sing	le		<b>Risk Ratio</b>	Risk Ra	itio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random	n, 95% CI
1.13.1 In all babies								
Crowther 2006	167	567	204	577	22.6%	0.83 [0.70, 0.99]	-	
Garite 2009	70	267	95	273	17.0%	0.75 [0.58, 0.98]		
McEvoy 2010	15	56	18	56	6.3%	0.83 [0.47, 1.48]		-3
Murphy 2008	175	1164	204	1140	21.6%	0.84 [0.70, 1.01]	-	
Peltoniemi 2007	93	159	87	167	20.9%	1.12 [0.92, 1.37]	-	
Wapner 2006 Subtotal (95% CI)	36	250 2463	60	242 2455	11.6%	0.58 [0.40, 0.84] 0.84 [0.71, 0.99]		
Total events	556		668				(	
Heterogeneity: Tau <sup>2</sup> =	0.02; Ch	i <sup>2</sup> = 12.	95, df = 5	(P = 0.	02); I <sup>2</sup> = 6	i1%		
Test for overall effect	Z=2.14	(P = 0.0)	(3)					
							m m mm	
							0.1 0.2 0.5 1	2 5 10

Favours repeat Favours single

.g			.9				
	Repe	at	Sing	le		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.4.1 In all babies							
Aghajafari 2002	2	9	2	7	1.3%	0.78 [0.14, 4.23]	
Crowther 2006	76	567	82	577	47.8%	0.94 [0.71, 1.26]	
Garite 2009	27	273	20	278	11.7%	1.37 [0.79, 2.39]	+
Guinn 2002	28	248	26	235	15.7%	1.02 [0.62, 1.69]	
Mazumder 2008	0	37	0	37		Not estimable	
Murphy 2008	19	1164	11	1140	6.5%	1.69 [0.81, 3.54]	
Peltoniemi 2007	15	159	14	167	8.0%	1.13 [0.56, 2.26]	
Wapner 2006	14	252	15	243	9.0%	0.90 [0.44, 1.82]	
Subtotal (95% CI)		2709		2684	100.0%	1.06 [0.87, 1.30]	<b>•</b>
Total events	181		170				
Heterogeneity: Chi <sup>2</sup> = 3	3.40, df =	6 (P =	0.76); l² =	= 0%			
Test for overall effect: 2	Z = 0.61	(P = 0.5	(4)				
1.4.2 In babies where	pregnar	icy con	nplicated	i by pre	eterm pre	labour rupture of membranes	_
Guinn 2002	15	81	19	79	100.0%	0.77 [0.42, 1.41]	
Subtotal (95% CI)		81		79	100.0%	0.77 [0.42, 1.41]	
Total events	15		19				
Heterogeneity: Not app	plicable						
Test for overall effect: 2	Z = 0.85	(P = 0.3)	(9)				
1.4.3 In babies expos	ed to one	e repea	t course	ofpre	natal cort	icosteroids	
Garite 2009	27	273	20	278	59.2%	1 37 [0 79 2 39]	<b>_</b>
Peltoniemi 2007	15	159	14	167	40.8%	1 13 [0 56 2 26]	
Subtotal (95% CI)	15	432	14	445	100.0%	1.27 [0.83, 1.96]	-
Total events	42		34				
Heterogeneity: Chi <sup>2</sup> = 0	0.19, df=	1 (P =	0.66); l² =	= 0%			
Test for overall effect: 2	Z = 1.09	(P = 0.2	27)				
							Favours repeat Favours single
							r arours repeat i arours single

### Figure 85: Chronic lung disease

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### Figure 86: Intraventricular haemorrhage

	Repe	at	Sing	le	<b>j</b> -	<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.5.1 In all babies	/						
Crowther 2006	34	567	39	577	28.1%	0.89 [0.57, 1.38]	
Garite 2009	19	272	25	274	18.1%	0.77 [0.43, 1.36]	
Guinn 2002	30	248	25	235	18.7%	1.14 [0.69, 1.87]	
Mazumder 2008	0	37	3	37	2.5%	0.14 [0.01, 2.67]	·
Peltoniemi 2007	31	159	27	167	19.2%	1.21 [0.76, 1.93]	
Wapner 2006	15	250	18	242	13.3%	0.81 [0.42, 1.56]	
Subtotal (95% CI)		1533		1532	100.0%	0.94 [0.75, 1.18]	•
Total events	129		137				
Heterogeneity: Chi <sup>2</sup> =	: 3.99, df =	5 (P =	0.55); 12:	= 0%			
Test for overall effect	Z= 0.50	(P = 0.6	51)				
1.5.2 In babies expo	sed to one	e repea	at course	of pre	natal cor	ticosteroids	
Garite 2009	19	272	25	274	48.6%	0.77 [0.43, 1.36]	
Peltoniemi 2007	31	159	27	167	51.4%	1.21 [0.76, 1.93]	
Subtotal (95% CI)		431		441	100.0%	0.99 [0.69, 1.42]	+
Total events	50		52				
Heterogeneity: Chi <sup>2</sup> =	1.46, df=	1 (P=	0.23); 12;	= 31%			
Test for overall effect	Z = 0.04	(P = 0.9	96)				
							0.1 0.2 0.5 1 2 5 1
							Favours repeat Favours single

-	Repe	at	Sing	le		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.6.1 In all babies							
Aghajafari 2002	0	9	1	7	5.8%	0.27 [0.01, 5.70]	
Crowther 2006	5	567	8	577	27.7%	0.64 [0.21, 1.93]	
Garite 2009	6	272	4	274	13.9%	1.51 [0.43, 5.30]	
Guinn 2002	9	248	2	235	7.2%	4.26 [0.93, 19.53]	
Murphy 2008	6	1164	9	1140	31.8%	0.65 [0.23, 1.83]	
Peltoniemi 2007	6	159	4	167	13.6%	1.58 [0.45, 5.48]	- <b>!-</b> -
Subtotal (95% CI)		2419		2400	100.0%	1.13 [0.69, 1.86]	<b>•</b>
Total events	32		28				
Heterogeneity: Chi <sup>2</sup> =	6.38, df =	: 5 (P =	0.27); l²:	= 22%			
Test for overall effect:	Z = 0.48	(P = 0.6	3)				
							Favours repeat Favours single

#### Figure 87: Intraventricular haemorrhage grades 3/4

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#### Figure 88: Periventricular leuomalacia

-	Repe	at	Sing	Single		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI		
1.7.1 In all babies									
Aghajafari 2002	0	9	0	7		Not estimable			
Crowther 2006	4	567	9	577	33.6%	0.45 [0.14, 1.46]			
Garite 2009	3	269	4	272	15.0%	0.76 [0.17, 3.36]			
Guinn 2002	2	248	3	235	11.6%	0.63 [0.11, 3.75]			
Mazumder 2008	0	37	0	37		Not estimable			
Murphy 2008	9	1164	10	1140	38.0%	0.88 [0.36, 2.16]			
Peltoniemi 2007	2	159	0	167	1.8%	5.25 [0.25, 108.51]			
Subtotal (95% CI)		2453		2435	100.0%	0.77 [0.43, 1.37]			
Total events	20		26						
Heterogeneity: Chi <sup>2</sup> =	2.47, df=	4 (P =	0.65); l² =	= 0%					
Test for overall effect:	Z = 0.89	(P = 0.3)	7)						
							Favours repeat Favours single		

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#### Figure 89: Early systemic neonatal infection



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Favours repeat Favours single



#### Figure 90: Birthweight adjusted for gestational age (Z scores)

Test for subgroup differences: Chi<sup>2</sup> = 0.38, df = 1 (P = 0.54), l<sup>2</sup> = 0%

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#### Figure 91: Major neurosensory disability at early childhood follow-up

	Repe	at	Sing	le		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.24.1 In all babies							
Crowther 2006	53	495	70	504	77.7%	0.77 [0.55, 1.08]	
Peltoniemi 2007	3	118	1	139	22.3%	3.53 [0.37, 33.52]	
Subtotal (95% CI)		613		643	100.0%	1.08 [0.31, 3.76]	-
Total events	56		71				
Heterogeneity: Tau <sup>2</sup> =	0.49; Ch	= 1.7	3, df = 1 (	P = 0.1	9); I= 42	96	
Test for overall effect:	Z=0.13	(P = 0.9	90)				
1.24.2 In babies expo	osed to or	ne repe	at cours	e of pr	enatal co	rticosteroids	0.000
Peltoniemi 2007	3	118	1	139	100.0%	3.53 [0.37, 33.52]	
Subtotal (95% CI)		118		139	100.0%	3.53 [0.37, 33.52]	
Total events	3		1				· · · · · · · · · · · · · · · · · · ·
Heterogeneity: Not ap	plicable						
Test for overall effect	Z=1.10	P = 0.2	27)				
			00000				
							1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
							0.001 0.1 1 10 10

Favours repeat Favours single

Favours repeat Favours single

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#### Figure 92: Any maternal side-effects of therapy

-	Repe	at	Sing	le		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	N	I-H, Rand	om, 95% C		
1.18.1 In all women											
Crowther 2006	47	489	24	493	48.9%	1.97 [1.23, 3.18]					
Wapner 2006 Subtotal (95% CI)	68	250 739	135	242 735	51.1% 100.0%	0.49 [0.39, 0.61]	_	-			
Total events	115		159								
Heterogeneity: Tau <sup>2</sup> =	0.98; Chi	i² = 27.0	82, df = 1	(P < 0.	00001); P	<sup>2</sup> = 96%					
Test for overall effect.	Z = 0.05 (	(P = 0.9)	16)								
							0.1.0.2	0.5	2	5 10	

Figure 93:	Puerp	eral	sepsi	s			
_	Repe	at	Sing	le		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.13.1 In all women							
Aghajafari 2002	0	6	0	6		Not estimable	
Guinn 2002	13	249	14	236	23.3%	0.88 [0.42, 1.83]	
Murphy 2008	34	935	25	918	40.8%	1.34 [0.80, 2.22]	+
Peltoniemi 2007	19	125	12	124	19.5%	1.57 [0.80, 3.10]	+
Wapner 2006 Subtotal (95% CI)	6	250 1565	10	242 1526	16.4% 100.0%	0.58 [0.21, 1.57] 1.15 [0.83, 1.60]	•
Total events	72		61				
Heterogeneity: Chi <sup>2</sup>	= 3.46, df=	3 (P =	0.33); l <sup>a</sup> :	= 13%			
Test for overall effect	t Z = 0.83	(P = 0.4)	(0)				
1.13.2 In women wi Guinn 2002 Subtotal (95% CI) Total events	here pregn 4 4	ancy c 81 81	omplicat 6	ed by p 79 79	reterm p 100.0% 100.0%	relabour rupture of membranes 0.65 [0.19, 2.22] 0.65 [0.19, 2.22]	
Heterogeneity: Not a	applicable						
Test for overall effect	t Z = 0.69	(P = 0.4	19)				
1.13.3 In women giv	ven one rej	peat co	ourse of p	prenata	I corticos	steroids	
Peltoniemi 2007 Subtotal (95% CI)	19	125 125	12	124 124	100.0% 100.0%	1.57 [0.80, 3.10] 1.57 [0.80, 3.10]	
Total events	19		12				
Heterogeneity: Not a	applicable						
Test for overall effect	t Z = 1.30	(P = 0.1)	9)				
			,				
							0.1 0.2 0.5 1 2 5 10
							Favours repeat Favours single

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### Magnesium sulphate for neuroprotection 1**b9**

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#### Figure 94: Stillbirth

0	Magnesium Sul	phate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Crowther et al., 2003	9	629	11	626	50.5%	0.81 (0.34, 1.95)	
Marret et al., 2007	2	352	3	336	14.0%	0.64 [0.11, 3.78]	
Rouse et al., 2008	5	1179	8	1252	35.5%	0.66 [0.22, 2.02]	
Total (95% CI)		2160		2214	100.0%	0.74 [0.39, 1.40]	•
Total events	16		22				
Heterogeneity: Chi <sup>2</sup> = 0.	11, df = 2 (P = 0.9	85); I <sup>2</sup> = 0	1%				
Test for overall effect: Z = 0.94 (P = 0.35)							Favours MgSO4 Favours control

### Figure 95: Neonatal mortality: before discharge

-	Magnesium Sulphate		Placebo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Crowther et al., 2003	76	629	92	626	47.6%	0.82 [0.62, 1.09]	-
Marret et al., 2007	31	352	32	336	16.9%	0.92 [0.58, 1.48]	-
Rouse et al., 2008	80	1179	71	1252	35.5%	1.20 [0.88, 1.63]	+
Total (95% CI)		2160		2214	100.0%	0.97 [0.80, 1.18]	+
Total events	187		195				
Heterogeneity: Chi <sup>2</sup> = 3. Test for overall effect: Z	12, df = 2 (P = 0.2 = 0.29 (P = 0.77)	21); I <sup>2</sup> = 3	6%				0.01 0.1 1 10 100 Favours MgSO4 Favours control

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#### Figure 96: Neonatal/paediatric mortality: between discharge and follow-up

0	Magnesium Su	Iphate	Place	bo	, 	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Crowther et al., 2003	2	629	4	626	19.6%	0.50 [0.09, 2.71]	
Rouse et al., 2008	18	1179	17	1252	80.4%	1.12 [0.58, 2.17]	
Total (95% CI)		1808		1878	100.0%	1.00 [0.55, 1.84]	+
Total events	20		21				
Heterogeneity: Chi <sup>2</sup> = (	).77, df = 1 (P = 0	.38); I <sup>2</sup> = (	0%				
Test for overall effect: 2	Z = 0.01 (P = 1.00)	)					Favours MgSO4 Favours control

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#### Figure 97: Total perinatal, neonatal and paediatric mortality

-	-				-		•
	Magnesium Su	lphate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Crowther et al., 2003	87	629	107	626	44.6%	0.81 [0.62, 1.05]	-
Marret et al., 2008	34	352	38	336	16.2%	0.85 [0.55, 1.32]	-+
Mittendorf et al., 2002	2	30	1	29	0.4%	1.93 [0.19, 20.18]	
Rouse et al., 2008	103	1179	96	1252	38.8%	1.14 [0.87, 1.49]	<b>†</b>
Total (95% CI)		2190		2243	100.0%	0.95 [0.80, 1.13]	•
Total events	226		242				
Heterogeneity: Chi <sup>2</sup> = 3.	82, df = 3 (P = 0.2	28); I <sup>2</sup> = 2	2%				
Test for overall effect Z	= 0.60 (P = 0.55)						Favours MgSO4 Favours control

### Figure 98: Findings on cranial ultrasound: grades III or IV intracranial haemorrhage

	Magnesium Sulpl	hate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Crowther et al., 2003	49	596	50	586	56.2%	0.96 [0.66, 1.40]	+
Mittendorf et al., 2002	0	30	2	29	2.8%	0.19 [0.01, 3.87]	<
Rouse et al., 2008	23	1112	38	1184	41.0%	0.64 [0.39, 1.07]	
Total (95% CI)		1738		1799	100.0%	0.81 [0.60, 1.09]	•
Total events	72		90				
Heterogeneity: Chi <sup>2</sup> = 2.4	46, df = 2 (P = 0.29)	; I <sup>2</sup> = 1	3%				
Test for overall effect Z	= 1.37 (P = 0.17)						Favours MoSO4 Favours control
							arous ingest i arous contor

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### Figure 99: Findings on cranial ultrasound: periventricular leukomalacia

	Magnesium Su	Iphate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Crowther et al., 2003	22	596	21	586	44.3%	1.03 [0.57, 1.85]	
Mittendorf et al., 2002	1	30	0	29	1.1%	2.90 [0.12, 68.50]	
Rouse et al., 2008	21	1112	27	1184	54.7%	0.83 [0.47, 1.46]	
Total (95% CI)		1738		1799	100.0%	0.94 [0.63, 1.40]	+
Total events	44		48				10 1 10 10 10 10 10 10 10 10 10 10 10 10
Heterogeneity: Chi <sup>2</sup> = 0	.78, df = 2 (P = 0.6	58); I <sup>#</sup> = 0	%				
Test for overall effect Z	(= 0.30 (P = 0.76)						Favours MgSO4 Favours control

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### Figure 100: Cerebral palsy: any

-	Magnesium Sulphate		Magnesium Sulphate Placebo		bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Crowther et al., 2003	36	620	42	621	28.9%	0.86 [0.56, 1.32]	-	
Marret et al., 2008	22	347	30	331	21.2%	0.70 [0.41, 1.19]		
Mittendorf et al., 2002	3	30	0	29	0.4%	6.77 [0.37, 125.65]		
Rouse et al., 2008	41	1133	74	1203	49.5%	0.59 [0.41, 0.85]	-	
Total (95% CI)		2130		2184	100.0%	0.71 [0.56, 0.91]	•	
Total events	102		146					
Heterogeneity: Chi <sup>2</sup> = 4.	02, df = 3 (P = 0.2)	6); I <sup>2</sup> = 2	5%					
Test for overall effect Z	= 2.71 (P = 0.007)						Favours MgSO4 Favours control	

### 144

### Figure 101: Cerebral palsy: moderate or severe (at 2 years)

0	Magnesium Si	ulphate	e Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Crowther et al., 2003	15	620	21	620	36.2%	0.71 [0.37, 1.37]	
Rouse et al., 2008	20	1041	38	1095	63.8%	0.55 [0.32, 0.95]	-=-
Total (95% CI)		1661		1715	100.0%	0.61 [0.40, 0.92]	*
Total events	35		59				2
Heterogeneity: Chi <sup>2</sup> = (	0.35, df = 1 (P = 0	.55); l <sup>2</sup> = (	1%				
Test for overall effect: 2	Z = 2.33 (P = 0.02	2)					Favours MgSO4 Favours control

### Figure 102: Maternal death

	Magnesium Sul	phate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Crowther et al., 2003	0	535	0	527		Not estimable	_
Marret et al., 2007	0	286	1	278	100.0%	0.32 [0.01, 7.92]	
Rouse et al., 2008	0	1096	0	1145		Not estimable	_
Total (95% CI)		1917		1950	100.0%	0.32 [0.01, 7.92]	
Total events	0		1				
Heterogeneity: Not appli	cable						
Test for overall effect: Z =	: 0.69 (P = 0.49)						Favours MgSO4 Favours control

### 146

### Figure 103: Maternal adverse effects: any

-	Magnesium Su	lphate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Crowther et al., 2003	476	535	199	527	50.1%	2.36 [2.10, 2.64]	
Rouse et al., 2008	833	1078	140	1125	49.9%	6.21 [5.30, 7.27]	
Total (95% CI)		1613		1652	100.0%	3.82 [1.38, 10.59]	•
Total events	1309		339				
Heterogeneity: Tau <sup>2</sup> = 0.54; Chi <sup>2</sup> = 109.57, df = 1 (P < 0.00001); I <sup>2</sup> =							
Test for overall effect: Z	= 2.58 (P = 0.01)						Favours MoSO4 Favours control

### 147

### Figure 104: Maternal adverse effects: leading to stopping of infusion

•	Magnesium 3	Sulphate	Place	bo	•	Risk Ratio	Risk	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI
Crowther et al., 2003	78	535	28	527	64.3%	2.74 [1.81, 4.15]		-
Rouse et al., 2008	45	1078	16	1125	35.7%	2.94 [1.67, 5.16]		
Total (95% CI)		1613		1652	100.0%	2.81 [2.01, 3.93]		•
Total events	123		44					
Heterogeneity: Chi <sup>2</sup> = (	0.04, df = 1 (P =	0.85); l <sup>2</sup> = 0	1%				0.01 01	10 100
Test for overall effect: 2	Z = 6.06 (P < 0.0	0001)					Favours MgSO4	Favours control

### 148

### Figure 105: Maternal adverse effects: cardiac or respiratory arrest

<u> </u>									
	Magnesium Su	Iphate	Place	bo		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	d, 95% Cl	
Crowther et al., 2003	0	535	0	527		Not estimable			
Marret et al., 2007	0	286	0	278		Not estimable			
Total (95% CI)		821		805		Not estimable			
Total events	0		0						
Heterogeneity: Not appl	licable						0.01 0.1	10 100	1
rest for overall effect. N	or abblicable						Favours MgSO4	Favours control	

## I130 Tocolysis

### Figure 106: Neonatal mortality

Comparison		Odds Ratio (95% Crl)
Placebo/control v.		
Prostaglandin inhibitors Magnesium sulfate Betamimetics Calcium channel blockers Nitrates Oxytocin receptor blockers Alcohol/ethanol Other treatments		1.1 (0.39, 3.4) 1.5 (0.56, 4.1) 1.0 (0.49, 2.1) 0.62 (0.21, 1.8) 0.98 (0.016, 62.) 0.73 (0.23, 2.2) 2.3 (0.41, 14.) 0.56 (0.11, 2.6)
Prostagiandin inhibitors v.		1 2 (0 45 2 0)
Betamimetics Calcium channel blockers Nitrates Oxytocin receptor blockers Alcohol/ethanol Other treatments		1.3 (0.45, 3.8) 0.90 (0.32, 2.4) 0.55 (0.16, 1.7) 0.86 (0.013, 56.) 0.64 (0.16, 2.4) 2.1 (0.29, 14.) 0.49 (0.078, 2.7)
Magnesium sulfate v.		
Betamimetics Calcium channel blockers Nitrates - Oxytocin receptor blockers Alcohol/ethanol Other treatments		0.68 (0.26, 1.8) 0.42 (0.13, 1.2) 0.65 (0.010, 42.) 0.49 (0.13, 1.7) 1.6 (0.24, 10.) 0.37 (0.065, 1.8)
Betamimetics v.		
Calcium channel blockers Nitrates Oxytocin receptor blockers Alcohol/ethanol Other treatments		0.61 (0.25, 1.4) 0.96 (0.016, 57.) 0.71 (0.26, 1.8) 2.3 (0.44, 12.) 0.54 (0.10, 2.6)
Calcium channel blockers v.		
Nitrates Oxytocin receptor blockers Alcohol/ethanol Other treatments		1.6 (0.024, 1.1e+02) 1.2 (0.36, 3.8) 3.7 (0.60, 25.) 0.89 (0.15, 5.1)
Nitrates v.		
Oxytocin receptor blockers - Alcohol/ethanol Other treatments -		0.74 (0.011, 50.) 2.4 (0.030, 1.9e+02) 0.57 (0.0071, 44.)
Oxytocin receptor blockers v	<i>ı</i> .	
Alcohol/ethanol Other treatments	<del></del>	3.2 (0.49, 22.) 0.76 (0.12, 4.7)
Other treatments		0.24 (0.031 1.6)
	7 1 20	0.24 (0.001, 1.0)
0.00	favours tr	reatment in bold

<Insert Note here>

### Figure 107: Perinatal mortality

Comparison		Odds Ratio (95% Crl)
Placebo/control v.		
Prostaglandin inhibitors Magnesium sulfate Betamimetics Calcium channel blockers Nitrates Oxytocin receptor blockers Alcohol/ethanol Other treatments		0.72 (0.22, 2.3) 1.2 (0.35, 3.7) 1.0 (0.48, 2.) 0.76 (0.25, 2.2) 0.10 (0.0030, 1.1) 0.86 (0.25, 2.6) 2.6 (0.50, 14.) 2.0 (0.41, 9.7)
Prostaglandin inhibitors v.		
Magnesium sulfate Betamimetics Calcium channel blockers Nitrates Oxytocin receptor blockers Alcohol/ethanol Other treatments		1.6 (0.44, 6.3) 1.4 (0.43, 4.5) 1.1 (0.25, 4.3) 0.14 (0.0036, 1.9) 1.2 (0.24, 5.4) 3.6 (0.54, 25.) 2.8 (0.41, 19.)
Magnesium sulfate v.		
Betamimetics Calcium channel blockers Nitrates Oxytocin receptor blockers Alcohol/ethanol Other treatments		0.85 (0.28, 2.7) 0.64 (0.18, 2.5) 0.085 (0.0022, 1.1) 0.72 (0.15, 3.3) 2.2 (0.34, 16.) 1.7 (0.26, 12.)
Betamimetics v.		
Calcium channel blockers Nitrates Oxytocin receptor blockers Alcohol/ethanol Other treatments		0.75 (0.31, 1.8) 0.10 (0.0031, 1.1) 0.85 (0.28, 2.4) 2.6 (0.57, 13.) 2. (0.42, 9.7)
Calcium channel blockers v	·.	
Nitrates Oxytocin receptor blockers Alcohol/ethanol Other treatments		0.13 (0.0037, 1.6) 1.1 (0.27, 4.4) 3.4 (0.60, 21.) 2.6 (0.43, 16.)
Nitrates v.		
Oxytocin receptor blockers Alcohol/ethanol Other treatments	 	8.4 (0.65, 3.1e+02) 26. (1.6, 1.2e+03) 20. (1.2, 8.7e+02)
Oxytocin receptor blockers	v.	
Alcohol/ethanol Other treatments		3.0 (0.50, 22.) 2.3 (0.37, 16.)
Alcohol/ethanol v.		
Other treatments		0.77 (0.13, 4.5)
0.0	02 1 20	ioo
	favours tr	reatment in bold

<Insert Note here>

### Figure 108: Respiratory distress syndrome

Comparison		Odds Ratio (95% Crl)
Placebo/control v.		
Prostaglandin inhibitors Magnesium sulfate Betamimetics Calcium channel blockers Oxytocin receptor blockers Alcohol/ethanol Other treatments		1.1 (0.68, 1.9) 1.2 (0.76, 1.9) 0.88 (0.65, 1.2) 0.81 (0.50, 1.3) 0.96 (0.66, 1.4) 2.5 (0.78, 9.1) 0.75 (0.26, 2.2)
Prostaglandin inhibitors v.		
Magnesium sulfate Betamimetics Calcium channel blockers Oxytocin receptor blockers Alcohol/ethanol Other treatments		1.1 (0.69, 1.7) 0.78 (0.49, 1.3) 0.71 (0.41, 1.3) 0.85 (0.52, 1.4) 2.2 (0.65, 8.4) 0.66 (0.20, 2.2)
Magnesium sulfate v.		
Betamimetics Calcium channel blockers Oxytocin receptor blockers Alcohol/ethanol Other treatments		0.73 (0.47, 1.2) 0.67 (0.41, 1.1) 0.80 (0.51, 1.3) 2.1 (0.62, 7.9) 0.63 (0.19, 2.0)
Betamimetics v.		
Calcium channel blockers Oxytocin receptor blockers Alcohol/ethanol Other treatments		0.92 (0.61, 1.4) 1.1 (0.77, 1.5) 2.9 (0.92, 9.8) 0.85 (0.28, 2.6)
Calcium channel blockers v	.	
Oxytocin receptor blockers Alcohol/ethanol Other treatments		1.2 (0.73, 1.9) 3.1 (0.93, 11.) 0.93 (0.28, 3.0)
Oxytocin receptor blockers	v.	
Alcohol/ethanol Other treatments		2.6 (0.80, 9.5) 0.79 (0.25, 2.4)
Other treatments		0 29 (0 057 1 5)
0.0	)5 1 for course	20
	lavour	s rearrient in Dolo

<Insert Note here>

### Figure 109: Intraventricular haemorrhage

Comparison		Odds Ratio (95% Crl)
Placebo/control v.		
Prostaglandin inhibitors Magnesium sulfate Betamimetics Calcium channel blockers Nitrates Oxytocin receptor blockers Other treatments –		0.76 (0.35, 1.6) 0.69 (0.33, 1.4) 0.79 (0.51, 1.2) 0.40 (0.21, 0.74) 0.34 (0.081, 1.1) 0.82 (0.48, 1.4) 0.14 (0.016, 0.77)
Prostaglandin inhibitors v.		
Magnesium sulfate Betamimetics Calcium channel blockers Nitrates Oxytocin receptor blockers Other treatments		0.91 (0.54, 1.5) 1.0 (0.53, 2.1) 0.53 (0.27, 1.0) 0.45 (0.096, 1.7) 1.1 (0.48, 2.4) 0.19 (0.023, 0.94)
Magnesium sulfate v.		
Betamimetics Calcium channel blockers Nitrates Oxytocin receptor blockers Other treatments		1.2 (0.58, 2.3) 0.58 (0.30, 1.1) 0.49 (0.11, 1.9) 1.2 (0.53, 2.7) 0.21 (0.026, 0.95)
Betamimetics v.		
Calcium channel blockers Nitrates Oxytocin receptor blockers Other treatments	- <del>-</del>	0.50 (0.30, 0.83) 0.43 (0.11, 1.4) 1.0 (0.63, 1.7) 0.18 (0.021, 0.96)
Calcium channel blockers v.		
Nitrates Oxytocin receptor blockers Other treatments		0.85 (0.20, 3.0) 2.1 (1.0, 4.1) 0.36 (0.042, 1.9)
Nitrates v.		
Oxytocin receptor blockers Other treatments		2.4 (0.68, 10.) 0.42 (0.037, 3.7)
Oxytocin receptor blockers v.		
Other treatments		0.17 (0.019, 0.98) 7 20
0.01	favo	urs treatment in bold

<Insert Note here>

Figure 110:	Mothers with adverse events requiring cessation of treatment
-------------	--

Comparison		Odds Ratio (95% Crl)
Placebo/control v.		
Magnesium sulfate Betamimetics Calcium channel blockers Nitrates Oxytocin receptor blockers		<ul> <li>16. (1.9, 1.8e+02)</li> <li>1.3e+02 ( 19., 1.3e+03)</li> <li>5.2 (0.35, 57.)</li> <li>5.6 (0.26, 1.6e+02)</li> <li>3.1 (0.31, 23.)</li> </ul>
Magnesium sulfate v.		
Betamimetics Calcium channel blockers Nitrates Oxytocin receptor blockers		8.0 (2.2, 34.) 0.32 (0.045, 1.4) 0.34 (0.013, 9.2) 0.19 (0.019, 1.1)
Betamimetics v.		
Calcium channel blockers Nitrates Oxytocin receptor blockers	 	0.039 (0.0059, 0.14) 0.042 (0.0015, 1.2) 0.023 (0.0033, 0.091)
Calcium channel blockers v	.	
Nitrates Oxytocin receptor blockers	 	1.1 (0.039, 49.) 0.59 (0.071, 5.3)
Nitrates v.		
Oxytocin receptor blockers	<del>0</del>	0.54 (0.013, 15.)
0.00	)1 1	2000
	favo	urs treatment in bold

<Insert Note here>

### Figure 111: Delay of birth by at least 48 hours

Comparison	Odds Ratio (95% Crl)
Placebo/control v.	
Prostaglandin inhibitors Magnesium sulfate Betamimetics Calcium channel blockers Nitrates — — — — — — — — — — — — — — — — — — —	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$
Prostaglandin inhibitors v.	
Magnesium sulfateBetamimeticsCalcium channel blockersNitratesOxytocin receptor blockersAlcohol/ethanolOther treatments	- 0.67 (0.33, 1.3) - 0.65 (0.32, 1.3) - 0.64 (0.31, 1.3) 0.28 (0.100, 0.78) - 0.61 (0.26, 1.4) 0.26 (0.035, 1.9) - 0.35 (0.099, 1.2)
Magnesium sulfate v.	
Betamimetics	→         0.97 (0.57, 1.7)           →         0.96 (0.56, 1.6)           →         0.43 (0.17, 1.1)           →         0.92 (0.45, 1.9)           →         0.40 (0.057, 2.7)           →         0.53 (0.17, 1.7)
Betamimetics v.	
Calcium channel blockersNitratesOxytocin receptor blockersAlcohol/ethanolOther treatments	<ul> <li>→ 0.99 (0.65, 1.5)</li> <li>0.44 (0.19, 1.0)</li> <li>→ 0.95 (0.54, 1.6)</li> <li>→ 0.41 (0.062, 2.6)</li> <li>→ 0.54 (0.18, 1.6)</li> </ul>
Calcium channel blockers v.	
Nitrates     o       Oxytocin receptor blockers	0.44 (0.19, 1.0) 0.96 (0.52, 1.7) 0.41 (0.060, 2.7) 0.54 (0.18, 1.6)
Nitrates v.	
Oxytocin receptor blockers	→         2.2 (0.85, 5.5)           →         0.93 (0.12, 7.0)           →         1.2 (0.34, 4.5)
Oxytocin receptor blockers v.	
Alcohol/ethanol Other treatments	
Alconol/ethanol v.	
Other treatments	● 1.3 (0.21, 8.6)
0.03 1	1 9
favours treatment in bold	

<Insert Note here>

### Figure 112: Neonatal sepsis

Comparison		Odds Ratio (95% Crl)
Placebo/control v.		
Prostaglandin inhibitors Magnesium sulfate Betamimetics Calcium channel blockers Oxytocin receptor blockers		1.6 (0.33, 9.3) 1.9 (0.43, 11.) 1.1 (0.25, 6.6) 0.83 (0.18, 4.7) 1.2 (0.22, 7.1)
Other treatments		1.3 (0.21, 8.0)
Prostaglandin inhibitors v.		
Magnesium sulfate Betamimetics Calcium channel blockers Oxytocin receptor blockers Other treatments –		1.2 (0.63, 2.4) 0.72 (0.29, 1.8) 0.52 (0.23, 1.1) 0.73 (0.25, 2.1) 0.81 (0.065, 9.)
Magnesium sulfate v.		
Betamimetics Calcium channel blockers Oxytocin receptor blockers Other treatments —		0.59 (0.26, 1.3) 0.43 (0.21, 0.86) 0.60 (0.22, 1.6) 0.67 (0.056, 7.0)
Betamimetics v.		
Calcium channel blockers Oxytocin receptor blockers Other treatments	 	0.72 (0.42, 1.2) 1.0 (0.55, 1.9) 1.1 (0.093, 12.)
Calcium channel blockers v.		
Oxytocin receptor blockers Other treatments		1.4 (0.65, 3.0) - 1.6 (0.13, 17.)
Oxytocin receptor blockers v.	.	
Other treatments 0.05	<del> </del> 1	1.1 (0.086, 13.) 20
	favour	e troatmont in hold

favours treatment in bold

<Insert Note here>

### Figure 113: Gestational age at birth

Comparison		Mean difference (95% Crl)
Placebo/control v.		
Prostaglandin inhibitors Magnesium sulfate Betamimetics Calcium channel blockers Nitrates Oxytocin receptor blockers		2.3 (1.3, 3.3) 1.3 (0.29, 2.3) 1.2 (0.40, 2.1) 1.7 (0.69, 2.7) 1.7 (0.52, 2.8) 0.68 (-1.3, 2.7)
Prostaglandin inhibitors v.		
Magnesium sulfate Betamimetics Calcium channel blockers Nitrates Oxytocin receptor blockers		-1.0 (-2.0, -0.039) -1.1 (-2.1, -0.054) -0.64 (-1.7, 0.42) -0.67 (-2., 0.67) -1.6 (-3.8, 0.52)
Magnesium sulfate v.		
Betamimetics Calcium channel blockers Nitrates Oxytocin receptor blockers		-0.040 (-0.99, 0.91) 0.40 (-0.51, 1.3) 0.36 (-0.88, 1.6) -0.61 (-2.7, 1.5)
Betamimetics v.		
Calcium channel blockers Nitrates Oxytocin receptor blockers		0.44 (-0.32, 1.2) 0.40 (-0.54, 1.4) -0.57 (-2.6, 1.5)
Calcium channel blockers v	<i>ı</i> .	
Nitrates Oxytocin receptor blockers	 	-0.033 (-1.2, 1.1) -1.0 (-3., 0.99)
Nitrates V.		0.00/.04.4.0
	4 0	-0.98 (-3.1, 1.2) 

favours treatment in bold

### Fetal monitoring 137

#### 1.158 **EFM versus IA**

No forest plots were generated for this review question. 159

#### 1.1602 Use of FSE

161 No forest plots were generated for this review question.

### I.1623 CTG interpretation

163 No forest plots were generated for this review question.

### I.1644 Blood sampling

165 No forest plots were generated for this review question.

### I112 Mode of birth

## **I.127** Planned immediate caesarean section versus planned vaginal delivery in singletons

### I.12891 Neonatal outcome



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### Figure 115: Intracranial pathology (outcome not pre-specified)



#### Figure 116: Hypoxic ischemic encephalopathy



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#### Figure 117: Respiratory distress syndrome



#### 1.1232 Immediate caesarean section versus planned vaginal delivery in singletons

#### 1.12.241 Maternal outcomes



### Figure 119: Maternal wound infection

5	Planne	d CS	Planned vaginal d	elivery		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2.6.1 Breech							
Zlatnik 1993	0	18	1	20	76.1%	0.37 [0.02, 8.51]	
Viegas 1985	1	12	0	15	23.9%	3.69 [0.16, 83.27]	
Subtotal (95% CI)		30		35	100.0%	1.16 [0.18, 7.70]	
Total events	1		1				
Heterogeneity: Chi <sup>2</sup> =	1.04, df	= 1 (P -	= 0.31); I <sup>2</sup> = 4%				
Test for overall effect:	Z = 0.16	(P = 0	.87)				
2.6.2 Cephalic							
Wallace 1984	0	23	0	15		Not estimable	
Subtotal (95% CI)		23		15		Not estimable	
Total events	0		0				
Heterogeneity: Not app	plicable						
Test for overall effect:	Not appl	cable					
Total (95% CI)		53		50	100.0%	1.16 [0.18, 7.70]	
Total events	1		1				
Heterogeneity: Chi <sup>2</sup> =	1.04, df	= 1 (P -	$= 0.31$ ; $l^2 = 4\%$				
Test for overall effect:	Z = 0.16	(P = 0)	.87)				Eavours caesarean section Eavours vaninal delivery
Test for subgroup diffe	erences: I	Not app	licable				ravours caesarean sectori ravours vaginai delivery

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### Figure 120: Other maternal infection

•	Planned	1 CS	Planned vaginal de	elivery		Risk Ratio	Risk	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fix	ed, 95% CI
2.7.1 Breech								
Zlatnik 1993	9	18	4	20	89.4%	2.50 [0.93, 6.73]	_	
Viegas 1985	1	12	0	15	10.6%	3.69 [0.16, 83.27]	•	
Subtotal (95% CI)		30		35	100.0%	2.63 [1.02, 6.78]		
Total events	10		4					
Heterogeneity: Chi <sup>2</sup> =	0.06, df	= 1 (P -	$= 0.81$ ; $l^2 = 0\%$					
Test for overall effect:	Z = 1.99	(P = 0	.05)					
2.7.2 Cephalic								
Wallace 1984	0	23	0	15		Not estimable		
Subtotal (95% CI)		23		15		Not estimable		
Total events	0		0					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Not appli	cable						
Total (95% CI)		53		50	100.0%	2.63 [1.02, 6.78]		
Total events	10		4					
Heterogeneity: Chi <sup>2</sup> =	0.06, df	= 1 (P -	$= 0.81$ ; $l^2 = 0\%$				0.5 0.7	100
Test for overall effect:	Z = 1.99	(P = 0)	.05)				Eavours caesarean section	Eavours vaninal delivery
Test for subgroup diff	erences: N	Not app	licable				ration's caesalean sector	ration's raginal demety

## I113 Timing of cord clamping

## **I.13**81 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

FIGULE IZI. IIII AIL GEALI	Figure	121:	Infant	death
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	More placenta	l trans	Less placental	l trans		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.1.1 Infant death ove	rall						
Ultee 2008	0	18	0	19		Not estimable	
Mercer 2003	0	16	0	16		Not estimable	
Kinmond 1993	0	17	0	19		Not estimable	
Strauss 2008	0	45	0	60		Not estimable	
Hofmeyr 1988	5	24	0	14	2.4%	6.60 [0.39, 111.10]	
Hofmeyr 1993	1	40	1	46	3.6%	1.15 [0.07, 17.80]	
Kugelman 2007	0	30	1	35	5.3%	0.39 [0.02, 9.16]	
Rabe 2000	0	19	1	20	5.6%	0.35 [0.02, 8.10]	
McDonnell 1997	0	23	2	23	9.6%	0.20 [0.01, 3.95]	
Baezinger 2007	0	15	3	24	10.5%	0.22 [0.01, 4.04]	
Oh 2002	2	16	3	17	11.2%	0.71 [0.14, 3.70]	
Hosono 2008	2	20	3	20	11.5%	0.67 [0.12, 3.57]	
Mercer 2006	0	36	3	36	13.4%	0.14 [0.01, 2.67]	• • • • • • • • • • • • • • • • • • •
Ranjit 2014	0	44	5	50	19.8%	0.10 [0.01, 1.81]	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)		363		399	92.8%	0.51 [0.26, 1.01]	-
Total events	10		22				
Heterogeneity: Chi <sup>2</sup> =	6.44, df = 9 (P =	0.70); l <sup>2</sup> = 1	0%				
Test for overall effect.	Z = 1.92 (P = 0.0	)5)					
1.1.2 Uterotonic used							
Hofmeyr 1988	5	24	0	14		Not estimable	
McDonnell 1997	0	19	1	20		Not estimable	
Rabe 2000	0	19	1	20		Not estimable	
Baezinger 2007	1	44	2	50	7.2%	0.57 [0.05, 6.05]	•
Subtotal (95% CI)		44		50	7.2%	0.57 [0.05, 6.05]	
Total events	1		2				
Heterogeneity: Not ap	plicable						
Test for overall effect.	Z = 0.47 (P = 0.6	54)					
Total (05% CI)		407		440	100.0%	0 52 10 27 0 001	
Total (55% CI)		-407	24	443	100.0%	0.52 [0.27, 0.99]	-
Hotoregonoity Chill -	11	0.70\/17	24				
Heterogeneity: Chi* =	0.45, 01 = 10 (P = 7 = 4.00 /D = 0.0	= 0.78); 1* =	0%				0.01 0.1 1 10 100
Test for overall effect.	2 = 1.98 (P = 0.0	15) 0.01 df 1	0-000 7-				More PT better Less PT better
lest for subgroup diffe	erences: Chi# = I	0.01, df = 1	(P = 0.94), P =	0%			
#### Figure 122: Intraventricular haemorrhage

•	More placental	trans	Less placental	trans	-	Risk Ratio	Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl					
1.2.1 New Subgroup												
Strauss 2008	1	45	1	60	1.1%	1.33 [0.09, 20.75]						
Ranjit 2014	0	44	1	50	1.8%	0.38 [0.02, 9.04]						
McDonnell 1997	0	15	1	16	1.9%	0.35 [0.02, 8.08]						
Oh 2002	4	16	3	17	3.8%	1.42 [0.37, 5.37]	<del></del>					
Rabe 2000	1	19	3	20	3.8%	0.35 [0.04, 3.09]						
Kugelman 2007	2	30	4	35	4.8%	0.58 [0.11, 2.96]						
Mercer 2003	3	16	5	16	6.5%	0.60 [0.17, 2.10]						
Hosono 2008	3	20	5	20	6.5%	0.60 [0.17, 2.18]						
Hofmeyr 1993	8	40	11	46	13.4%	0.84 [0.37, 1.87]						
Hofmeyr 1988	8	23	10	13	16.7%	0.45 [0.24, 0.85]						
Mercer 2006	5	36	13	36	17.0%	0.38 [0.15, 0.97]						
Subtotal (95% CI)		304		329	77.6%	0.59 [0.41, 0.84]	•					
Total events	35		57									
Heterogeneity: Chi <sup>2</sup> =	Heterogeneity: Chi <sup>a</sup> = 4.62, df = 10 (P = 0.92); i <sup>a</sup> = 0%											
Test for overall effect.	Z = 2.88 (P = 0.0	04)										
1.2.2 Uterotonic used												
McDonnell 1997	0	15	1	16	1.9%	0.35 [0.02, 8.08]						
Rabe 2000	4	16	3	17	3.8%	1.42 [0.37, 5.37]						
Hofmeyr 1988	8	23	10	13	16.7%	0.45 [0.24, 0.85]						
Subtotal (95% CI)		54		46	22.4%	0.61 [0.34, 1.08]	-					
Total events	12		14									
Heterogeneity: Chi <sup>2</sup> =	2.50, df = 2 (P = )	0.29); I <sup>2</sup> =	20%									
Test for overall effect.	Z = 1.71 (P = 0.0	9)										
Total (95% CI)		358		375	100.0%	0.59 (0.44, 0.81)	•					
Total coonto	47	550	71	515	100.074	0.00 [0.14, 0.01]	•					
Heterogeneity Chi?-	97 7 00 /4f - 12 /P -	0.001/17	- 0%									
Test for overall effect	7 - 2 24 /P = 0.0	0.30), 1	= 0.20				0.01 0.1 1 10 100					
Test for subgroup diff:	L = 3.34 (P = 0.0)	000)	1/P = 0.02) #=	n%			More PT better Less PT better					
rest for subdroup dim	erences: Chir = 0	Test for subgroup differences: Chi#= 0.01, df = 1 (P = 0.92), I#= 0%										

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# Figure 123: Severe intraventricular haemorrhage

	More placenta	l trans	Less placental	trans		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 New Subgroup										
Mercer 2003	0	16	0	16		Not estimable				
Rabe 2000	0	19	0	20		Not estimable				
Hofmeyr 1988	2	23	0	13	7.3%	2.92 [0.15, 56.51]				
Mercer 2006	0	36	1	36	17.4%	0.33 [0.01, 7.92]				
Hofmeyr 1993	1	40	2	46	21.6%	0.57 [0.05, 6.11]				
Hosono 2008	2	20	4	20	46.4%	0.50 [0.10, 2.43]				
Subtotal (95% CI)		154		151	92.7%	0.68 [0.23, 1.96]	-			
Total events	5		7							
Heterogeneity: Chi <sup>2</sup> =	1.28, df = 3 (P =	0.73); P =	0%							
Test for overall effect	Z = 0.72 (P = 0.4	7)								
1.3.2 Uterotonic used	1									
Rabe 2000	- 0	19	0	20		Not estimable				
Hofmeyr 1988	2	23	ŏ	13	7.3%	2.92 [0.15, 56, 51]				
Subtotal (95% CI)	-	42	*	33	7.3%	2.92 [0.15, 56.51]				
Total events	2		0							
Heterogeneity: Not ap	plicable									
Test for overall effect	Z=0.71 (P=0.4	8)								
Total (95% CI)		196		184	100.0%	0.84 [0.32, 2.22]	<b>•</b>			
Total events	7		7							
Heterogeneity: Chi <sup>2</sup> =	Heterogeneity: Chi <sup>2</sup> = 2.20, df = 4 (P = 0.70); i <sup>2</sup> = 0%									
Test for overall effect:	Test for overall effect. Z = 0.35 (P = 0.73)									
Test for subgroup differences: Chi#= 0.83, df = 1 (P = 0.36), i#= 0%										

## Figure 124: Ventilated for respiratory distress syndrome

-	More placenta	l trans	Less placental	trans		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.4.1 New Subgroup							
Strauss 2008	3	45	7	60	7.9%	0.57 [0.16, 2.09]	
Ranjit 2014	5	44	8	50	9.9%	0.71 [0.25, 2.01]	
Rabe 2000	9	19	8	20	10.3%	1.18 [0.58, 2.42]	
McDonnell 1997	9	23	9	23	11.8%	1.00 [0.49, 2.06]	
Baezinger 2007	6	15	12	24	12.1%	0.80 [0.38, 1.67]	
Kinmond 1993	13	17	13	19	16.1%	1.12 [0.75, 1.67]	
Subtotal (95% CI)		163		196	68.1%	0.93 [0.69, 1.25]	<b>+</b>
Total events	45		57				
Heterogeneity: Chi <sup>2</sup> =	2.25, df = 5 (P =	0.81); I <sup>a</sup> =	0%				
Test for overall effect:	Z = 0.49 (P = 0.6	3)					
1.4.2 Uterotonic used	1						
Rabe 2000	3	45	7	60	7.9%	0.57 [0.16, 2.09]	
McDonnell 1997	9	23	9	23	11.8%	1.00 [0.49, 2.06]	
Baezinger 2007	6	15	12	24	12.1%	0.80 [0.38, 1.67]	
Subtotal (95% CI)		83		107	31.9%	0.82 [0.50, 1.33]	-
Total events	18		28				
Heterogeneity: Chi <sup>2</sup> =	0.60, df = 2 (P =	0.74); I <sup>2</sup> =	0%				
Test for overall effect:	Z = 0.81 (P = 0.4	2)					
Total (95% CI)		246		303	100.0%	0.89 [0.69, 1.15]	•
Total events	63	2.00	85				•
Heterogeneitr Chi?=	3 24 df = 8 (P = 1	0.921-12=	.0%				
Test for overall effect	7 = 0.87 / P = 0.3	8)					0.1 0.2 0.5 1 2 5 10
restror overall effect.	2 - 0.01 (r = 0.5	0,					More PT better Less PT better

Test for subgroup differences: Chi#= 0.19, df= 1 (P = 0.66), I#= 0%

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#### Figure 125: Hyperbilirubinemia

•	More placenta	l trans	Less placenta	l trans		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.5.1 New Subgroup							
Ultee 2008	6	18	8	19	13.4%	0.79 [0.34, 1.83]	
Rabe 2000	12	19	12	20	20.2%	1.05 [0.64, 1.73]	
Strauss 2008 Subtotal (95% CI)	33	45	31	59	46.3%	1.40 [1.03, 1.88]	
Total events	51	02	51	00	10.04	121 [0:04, 1:00]	
Heterogeneity: Chi <sup>a</sup> =	2.16, df = 2 (P =	0.34); I <sup>a</sup> =	8%				
Test for overall effect	Z = 1.49 (P = 0.1	4)					
1.5.2 Uterotonic use	d						
Rabe 2000	12	19	12	20	20.2%	1.05 [0.64, 1.73]	
Subtotal (95% CI)		19		20	20.2%	1.05 [0.64, 1.73]	
Total events	12		12				
Heterogeneity: Not ap	oplicable						
Test for overall effect	Z = 0.20 (P = 0.8	4)					
Total (95% CI)		101		118	100.0%	1.18 [0.94, 1.47]	◆
Total events	63		63				
Heterogeneity: Chi <sup>2</sup> =	2.49, df = 3 (P =	0.48); l <sup>a</sup> =	: 0%				
Test for overall effect:	Z = 1.43 (P = 0.1	5)					More PT hetter Less PT hetter
Test for subgroup diff	ferences: Chi#= (	).24, df=	1 (P = 0.63), I <sup>2</sup> =	0%			more ri bewer Less ri bewer

#### Figure 126: Transfused for anaemia

U	More placenta	l trans	Less placental	trans		Risk Ratio	Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI					
1.6.1 New Subgroup												
Strauss 2008	2	45	5	59	4.5%	0.52 [0.11, 2.58]						
Kugelman 2007	3	30	5	35	4.9%	0.70 [0.18, 2.69]						
McDonnell 1997	4	23	6	23	6.3%	0.67 [0.22, 2.05]						
Kinmond 1993	1	13	7	13	7.4%	0.14 [0.02, 1.00]						
Hosono 2008	7	20	14	20	14.7%	0.50 [0.26, 0.97]						
Rabe 2000	9	19	16	20	16.4%	0.59 (0.35, 1.00)						
Mercer 2006	18	36	22	36	23.1%	0.82 [0.54, 1.24]	-					
Subtotal (95% CI)		186		206	77.3%	0.61 [0.46, 0.81]	◆					
Total events	44		75									
Heterogeneity: Chi# = 4.50, df = 6 (P = 0.61); I# = 0%												
Test for overall effect	Z = 3.46 (P = 0.0	005)										
1.6.2 Uterotonic use	d											
McDonnell 1997	4	23	6	23	6.3%	0.67 [0.22, 2.05]						
Rabe 2000	9	19	16	20	16.4%	0.59 [0.35, 1.00]						
Subtotal (95% CI)		42		43	22.7%	0.61 [0.37, 1.00]	•					
Total events	13		22									
Heterogeneity: Chi <sup>2</sup> =	0.04, df = 1 (P =	0.85); I <sup>2</sup> =	0%									
Test for overall effect	Z = 1.94 (P = 0.0	5)										
T-1-LOFF CD		220		240	400.00	0.04 10 40 0.703						
Total (95% CI)		228		249	100.0%	0.61 [0.48, 0.78]	•					
Total events	57		97									
Heterogeneity: Chi <sup>2</sup> =	4.53, df = 8 (P =	0.81); I <sup>2</sup> =	0%				0.01 0.1 1 10 100					
Test for overall effect	Z = 3.97 (P < 0.0	001)					More PT better Less PT better					
Test for subgroup diff												

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# Figure 127: Apgar score at 5th minute < 8

	More placental	trans	Less placental	trans		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
1.8.1 New Subgroup								
Hofmeyr 1988	0	14	4	24	14.4%	0.19 [0.01, 3.20]		
Hofmeyr 1993	8	39	7	45	27.6%	1.32 [0.53, 3.31]		
Rabe 2000	5	19	7	20	29.0%	0.75 [0.29, 1.96]		
Subtotal (95% CI)		72		89	71.0%	0.86 [0.45, 1.62]	<b>•</b>	
Total events	13		18					
Heterogeneity: Chi <sup>2</sup> =	2.02, df = 2 (P =	0.36); I <sup>a</sup> =	1%					
Test for overall effect	Z = 0.47 (P = 0.6	4)						
1.8.2 Uterotonic used	1							
Hofmeyr 1988	14	0	4	24		Not estimable		
Rabe 2000	5	19	7	20	29.0%	0.75 [0.29, 1.96]		
Subtotal (95% CI)		19		44	29.0%	0.75 [0.29, 1.96]	-	
Total events	19		11					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.58 (P = 0.5	6)						
Total (05% CI)		01		133	100.0%	0.93 (0.40, 4.44)		
Total (55% Cl)		91	20	155	100.0%	0.05 [0.45, 1.41]	$\mathbf{T}$	
I otal events	32		29					
Heterogeneity: Chi* =	Heterogenety: Chi" = 2.12, df = 3 (P = 0.55); I" = 0%							
Test for overall effect: Z = 0.70 (P = 0.48) More PT better Less PT better								
Test for subgroup diff	erences: Chi# = 0	1.05, df =	1 (P = 0.82), I <sup>z</sup> =	0%				

#### Figure 128: Haematocrit at 4 hours of life (%)

0							· · /		
	More pla	acental tr	ans	Less placental trans Mean Difference				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.9.1 New Subgroup									
Baezinger 2007	55.56	8.42	15	50.2	7.73	24	8.7%	5.36 [0.09, 10.63]	
Oh 2002	44.4	7	16	40	5.6	17	12.8%	4.40 [0.06, 8.74]	
Nelle 1998	55	5	11	46	4	8	14.7%	9.00 [4.95, 13.05]	
McDonnell 1997	55	7	23	52.5	7	23	14.7%	2.50 [-1.55, 6.55]	
Kinmond 1993	56.4	4.8	17	50.9	4.5	19	25.9%	5.50 [2.45, 8.55]	
Subtotal (95% CI)			82			91	76.6%	5.40 [3.62, 7.17]	•
Heterogeneity: Chi <sup>2</sup> = 5	5.22, df = 4	(P = 0.2)	7); I <sup>a</sup> = 23	3%					
Test for overall effect 2	Z = 5.97 (P	< 0.0000	)1)						
1.9.2 Uterotonic used									
Baezinger 2007	55.56	8.42	15	50.2	7.73	24	8.7%	5.36 [0.09, 10.63]	
McDonnell 1997	55	7	23	52.5	7	23	14.7%	2.50 [-1.55, 6.55]	
Subtotal (95% CI)			38			47	23.4%	3.56 [0.35, 6.77]	-
Heterogeneity: Chi <sup>2</sup> = (	0.71, df = 1	(P = 0.4)	0); $I^{2} = 0$ ?	%					
Test for overall effect 2	Z = 2.18 (P	= 0.03)							
Total (95% CI)			120			138	100.0%	4.97 [3.42, 6.52]	•
Heterogeneity: Chi <sup>2</sup> = 6	6.89, df = 6	i (P = 0.3	3); I <sup>a</sup> = 13	3%					
Test for overall effect 2	Z = 6.28 (P	< 0.0000	)1)						More PT lower Less PT lower
Test for subgroup diffe	rences: C	hi# = 0.96	, df = 1 (	P = 0.33).	I <sup>2</sup> = 0%				moleritonel Cessritonel

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#### Figure 129: Haematocrit at 24 hours after birth (%)

•	More pla	cental tr	rans	Less pla	acental t	rans		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.10.1 New Subgroup									
Baezinger 2007	55.93	7.19	15	49.74	8.34	23	7.5%	6.19 [1.20, 11.18]	
Strauss 2008	56	8.32	41	53	8.16	55	16.8%	3.00 [-0.34, 6.34]	
Kugelman 2007	52.8	5.2	30	50.2	6	35	25.2%	2.60 [-0.12, 5.32]	
Ranjit 2014	58.5	5.1	44	50.8	5.2	50	43.0%	7.70 [5.61, 9.79]	
Subtotal (95% CI)			130			163	92.5%	5.55 [5.91, 6.76]	
Heterogeneity: Chi* = 10 Test for overall effect: Z =	1.81, df = = 7.36 (P	3 (P = 0. < 0.0000	01); P = 01)	72%					
1.10.2 Uterotonic used									
Baezinger 2007	55.93	7.19	15	49.74	8.34	23	7.5%	6.19 [1.20, 11.18]	
Subtotal (95% CI)			15			23	7.5%	6.19 [1.20, 11.18]	
Heterogeneity: Not appli	cable								
Test for overall effect Z =	= 2.43 (P	= 0.01)							
Total (95% CI)			145			186	100.0%	5.40 [4.03, 6.77]	•
Heterogeneity: Chi <sup>a</sup> = 10	.92, df=	4 (P = 0.)	03); I <sup>2</sup> =	63%					
Test for overall effect: Z =	= 7.74 (P		-10 -5 0 5 10 More PT Jower Less PT Jower						
Test for subgroup differe	ences: Cl		more Fridwei Less Fillowei						

# **1.18 More** placental transfusion versus less placental transfusion: subgroup analysis by strategy for more placental transfusion

#### Figure 130: Infant death

-	More placental	trans	Less placental	trans		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
2.1.1 Delayed clampi	ng						
Ultee 2008	0	18	0	19		Not estimable	
Kinmond 1993	0	17	0	19		Not estimable	
Strauss 2008	0	45	0	60		Not estimable	
Mercer 2003	0	16	0	16		Not estimable	
Hofmeyr 1988	5	24	0	14	3.3%	6.60 [0.39, 111.10]	
Hofmeyr 1993	1	40	1	46	4.9%	1.15 [0.07, 17.80]	
Kugelman 2007	0	30	1	35	7.3%	0.39 [0.02, 9.16]	
Rabe 2000	0	19	1	20	7.7%	0.35 [0.02, 8.10]	
McDonnell 1997	0	23	2	23	13.1%	0.20 [0.01, 3.95]	
Baezinger 2007	0	15	3	24	14.3%	0.22 [0.01, 4.04]	
Oh 2002	2	16	3	17	15.3%	0.71 [0.14, 3.70]	
Mercer 2006	0	36	3	36	18.4%	0.14 [0.01, 2.67]	
Subtotal (95% CI)		299		329	84.2%	0.62 [0.28, 1.36]	-
Total events	8		14				
Heterogeneity: Chi <sup>2</sup> =	5.12, df = 7 (P = 1	0.65); I² =	0%				
Test for overall effect:	Z = 1.19 (P = 0.2	3)					
2.1.2 Cord milking							
Hosono 2008	2	20	3	20	15.8%	0.67 [0.12, 3.57]	
Subtotal (95% CI)		20		20	15.8%	0.67 [0.12, 3.57]	
Total events	2		3				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.47 (P = 0.6	4)					
Total (95% CI)		319		349	100.0%	0.63 [0.31, 1.28]	•
Total events	10		17				
Heterogeneity: Chi <sup>2</sup> =	5.14. df = 8 (P = 1	0.74): P=	0%				kan ala da sad
Test for overall effect	Z = 1.28 (P = 0.2	0)					0.01 0.1 1 10 100
Test for subgroup diff	erences: Chi#= 0	.01. df=	1 (P = 0.94), I <sup>2</sup> = 1	0%			More Pil better Less Pil better

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#### Figure 131: Severe intraventricular haemorrhage

0									
	More placental	trans	Less placental	trans		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
2.2.1 Delayed clampi	ng								
Mercer 2003	0	16	0	16		Not estimable			
Rabe 2000	0	19	0	20		Not estimable			
Hofmeyr 1988	2	23	0	13	7.9%	2.92 [0.15, 56.51]			
Mercer 2006	0	36	1	36	18.8%	0.33 [0.01, 7.92]			
Hofmeyr 1993	1	40	2	46	23.3%	0.57 [0.05, 6.11]			
Subtotal (95% CI)		134		131	50.0%	0.85 [0.20, 3.66]		-	
Total events	3		3						
Heterogeneity: Chi <sup>2</sup> =	1.11, df = 2 (P =	0.58); I <sup>a</sup> =	: 0%						
Test for overall effect.	Z = 0.21 (P = 0.8	3)							
2.2.2 Cord milking									
Hosono 2008	2	20	4	20	50.0%	0.50 [0.10, 2.43]			
Subtotal (95% CI)		20		20	50.0%	0.50 [0.10, 2.43]			
Total events	2		4						
Heterogeneity: Not ap	plicable								
Test for overall effect.	Z = 0.86 (P = 0.3	9)							
Total (95% CI)		154		151	100.0%	0.68 [0.23, 1.96]		-	
Total events	5		7						
Heterogeneity: Chi <sup>2</sup> =	1.28, df = 3 (P =	0.73); I <sup>a</sup> =	0%				+ 000		500
Test for overall effect	Z = 0.72 (P = 0.4	7)					0.002	U.1 1 10 More PT hetter	500
Test for subgroup diff	erences: Chi#= (	).24, df =	1 (P = 0.62), I <sup>2</sup> = 0	0%				More Pri better Less Pri better	

Figure 132:	Transfused for anaemia
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	•	More placental	trans	Less placental	trans		Risk Ratio	Risk Ratio
_	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
	2.12.1 Delayed Clamp	bing						
	Strauss 2008	2	45	5	59	4.7%	0.52 [0.11, 2.58]	
	Kugelman 2007	3	30	5	35	5.1%	0.70 [0.18, 2.69]	
	McDonnell 1997	4	23	6	23	6.6%	0.67 [0.22, 2.05]	
	Kinmond 1993	1	13	7	13	7.7%	0.14 [0.02, 1.00]	
	Rabe 2000	9	19	16	20	17.1%	0.59 [0.35, 1.00]	
	Mercer 2006	18	36	22	36	24.1%	0.82 [0.54, 1.24]	-
	Subtotal (95% CI)		166		186	65.3%	0.63 [0.46, 0.87]	•
	Total events	37		61				
	Heterogeneity: Chi <sup>2</sup> = 3	3.83, df = 5 (P = 0	0.57); I <sup>e</sup> =	0%				
	Test for overall effect.	Z = 2.87 (P = 0.0	04)					
	2.12.2 Cord milking							
	Hosono 2008	7	20	14	20	15.3%	0.50 [0.26, 0.97]	
	March 2011	17	21	16	17	19.4%	0.86 [0.68, 1.09]	
	Subtotal (95% CI)		41		37	34.7%	0.70 [0.53, 0.94]	◆
	Total events	24		30				
	Heterogeneity: Chi2 = 3	3.81, df = 1 (P = 0	0.05); I <sup>2</sup> =	74%				
	Test for overall effect.	Z = 2.42 (P = 0.0)	2)					
	Total (95% CI)		207		223	100.0%	0.66 [0.52, 0.82]	•
	Total events	61		91				-
	Heterogeneity: Chi <sup>2</sup> =	9.17, df = 7 (P = (	0.24); I <sup>2</sup> =	24%				have also be used
	Test for overall effect	Z = 3.66 (P = 0.0	002)					0.01 0.1 1 10 100
	Test for subgroup diffe	erences: Chi#= 0	22 df=	$1 (P = 0.64), I^2 =$	0%			More Producer Less Producer

194

# Appendix J:Network meta-analysis of tocolytics

# Jan Summary

198 Tocolytics are given to women in preterm labour to delay birth and therefore improve

outcomes for the newborn. Whilst the treatment is given to the mother, the aim is to improveoutcomes for the infant.

Network meta-analyses (NMA) of outcomes considered important to assess efficacy and safety were conducted. Eight outcomes were suitable for NMA:

- 203 1. IVH (infant)
- 204 2. RDS (infant)
- 205 3. Neonatal mortality (infant)
- 206 4. Neonatal sepsis (infant)
- 207 5. Perinatal mortality (infant)
- 208 6. Delay of birth by at least 48 hours (mother)
- 209 7. Termination of treatment due to adverse events (mother)
- 210 8. Estimated gestational age (EGA) at delivery (mother)
- 211 The first 7 outcomes are reported as the number of observed events out of the total number
- of infants or mothers, whilst EGA is reported as a continuous outcome (mean EGA) with a
- 213 standard deviation. Because some studies included multiple births, allowing more than one
- 214 infant per mother, it was not always clear which was the most appropriate number of
- individuals to consider for outcomes on the infant. Where available we used the number of
- 216 infants as the denominator. Although this does not account for the expected correlation in

- outcomes of infants from the same mother, it prevents double counting of infants from thesame mother who may both have had an event.
- A total of 35 treatments (including Placebo and combinations of treatments) were evaluated in relevant trials. These treatments were classified into 9 classes (Table 1).

A NMA class model (Kew 2014) was used to estimate the relative effects of each treatment class compared to Placebo/control. Since there was no evidence of within-class variability for any of the outcomes considered, all the results presented assume that all treatments in a class have the same relative effect.

A binomial / logit model was used to model outcomes 1 to 7 and a normal model with identity link was used to model EGA (Dias 2011).

The final dataset consisted of data from 93 trials comparing 35 treatments, although not all trials report all the outcomes of interest. Studies reporting zero events on all arms were removed from the NMA as they do not contribute information on the relative treatment effects. Treatments were assigned to classes according to Table 2.

# ab2 Methods

232 In order to take all trial information into consideration, without ignoring part of the evidence 233 and without introducing bias by breaking the rules of randomisation (for example, by "naively" 234 combining data across treatment arms from all RCTs), Mixed Treatment Comparison meta-235 analytic techniques, also termed Network meta-analysis (NMA), were employed. NMA is a generalization of standard pairwise meta-analysis for A versus B trials, to data structures that 236 237 include, for example, A versus B, B versus C, and A versus C trials (Dias 2001; Lu 2004; 238 Caldwell 2005). A basic assumption of NMA methods is that direct and indirect evidence 239 estimate the same parameter, that is, the relative effect between A and B measured directly 240 from a A versus B trial, is the same as the relative effect between A and B estimated 241 indirectly from A versus C and B versus C trials. NMA techniques strengthen inference 242 concerning the relative effect of two treatments by including both direct and indirect 243 comparisons between treatments, and, at the same time, allow simultaneous inference on all 244 treatments while respecting randomisation (Lu 2004; Caldwell 2005). Simultaneous inference 245 on the relative effects of all treatments is possible whenever treatments are part of a single 246 "network of evidence", that is, every treatment is linked to at least one of the other treatments 247 under assessment. The correlation between the random effects of multi-arm trials (i.e. those 248 with more than 2 arms) in the network is taken into account in the analysis (Dias 2011).

A Bayesian framework is used to estimate all parameters, using Markov chain Monte Carlo simulation methods implemented in WinBUGS 1.4.3 (Lunn 2000; Lunn 2013). In order to test whether starting values have an impact on the results, three chains with different initial values were run simultaneously. Convergence was assessed by inspection of the Gelman– Rubin diagnostic plots and by examining the history plots. Pre-convergence iterations were discarded, and further iterations on all chains were run on which results are based.

255 Sample WinBUGS code is provided in Section J.6.

# J226 Baseline probability (IVH, RDS and neonatal mortality)

Please see Health Economic Appendix K for details on calculating baseline probabilities for
 IVH, RDS and neonatal mortality.

# J2292 Relative effects model

260 Models allowing for within-class differences in treatment effects were considered with both 261 fixed and random treatment effects. These were compared with models assuming no within-

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262 class variability (i.e. all treatments in a class have the same relative effect), allowing for fixed 263 or random treatment effects. Goodness of fit was tested using the posterior mean of the residual deviance, which was compared to the number of data points in the model and by 264 265 inspecting the fit of each data point. Models were compared using the deviance information 266 criteria (DIC) (Spiegelhalter 2002). The model with the lowest DIC was chosen, with differences of 5 considered meaningful. When models had very similar DIC (differences less 267 than 5), simpler models were preferred, provided the posterior mean of the residual deviance 268 269 was still close to the number of data points.

# J2203 NMA model for binary data (outcomes 1 to 7)

A logit model was used to obtain the log-odds ratios of each treatment relative to Placebo. For each arm k of a trial *i*, the number of events,  $r_{ik}$ , have a binomial likelihood

273 
$$r_{ik} \sim \text{Binomial}(p_{ik}, n_{ik})$$

where  $p_{ik}$  is the probability of an event and  $n_{ik}$  the total number of patients in arm k of trial i.

The parameters of interest are the probabilities of an event and these are modelled using aNMA model on the log-odds scale using a logit link such that

 $logit(p_{ik}) = \mu_i + \delta_{ik}$ 

with  $\mu_i$  being given non-informative normal priors, Normal(0,1000), and  $\delta_{i1} = 0$  since there is no relative treatment effect estimated for arm 1 of each trial.

In a random effects (RE) model the trial-specific treatment effects of the treatment in arm k,
relative to the treatment in arm 1, are drawn from a common random effects distribution,
under the assumption of consistency:

 $\delta_{ik} \sim N(d_{i_{ik}} - d_{i_{i_{i}}}, \tau^2)$ 

where  $d_{i_k}$  represents the mean effect of the treatment in arm k in trial i,  $t_{ik}$ , relative to Placebo,

and  $\tau^2$  represents the between-trial variability in treatment effects (heterogeneity). The

between-trials standard deviation,  $\tau$ , was given a Uniform(0,5) prior.

287 In the FE model we replace equation (2) with

288  $logit(p_{ik}) = \mu_i + d_{i_k} - d_{i_1}$ 

# J2294 NMA model for continuous data (EGA)

For each arm k of a trial i, the observed mean EGA,  $y_{ik}$ , has a normal likelihood

291  $y_{ik} \sim \text{Normal}\left(\theta_{ik}, s_{ik}^2\right)$ 

where  $\theta_{ik}$  is the underlying (true) mean EGA and  $s_{ik}$  is the standard error of the mean EGA in arm *k* of trial *i*.

294 The mean EGA is modelled using a NMA model such that

$$\theta_{ik} = \mu_i + \delta_{ik}$$

with  $\mu_i$  being given non-informative normal priors, Normal(0,1000), and  $\delta_{i1} = 0$ , since there is no relative treatment effect estimated for arm 1 of each trial. In a random effects (RE) model the trial-specific treatment effects of the treatment in arm k, relative to the treatment in arm 1, are drawn from a common random effects distribution, under the assumption of consistency (equation (3)). The between-trials standard deviation was given a Uniform(0,20) prior.

302 In the FE model we replace equation (5) with

$$\theta_{ik} = \mu_i + d_{i_{ik}} - d_{i_{il}}$$

For studies not reporting the standard error, this was calculated using imputed standard deviations (SD). For each treatment for which a SD was not reported, it was imputed based on the median SD for that treatment reported in other studies. When there were fewer than 2 other studies reporting SD for a given treatment, the SD was imputed based on the median of reported SDs for that class. A sensitivity analysis imputing the upper quartile instead of the median was carried out.

# J3205 Class model

- 311 Due to the sparseness of the network, with most comparisons being informed by only a few 312 trials, a class model was used to borrow strength within treatment classes.
- 313 Two models for class were explored: an **exchangeable class effects** model, where the 314 pooled relative treatment effects were assumed exchangeable within class

$$d_{1,k} \sim N(m_{D_k}, \tau_D^2)$$

- 316 with  $D_k$  indicating the class to which treatment k belongs to; and a **fixed class effects** model,
- 317 where the pooled relative treatment effects are assumed equal for all treatments in a class
- 318  $d_{1,k} = m_{D_k}$ . Magnesium sulphate belongs to a class formed only of itself (Class 3), so its
- 319 relative treatment effect was assumed to be equal to its class effect in both models.
- Both class models were considered with fixed or random treatment effects. The within-class mean treatment effects were given vague priors  $m_i \sim N(0,100^2)$  and the within-class standard
- deviations were assumed equal for all classes (due to insufficient data) and given Uniform(0,2) priors.

# J3246 Consistency

Consistency was assessed by checking the agreement of direct and indirect evidence using a node-split model (Dias 2009) fitted in R (Anonymous 2010) through the GeMTC package (van Valkenhoef 2012). Bayesian p-values for agreement between direct and indirect evidence were calculated. When these were lower than 0.05, included trials were inspected to help determine reasons for the potential inconsistency, bearing in mind that multiple probabilities of disagreement are being calculated and there is the potential to find spurious results.

# 383 Results

# J333 Baseline models (IVH, RDS, neonatal mortality)

Convergence was satisfactory by at least 20,000 iterations in all cases. Models were then run for a further 50,000 iterations on three separate chains, and all results are based on this further sample.

- 337 Results from these models are used in the relative effects model to generate a baseline 338  $A \sim Normal(m, sd^2)$  on the log-odds scale on which relative effects were added at each iteration,
- to deliver the posterior summaries on the absolute probability scale for each treatment (Dias2011a; Dias 2011b).
- 341 The estimated probabilities of events were very imprecise and there was large between-
- 342 study heterogeneity in the log-odds of an event. This suggests that the included studies are 343 very different in their baseline event rates and that they are perhaps not all representative of
- 344 the UK population.

# **J3352** Imputing standard deviations (EGA)

- 51 studies were used in the NMA for EGA. 5 studies (Merkatz 1980, Leveno 1986, Larsen
  1986, Rasanen 1995, Holleboom 1996) did not report the standard deviation (SD).
- 348 19 treatments were included in the network. No treatments in Class 8 (Alcohol/ethanol) were349 compared in trials reporting this outcome.
- Five studies did not report SD for EGA (Merkatz 1980, Leveno 1986, Larsen 1986, Rasanen
  1995, Holleboom 1996). This meant that the SD had to be imputed for 4 treatments: Placebo,
  Indomethacin, Sulindac and Ritodrine.
- 353 Placebo: 11 studies comparing this treatment to other treatments reported the SD, whilst 3
   354 did not. The range of reported SD was 0.5 to 6.6 (Figure 133).
- Indomethacin: 10 studies comparing this treatment to other treatments reported the SD,
   whilst 1 did not. The range of reported SD was 0.7 to 5.6 (Figure 133).
- **Sulindac:** only 1 study comparing this treatment to other treatments reported the SD, whilst one other did not. The reported SD for other treatments of the same class (Class 2) were used as the basis for imputation. The range of reported SD for this class was 0.5 to 5.6 (Figure 133).
- 361 **Ritodrine:** 13 studies comparing this treatment to other treatments reported the SD, whilst 4 362 did not. The range of reported SD was 1.7 to 4.7 (Figure 133).
- Imputed values for the main analysis were based on the median SD (Table 4, Figure 133). A
   sensitivity analysis using the upper quartile of the reported SD was also carried out (Table 4).
- Model comparison using the DIC showed the fixed class with random treatment effects model as the preferred model (**Error! Reference source not found.**). The model with fixed lass and treatment effects was not fitted as it was expected to have a very poor fit, given the results of the exchangeable class, fixed effects model. Node-split models compared direct and indirect evidence on 11 comparisons. Some evidence of inconsistency was found for comparisons of placebo and magnesium sulphate (p=0.01).

# J33.3 Sensitivity to imputed SD

When imputing the upper quartile of the reported SD, the fixed class with fixed treatment effects model was preferred, although there were some poorly fitting data points and there was evidence of inconsistency for comparisons of placebo and prostaglandin inhibitors (p=0.02) and placebo and betamimetics (p=0.49). Apart from increased uncertainty the main results were not affected.

377	Table 1:	Class descriptions
		Classes
	1	Placebo/control
	2	Prostaglandin inhibitors

	Classes
3	Magnesium sulfate
4	Betamimetics
5	Calcium channel blockers
6	Nitrates
7	Oxytocin receptor blockers
8	Alcohol/ethanol
9	Other treatments

# 378 Table 2: Treatments with class assignments

	Treatment	class
1	Placebo	1
2	No treatment	1
3	Bed rest	1
4	Celecoxib	2
5	Indomethacin	2
6	Ketorolac	2
7	Mefenic Acid	2
8	Nimeluside	2
9	Rofecoxib	2
10	Sulindac	2
11	Magnesium Sulfate	3
12	Beta-Mimetics	4
13	Fenoterol	4
14	Hexoprenaline	4
15	Isoxsuprine	4
16	Ritodrine	4
17	Salbutamol	4
18	Terbutaline	4
19	Nylidrin	4
20	Calcium-Channel Blocker	5
21	Nicardipine	5
22	Nifedipine	5
23	Nitric Oxide	6
24	Nitroglycerin	6
25	Atosiban	7
26	Barisiban 1.0	7
27	Barusiban 0.3	7
28	Barusiban 10	7
29	Barusiban 3.0	7
30	Alcohol	8
31	Ethanol	8
32	Beta-Mimetics + Mag	9
33	Alcohol + Indomethacin	9
34	Other Tocolytic(s)	9
35	Tocolysis	9

379 Treatment classes are defined in Table 1

Outcome (number of		Exchangeable class effe	ects	Fixed class effects		
data points)	Measures of model fit	RE	FE	RE	FE	
IVH (61)	$ar{D}_{res}$	65.7	68.6	66.1	69.2	
	DIC	285.1	284.2	284.0	282.9	
	between-study standard deviation	0.27 (0.01, 0.83)	-	0.27 (0.01, 0.81)	-	
	within-class standard deviation	0.44 (0.02, 1.78)	0.43 (0.02, 1.77)	-	-	
RDS (102)	$ar{D}_{res}$	110.0	114.3	112.3	121.3	
	DIC	506.5	505.8	506.9	507.6	
	between-study standard deviation	0.20 (0.01, 0.50)	-	0.25 (0.02, 0.54)	-	
	within-class standard deviation	0.30 (0.02, 0.87)	0.36 (0.04, 0.92)	-	-	
Neonatal mortality	$\overline{D}_{res}$	111.6	132.5	112.2	144.0	
(102)	DIC	429.1	437.4	429.2	443.3	
	between-study standard deviation	0.79 (0.24, 1.42)	-	0.86 (0.39, 1.47)	-	
	within-class standard deviation	0.79 (0.04, 1.90)	1.16 (0.14, 7.95)	-	-	
Neonatal sepsis (39)	$ar{D}_{res}$	42.8	45.4	44.0	47.0	
	DIC	181.2	180.1	181.0	179.8	
	between-study standard deviation	0.44 (0.02, 1.49)	-	0.41 (0.02, 1.41)	-	
	within-class standard deviation	0.65 (0.03, 1.87)	0.60 (0.03, 1.84)	-	-	
Perinatal mortality (88)	$ar{D}_{res}$	*	*	95.6	115.1	
	DIC	*	*	365.1	371.8	
	between-study	*	*	0.79 (0.19, 1.47)	-	

# Table 3: Posterior mean of the residual deviance ( $\bar{D}_{res}$ ) DIC for all models

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Outcome (number of		Exchangeable class effe	cts	Fixed class effects		
data points)	Measures of model fit	RE	FE	RE	FE	
	standard deviation					
	within-class standard deviation	*	*	-	-	
Delay by 48hrs (132)	$\overline{D}_{res}$	130.7	301.0	130.7	NA	
	DIC	727.9	862.6	727.2	NA	
	between-study standard deviation	0.89 (0.68, 1.16)	-	0.89 (0.68, 1.14)	-	
	within-class standard deviation	0.14 (0.01, 0.55)	0.29 (0.05, 0.61)	-	-	
Termination due to AE	$\overline{D}_{res}$	80.1	103.2	82.0	102.5	
(75)	DIC	297.7	308.7	298.5	306.7	
	between-study standard deviation	1.34 (0.26, 2.68)	-	1.17 (0.18, 2.74)		
	within-class standard deviation	0.36 (0.02, 1.60)	0.18 (0.01, 0.97)	-	-	
EGA (101)	$\overline{D}_{res}$	100.3	352.7	100.0	NA	
	DIC	191.0	418.4	190.4	NA	
	between-study standard deviation	1.25 (0.96, 1.64)	-	1.25 (0.98, 1.62)	-	
	within-class standard deviation	0.25 (0.01, 0.98)	1.53 (0.96, 2.67)	-	-	

'NA' indicates the model was not fitted as it was expected to be a poor fit, and '\*' indicated that the model was not fitted because there was not enough evidence to estimate all the parameters. Shaded cells indicate the preferred model. The median and 95% Credible Intervals of the between-study deviation (heterogeneity) and within-class standard deviation are also presented, A '-' indicates that this value was fixed at zero in the model.

Table 4: Vales	used for the i	mputation of SD wit	h these were not reported
Treatment	Median	Upper quartile	
Placebo	2.1	3.35	
Indomethacin	2.555	3.675	
Sulindac	2.555	3.625	
Ritodrine	3.1	4.1	

1

# J.4 Figures

Figure 133: Reported standard deviations (SD) in trials comparing the difference treatments, or treatments of the same class (open circles); SD in the only sulindac trial to report it (filled circle); imputed values (red crosses) and median SD, plotted against sample size



# J.5 References

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Ν

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- 40

# J46 Sample WINGBUGS code for binary outcome analyses

FIXED CLASS, FIXED TREATMENT EFFECTS

```
Tocolytics: outcome is IVH
Class model - treatments exchangeable within class,
within-class variance is zero (fixed class effects)
_____
21 May 2014
Treatments (code, Class, Treat)
          Placebo
1
     1
2
     2
         Indomethacin
3
     2
         Ketorolac
         Rofecoxib
4
     2
5
    3
        Magnesium Sulfate
6
    4
         Beta-Mimetics
7
    4
         Ritodrine
8
    4
         Salbutamol
         Terbutaline
9
    4
10 4
         Nylidrin
                   (NOT TO BE USED FOR RANKING)
    5
         Nifedipine
11
12
    6
         Nitric Oxide
13
    7
          Atosiban
   8
         Other Tocolytic(s)
                             (NOT TO BE USED FOR RANKING)
14
Class "Alcohol/ethanol" not compared
Class 8 not to be used for ranking
_____
# Binomial likelihood, logit link
# Fixed effects model
# class effects - zero within-class variance
                # *** PROGRAM STARTS
model{
   for(i in l:ns) {
      r[i,k] ~ dbin(p[i,k],n[i,k])  # binomial likelihood
# model for linear predictor
      logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
# expected value of the numerators
      rhat[i,k] <- p[i,k] * n[i,k]
#Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))</pre>
          + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))
     }
# summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,l:na[i]])
totresdev <- sum(resdev[])</pre>
                       # Total Residual Deviance
# treatment effects from Class - fixed class effects
for (k in 2:nt) { d[k] <- m[D[k]] }
```

```
m[1] < - 0
for (k in 2:nc) { m[k] ~ dnorm(0, .0001) } # priors for mean class effect
# all pairwise ORs
for (c in 1:(nt-1)) {
    for (k in (c+1):nt)
         lor[c,k]<- d[k]-d[c]
         OR[c,k] <- exp(lor[c,k])
       }
  3
# select treatments to be used for ranking and economic analysis
for(k in 1:9){ dR[k] <- d[k] }</pre>
# not treatment 10
for(k in 11:13) { dR[k-1] <- d[k] }
# not treatment 14
# ranking on relative scale
for (k in l:ntR) {
     rk[k] \leq (ntR+1) - rank(dR[],k)
                                           # events are "good"
±.
                                          # events are "bad"
    rk[k] < - rank(dR[],k)
    best[k] <- equals(rk[k],1)</pre>
                                         # rank=1 is best
#calculate probability that treat k is h-th best
    for (h in 1:nt) { prob[h,k] <- equals(rk[k],h) }</pre>
# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:ntR) { logit(T[k]) <- A + dR[k] }
# all pairwise ORs for classes
for (c in 1: (nc-1)) {
    for (k in (c+1):nc) {
         lorClass[c,k] <- m[k] - m[c]</pre>
         ORClass[c,k] \le exp(m[k] - m[c])
    }
 }
# rank all classes except last
for (k in 1:nc-1) {
     rkClass[k] <- (nc+1)-rank(m[],k)</pre>
                                                 # events are "good"
    rkClass[k] <- rank(m[1:(nc-1)],k)
                                                           # events are "bad"
    bestClass[k] <- equals(rkClass[k],1)  # rank=1 is best</pre>
# prob class k is h-th best, prob[1,k]=best[k]
    for (h in l:nc-l) { probClass[h,k] <- equals(rkClass[k],h) }</pre>
     }
                                        # *** PROGRAM ENDS
}
Data
# ns= number of studies; nt=number of treatments; nc=number of classes; D=index of classes
# ntR = number of treat for ranking
list(ns=29, nt=14, nc=8, meanA=-2.814, precA=0.9861, ntR=12,
D=c(1, 2, 2, 2, 3, 4, 4, 4, 4, 4, 5, 6, 7, 8))
                                                n[,1]
                                                              n[,3]
na[]
       t[,1]
              t[,2]
                     t[,3]
                                  r[,2]
                                         r[,3]
                                                      n[,2]
                                                                     #Study Year
                            r[,1]
                     g
                                                        16
                                                               19
                                                                     #Cotton 1984
3
                                                 19
       1
              5
                            3
                                          2
                                                       95
                                   1
              5
3
       2
                     11
                            14
                                  11
                                          10
                                                 103
                                                              119
                                                                     #Klauser 2012
       7
2
              13
                     13
                            5
                                                56
                                                       61
                                                              58
                                                                     #Goodwin
                                                                                   1006
                                  7
                                         4
```

2	1	2	NA	0	1	NA	20	19	NA	#Panter	1999
2	1	5	NA	4	4	NA	89	78	NA	#Cox	1990
2	1	7	NA	4	2	NA	55	56	NA	#Leveno	1986
2	1	7	NA	31	21	NA	391	380	NA	#CPLIG	1992
2	1	12	NA	1	2	NA	79	74	NA	#Smith	2007
2	1	13	NA	19	16	NA	246	243	NA	#Romero	2000
2	2	5	NA	4	4	NA	49	52	NA	#Morales	1993
2	2	5	NA	4	6	NA	14	18	NA	#Parilla	1997
2	2	7	NA	1	4	NA	47	50	NA	#Morales	1989

	2 2	7	NA	3	2	NA	25	20	NA	#Besinger	1991
	2 2	10	NA NA	2	0	NA	30	30	NA	#Kurki 1991	
	2 3	5	NA	1	0	NA	45	43	NA	#Schorr 1998	
	2 4	5	NA	6	7	NA	92	102	NA	#McWhorter	2004
	2 5	11	NA	3	2	NA	106	110	NA	#Lyell 2007	
	2 5	14	NA	8	2	NA	55	51	NA	#Mittendorf MAGr	1et2002
	26	12	NA NA	8	2	NA	116	120	NA	#Bisits 2004	
	27	7	NA	15	4	NA	111	111	NA	#Holleboom	1996
	27	11	NA	1	1	NA	35	35	NA	#Maitra 2007	
	27	11	NA	7	4	NA	43	48	NA	#Van de Water	2008
	27	11	NA	28	17	NA	90	95	NA	#Papatsonis (199	7/2000)
	27	13	NA NA	1	3	NA	63	63	NA	#Shim 2006	
	27	13	NA NA	5	3	NA	107	107	NA	#Moutquin	2000
	28	13	NA NA	2	4	NA	99	109	NA	#French/Australia	n 2001
	2 9	11	NA	3	0	NA	16	20	NA	#Laohapojanart	2007
	2 9	13	NA NA	4	3	NA	105	101	NA	#European	2001
	2 1	1 11	NA	0	4	NA	48	52	NA	#Nassar 2009	
1	END										

#### FIXED CLASS, RANDOM TREATMENT EFFECTS

# Tocolytics: outcome is RDS Class model - treatments exchangeable within class, within-class variance is zero (fixed class effects)

# Treatments (code, Class, Treat)

1	1	Placebo	
2	2	Celecoxib	
3	2	Indomethacin	
4	2	Ketorolac	
5	2	Rofecoxib	
6	2	Sulindac	
7	3	Magnesium Sulfate	(TREATMENT IS ITS OWN CLASS)
8	4	Fenoterol	
9	4	Hexoprenaline	
10	4	Ritodrine	
11	4	Salbutamol	
12	4	Terbutaline	
13	4	Nylidrin (NOT	TO BE USED FOR RANKING)
14	5	Nicardipine	
15	5	Nifedipine	
16	6	Atosiban	
17	6	Barisiban 1.0	(NOT TO BE USED FOR RANKING)
18	6	Barusiban 0.3	NOT TO BE USED FOR RANKING
19	6	Barusiban 10	NOT TO BE USED FOR RANKING
20	6	Barusiban 3.0	NOT TO BE USED FOR RANKING
21	7	Ethanol (NOT TO BE U	ISED FOR RANKING)
22	8	Tocolvsis	(NOT TO BE USED FOR RANKING)
<pre># Bind # Rand # class model for(i</pre>	omial 1 dom eff ss effe ( in 1:r	likelihood, logit fects model for mu ects - zero within ns){	====== link lti-arm trials -class variance # *** PROGRAM STARTS # LOOP THROUGH STUDIES
# Bind # Rand # clas model for(i W	omial ] dom eff ss effe ( in l:r [i,1] <	likelihood, logit fects model for mu ects - zero within ns){ <- 0	<pre>ink lti-arm trials -class variance</pre>
# Bind # Rand # clas model for(i w) arm	omial 1 dom eff ss effe ( in 1:r [i,1] <	likelihood, logit fects model for mu ects - zero within ns){ <- 0	<pre>link lti-arm trials -class variance</pre>
# Bind # Rand # clas model; for(i w) arm de	omial ] dom eff ss effe ( in l:r [i,1] < elta[i,	likelihood, logit fects model for mu ects - zero within ns){ <- 0	<pre>i====== link lti-arm trials -class variance</pre>
# Bind # Rand # class model; for(i w) arm de mu	omial ] dom eff ss effe ( in l:r [i,l] < elta[i, a[i] ~	likelihood, logit fects model for mu ects - zero within (- 0	<pre>i====== link lti-arm trials -class variance</pre>
# Bind # Rand # clas model; for(i w arm de mu	omial ] dom eff ss effe ( in l:r [i,l] < elta[i, a[i] ~ or (k i st	<pre>likelihood, logit fects model for mu ects - zero within (- 0</pre>	<pre>i====== link lti-arm trials -class variance</pre>
# Bind # Rand # clas model: for(i w arm de mu	omial 1 dom eff ss effe ( in 1:r (i,1) < elta[i, ,1[i] ~ or (k i r[i, r[i,	<pre>likelihood, logit fects model for mu ects - zero within ns){ - 0</pre>	<pre>image: image: imag</pre>
# Bind # Rand # clas model: for(i w arm de for fo	omial 1 dom eff ss effe ( in l:r (i,l) < elta[i, a[i] ~ or (k i r[i, logi	<pre>likelihood, logit fects model for mu ects - zero within - 0</pre>	<pre>link lti-arm trials -class variance</pre>
<pre># Bind # Rand # clas model: for(i wlarm de mu fo</pre>	omial 1 dom eff ss effe ( in 1:r (i,1] < elta[i, a[i] ~ or (k i r[i, logi rhat	<pre>likelihood, logit fects model for mu ects - zero within ns){ - 0</pre>	<pre>link lti-arm trials -class variance</pre>
<pre># Bind # Rand # clas model: for(i w arm de mu f( #Devia</pre>	omial 1 dom eff ss effe ( in l:r (i,l] < elta[i, a[i] ~ or (k i r[i, logi rhat ance co	<pre>likelihood, logit fects model for mu ects - zero within ns){</pre>	<pre>link lti-arm trials -class variance</pre>
<pre># Bind # Rand # clas model; for(i W arm de mu fo for fo # Devis</pre>	omial 1 dom eff ss effe ( in l:r [i,1] < elta[i, a[i] ~ or (k i r[i, logi rhat ance co dev	<pre>likelihood, logit fects model for mu ects - zero within ns){ - 0</pre>	<pre>link lti-arm trials -class variance</pre>
<pre># Bind # Rand # clas model; for(i w arm de m fo fo fo fo fo fo fo fo fo fo fo fo fo</pre>	omial 1 dom eff ss effe ( in l:r [i,1] < elta[i, a[i] ~ or (k i r[i, logi rhat ance co dev	<pre>likelihood, logit fects model for mu ects - zero within - 0</pre>	<pre>link lti-arm trials -class variance</pre>
<pre># Bind # Bind # Class model; for(i W arm de mu fo for fo for fo for fo for fo for fo for fo fo fo fo fo fo fo fo fo fo fo fo fo</pre>	<pre>omial 1 dom eff ss effe (     in l:r [i,1] &lt; elta[i, a[i] ~ or (k i     r[i,     logi     rhat ance co     dev [ i,k]))) mmed ref </pre>	<pre>likelihood, logit fects model for mu ects - zero within (- 0</pre>	<pre>link lti-arm trials -class variance</pre>
<pre># Bind # Bind # Clas model: for(i w arm de mu fo for fo for for for for for for for f</pre>	<pre>omial 1 dom eff ss effe (     in l:r [i,1] &lt; elta[i, a[i] ~ or (k i     r[i,     logi     rhat ance co     dev [ i,k]))) mmed re asdev[ </pre>	<pre>likelihood, logit fects model for mu ects - zero within (- 0</pre>	<pre>link lti-arm trials -class variance</pre>
<pre># Bind # Rand # clas model: for(i w) arm de mu fo for fo for for for for for for for f</pre>	omial 1 dom eff ss effe ( in l:r [i,1] < elta[i, a[i] ~ or (k i r[i, logi rhat ance co dev (k, k]))) mmed res esdev[i or (k i	<pre>likelihood, logit fects model for mu ects - zero within ns){ - 0</pre>	<pre>link lti-arm trials -class variance</pre>
<pre># Bind # Rand # clas model: for(i w) arm de mu fo for for for for for for for for for</pre>	<pre>omial 1 dom eff ss effe (     in l:r     [i,1] &lt; elta[i,     li] ~ or (k i     r[i,     logi     rhat ance cc     dev[ i,k]))) mmed re esdev[i or (k i al-spec</pre>	<pre>likelihood, logit fects model for mu ects - zero within ns){</pre>	<pre>link lti-arm trials -class variance</pre>
<pre># Bind # Rand # clas model: for(i w) arm de mu fo for for for for for for for for for</pre>	<pre>omial 1 dom eff ss effe (     in l:r     [i,1] &lt; elta[i,     li] ~ or (k i     r[i,     logi     rhat ance cc     dev[ i,k]))) mmed re esdev[i or (k i al-spec     delt</pre>	<pre>likelihood, logit fects model for mu ects - zero within ns){ - 0</pre>	<pre>link lti-arm trials -class variance</pre>
<pre># Bind # Rand # clas model: for(i w) arm de mu fo # Devia * * un fo * * un fo * * * * * * * * * * * * * * * * * *</pre>	<pre>omial 1 dom eff ss effe (     in l:r     [i,1] &lt; elta[i,     li] ~ or (k i     r[i,     logi     rhat ance cc     dev[ i,k]))) mmed re esdev[i or (k i al-spec     delt h of LC</pre>	<pre>likelihood, logit fects model for mu ects - zero within ns){ - 0</pre>	<pre>link lti-arm trials -class variance</pre>

```
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])</pre>
# cumulative adjustment for multi-arm trials
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)</pre>
      }
  }
totresdev <- sum(resdev[])</pre>
                                       # Total Residual Deviance
              # treatment effect is zero for reference treatment
d[1]<-0
# treatment effects from Class - fixed class effects
for (k in 2:nt) { d[k] <- m[D[k]]</pre>
sd ~ dunif(0,5)
                    # vague prior for between-trial SD
                   # between-trial precision = (1/between-trial variance)
tau <- pow(sd,-2)
m[1] <- 0
for (k in 2:nc) { m[k] ~ dnorm(0, .0001) } # priors for mean class effect
# all pairwise ORs
for (c in 1:(nt-1)) {
    for (k in (c+1):nt) {
       lor[c,k]<- d[k]-d[c]</pre>
        OR[c,k] <- exp(lor[c,k])
      }
 -}
# select treatments to be used for ranking and economic analysis
for(k in 1:12) { dR[k] <- d[k] }
# not treatment 13
for(k in 14:16) { dR[k-1] <- d[k] }
# not treatments 17-22
# ranking on relative scale
for (k in 1:ntR) {
    rk[k] \leq (ntR+1) - rank(dR[],k)
                                        # events are "good"
#
    rk[k] < - rank(dR[],k)
                                       # events are "bad"
    best[k] <- equals(rk[k],1)</pre>
                                       # rank=1 is best
#calculate probability that treat k is h-th best
    for (h in 1:nt) { prob[h,k] <- equals(rk[k],h) }
# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:ntR) { logit(T[k]) <- A + dR[k] }
# all pairwise ORs for classes
for (c in 1: (nc-1)) {
    for (k in (c+1):nc) {
        lorClass[c,k] <- m[k] - m[c]</pre>
        ORClass[c,k] \le exp(m[k] - m[c])
    }
 3
# rank all classes except last two
for (k in 1:nc-2) {
    rkClass[k] <- rank(m[1:(nc-2)],k)
                                              # events are "bad"
    rkClass[k] <- rank(m[1:(nc-2)],k)  # events are "ba
bestClass[k] <- equals(rkClass[k],1)  # rank=1 is best</pre>
# prob class k is h-th best, prob[1,k]=best[k]
    for (h in 1:nc-2) { probClass[h,k] <- equals(rkClass[k],h) }</pre>
    ł
                                       # *** PROGRAM ENDS
}
```

# ns= number of studies; nt=number of treatments; nc=number of classes; D=index of classes # ntR = number of treat for ranking list(ns=47, nt=22, nc=8, meanA=-1.75, precA=0.555, ntR=15, D=c(1, 2, 2, 2, 2, 2, 3, 4, 4, 4, 4, 4, 5, 5, 6, 6, 6, 6, 6, 7, 8))

na[]	t[,1] n[,3]	t[,2] n[,4]	t[,3] n[,5]	t[.4] #	t[,5] Study	r[,1]	r[,2]	r[,3]	r[,4]	r[,5]	n[,1]	n[,2]
5	1 32	17 36	18 32	19 #	20 Thornton	1 2009	2	0	7	2	32	31
4	1 41	10 46	10 NA	10 #	NA	1 1980	4	5	2	NA	45	44
3	1	7	12	ŇA	NA	6	6	4	NA	NA	19	16
3	3	7	18	ŇA	NA	41	39	34	NA	NA	103	95
3	119	NA 16	NA 16	# NA	Klauser NA	2012 5	8	7	3	2	56	61
2	58 1	62 3	57 NA	# NA	Goodwin NA	1996 2	3	NA	NA	NA	15	16
2	NA 1	NA 3	NA	# NA	Niebyl	1980	4	NA	NΔ	NA	20	10
2	ŇA	ŇA	NA	#	Panter	1999		NA	NA	NA	10	10
2	NA	NA	NA	#	Zuckerm	an	1984	NA	NA	NA	10	10
2	1 NA	7 NA	NA NA	NA #	NA Cox	15 1990	15	NA	NA	NA	89	78
2	1 NA	10 NA	NA	NA #	NA Spellacy	3	0	NA	NA	NA	15	14
2	1	10	NA	ŇA	NA	6	3	NA	NA	NA	50	49
2	1 1	10	NA	# NA	NA	24	20	NA	NA	NA	122	187
2	NA 1	NA 10	NA NA	# NA	Merkatz NA	1980 24	25	NA	NA	NA	55	56
2	NA 1	NA 10	NA NA	# NA	Leveno NA	1986 90	69	NA	NA	NA	391	380
2	NA	NA 16	NA	#	CPLIG	1992	2	NA	NA	NA	57	57
-	NA	NA	NA	#	Goodwin	1994		110		110	57	57
2	1 NA	16 NA	NA NA	NA #	NA Romero	54 2000	64	NA	NA	NA	292	283
2	1 NA	22 NA	NA NA	NA #	NA Weiner	22 1988	15	NA	NA	NA	42	33
2	2 NA	3	NA	NA #	NA	1	1	NA	NA	NA	12	12
2	3	6	NA	ŇA	NA	1	0	NA	NA	NA	10	10
2	NA 3	NA 7	NA NA	# NA	Rasanen NA	1995 5	5	NA	NA	NA	49	52
2	NA 3	NA 7	NA NA	# NA	Morales NA	1993 5	5	NA	NA	NA	14	18
2	NA 3	NA 10	NA	# NA	Parilla	1997	12	NA	NA	NA	47	50
-	ŇA	NA	NA	#	Morales	1989						
2	3 NA	NA NA	NA	NA #	NA Kurki	3 1991	2	NA	NA	NA	30	30
2	4 NA	7 NA	NA NA	NA #	NA Schorr	2 1998	4	NA	NA	NA	45	43
2	5 NA	7 NA	NA NA	NA #	NA McWhort	18 er	19 2004	NA	NA	NA	92	102
2	7	12	NA	ŇA	NA	3	2	NA	NA	NA	15	16
2	7	15	NA	ŇA	NA	4	5	NA	NA	NA	40	50
2	NA 7	NA 15	NA NA	# NA	Floyd NA	1995 24	21	NA	NA	NA	106	110
2	NA 8	NA 10	NA NA	# NA	Lyell NA	2007 4	2	NA	NA	NA	48	48
2	NA	NA 11	NA	# NA	Essed	1978	4	NA	NA	NA	70	70
2	ŇA	NA	NA	#	Gummen	us	1983					
2	10 NA	NA NA	NA	NA #	NA Holleboo	1/ m	12 1996	NA	NA	NA	111	111
2	10 NA	12 NA	NA NA	NA #	NA Caritis	2 1984	5	NA	NA	NA	31	26
2	10 NA	15 NA	NA	NA #	NA Maitra	1 2007	0	NA	NA	NA	35	35
2	10 NA	15 NA	NA	NA #	NA	3	2	NA	NA	NA	39	39
					Cararaci	2000						

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2	10	15	NA	NA	NA	3	3	NA	NA	NA	43	48
	NA	NA	NA	#	Van de W	/ater	2008					
2	10	15	NA	NA	NA	4	4	NA	NA	NA	28	30
	NA	NA	NA	#	Al-Qattar	2000						
2	10	15	NA	NA	NA	31	23	NA	NA	NA	90	95
	NA	NA	NA	#	Papatson	is (1997)	(2000)	1997				
2	10	16	NA	NA	NA	0`	3	NA	NA	NA	63	63
	NA	NA	NA	#	Shim	2006						
2	10	16	NA	NA	NA	1	0	NA	NA	NA	22	23
	NA	NA	NA	#	Lin	2009						
2	10	16	NA	NA	NA	14	15	NA	NA	NA	107	107
	NA	NA	NA	#	Moutquin	2000						
2	10	21	NA	NA	NA .	6	15	NA	NA	NA	73	76
	NA	NA	NA	#	Lauersen	1977						
2	11	14	NA	NA	NA	3	5	NA	NA	NA	21	24
	NA	NA	NA	#	Trabelsi	2008						
2	11	16	NA	NA	NA	10	14	NA	NA	NA	99	109
	NA	NA	NA	#	French/A	ustralian	2001					
2	12	15	NA	NA	NA	2	2	NA	NA	NA	16	20
	NA	NA	NA	#	Laohapoi	anart	2007					
2	12	16	NA	NA	NA	28	17	NA	NA	NA	105	101
	NA	NA	NA	#	Europear	1	2001					
2	15	15	NA	NA	NA	6	10	NA	NA	NA	48	52
-	NA	NA	NA	#	Nassar	2009						
2	15	16	NA	NA	NA	10	5	NA	NA	NA	23	25
-	NA	NA	NA	#	Al-Omari	2006	-					
END												

# SAMPLE WINBUGS CODE FOR EGA

#### FIXED CLASS, RANDOM TREATMENT EFFECTS

# Tocolytics: outcome is EGA at delivery Class model - treatments exchangeable within class, within-class variance is zero (fixed class effects)

```
_____
```

1 August 2014

#### Treatments (code, Class, Treat)

1	1	Placebo
2	2	Celecoxib
3	2	Indomethacin
4	2	Ketorolac
5	2	Nimeluside
6	2	Rofecoxib
7	2	Sulindac
8	3	Magnesium Sulfate (TREATMENT IS ITS OWN CLASS)
9	4	Fenoterol
10	4	Isoxsuprine
11	4	Ritodrine
12	4	Salbutamol
13	4	Terbutaline
14	4	Nylidrin (NOT TO BE USED FOR RANKING)
15	5	Nicardipine
16	5	Nifedipine
17	6	Nitric Oxide
18	7	Atosiban
19	8	Tocolysis (NOT TO BE USED FOR RANKING)
Class	"Alcoh	ol/ethanol" not compared

# Class 8 not to be used for ranking

\_\_\_\_\_

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

```
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
  }
totresdev <- sum(resdev[])</pre>
                                         #Total Residual Deviance
              # treatment effect is zero for control arm
d[11<-0
# treatment effects from Class - fixed class effects
for (k \text{ in } 2:nt) \{ d[k] \leq -m[D[k]] \}
sd ~ dunif(0,20)
                    # vague prior for between-trial SD
tau <- pow(sd,-2)  # between-trial precision = (1/between-trial variance)
m[1] <- 0
for (k in 2:nc) { m[k] ~ dnorm(0, .0001) } # priors for mean class effect
# all pairwise differencess
for (c in 1: (nt-1)) {
    for (k in (c+1):nt) { diff[c,k] <- d[k]-d[c] }
  3
# select treatments to be used for ranking
for(k in 1:13) { dR[k] <- d[k] }</pre>
# not treatment 14
for(k in 15:18) { dR[k-1] <- d[k] }
# not treatment 19
# ranking on relative scale
for (k in 1:ntR) {
    rk[k] \leq (ntR+1) - rank(dR[],k)
                                       # larger values are "good"
     rk[k] < - rank(dR[],k)
                                         # larger values are "bad"
    best[k] <- equals(rk[k],1)</pre>
                                       # rank=1 is best
#calculate probability that treat k is h-th best
   for (h in 1:nt) { prob[h,k] <- equals(rk[k],h) }</pre>
  }
# all pairwise differences for classes
for (c in 1: (nc-1)) {
    for (k in (c+1):nc) { diffClass[c,k] <- m[k] - m[c] }</pre>
# rank all classes except 8
for (k in 1:nc-1) {
    rkClass[k] <- nc-rank(m[l:(nc-l)],k) # larger values are "good"
bestClass[k] <- equals(rkClass[k],l) # rank=l is best</pre>
# prob class k is h-th best, prob[1,k]=best[k]
    for (h in l:nc-1) { probClass[h,k] <- equals(rkClass[k],h) }</pre>
    3
                                         # *** PROGRAM ENDS
}
```

#### Data

```
# ns= number of studies; nt=number of treatments; nc=number of classes; D=index of classes
# ntR = number of treat for ranking
list(ns=49, nt=19, nc=8, ntR=17,
D=c(1, 2, 2, 2, 2, 2, 3, 4, 4, 4, 4, 4, 5, 5, 6, 7, 8))
```

na[] 3	t[,1] 1	t[,2] 8	t[,3] 13	y[.1] 32	y[,2] 31	y[,3] 33.1	se[,1] se[,2] 0.780013495	se[,3] 0.475	# 0.75707	Study 1922	Year #
3	Cotton 3	1984 5	7	37.2	38.4	38.1	0.632455532	0.15811	3883	0.31622	7766
3	# 3	Sawdy 8	2003 16	31.8	31.2	31.8	0.450287265	0.423014	4393	0.44126	1304
	#	Klauser	2012								

2	1.	3	NA	31.2	36.4	NA	0.164991	582	0.164991	582	NA	#
2	Zuckerma 1	in 3	1984 NA	33	35.2	NA	0.309838	668	0.284018	779	NA	#
2	Niebyl 1	1980 3	NA	29.1	29.1	NA	1.107800	624	1.4	NA	#	
2	Panter 1	1999 8	NA	33	33.8	NA	0.055901	699	0.057353	933	NA	#
2	Cox 1	1990 8	NA	36.5	35.7	NA	0.401663	209	0.367423	461	NA	#
2	How 1	2006 10	NA	32.9	38.7	NA	0.242535	625	0.114707	867	NA	#
2	Casapo 1	1977 11	NA	33.4	34	NA	0.095399	809	0.090610	304	NA	#
2	CPLIG 1	1992 11	NA	32.5	34.6	NA	0.190125	067	0.226694	451	NA	#
2	Merkatz 1	1980 11	NA	32.6	32.8	NA	0.291217	603	0.421856	567	NA	#
2	Leveno 1	1986 11	NA	36.3	37.2	NA	0.296984	848	0.442857	143	NA	#
2	Larsen 1	1986 17	NA	34.1	35.2	NA	0.742558	015	0.569613	43	NA	#
2	Smith	2007	NA	38.3	37.8	NA	0.280824	304	0 487707	173	NA	#
2	Goodwin	1994	NA	30.1	31	NA	0.500201	055	0.504825	202	NA	#
2	Weiner	1988	NA	35.7	25.7	NA	1.069007	008	0.052627	044	NA	#
2	Stika	2002	NA	35.5	25.7	NA	0.201217	803	0.402157	842	NA	#
2	Borna	2007	NA	30	30.7	NA	0.201211	042	0.907081	042	NA	#
2	Rasanen	1995		20.0	24.4	NA	4.0000005	544	4.044000	070		-
2	Parilla	1997	NA	30.6	31.1	NA	1.090900	005	1.241303	400	NA NA	#
2	3 Besinger	1991	NA	30.0	33.8	NA	0.020414	080	0.803242	183	NA	
2	3 Kurki	14 1991	NA	36.7	35.2	NA	0.146058	349	0.146059	349	NA	#
2	3 Kashania	10 n	NA 2011	35.2	34.1	NA	0.352281	938	0.432049	38	NA	#
2	4 Schorr	8 1998	NA	34.9	34.8	NA	0.536656	315	0.655743	852	NA	#
2	6 McWhorte	8 er	NA 2004	35.3	34.7	NA	0.331806	025	0.402287	04	NA	#
2	8 13 Surichamorn		NA 2001	36.21	36.01	NA	0.46	0.474976	891	NA	#	
2	8 Larmon	15 1999	NA	35.5	35.6	NA	0.396911	151	0.490076	972	NA	#
2	8 Taherian	16 2007	NA	34.1	34.3	NA	0.191502	0.176162	803	NA	#	
2	8 Glock	16	NA	35.2	34.5	NA	0.484138	662	0.448358	831	NA	#
2	8 2007	16	NA	35.8	36	NA	0.354474	504	0.31	NA	#	Lyell
2	9 Essed	11	NA	37.4	36.9	NA	0.346410	162	0.404145	188	NA	#
2	10 Sirohiwal	11 2001	NA	35	35.6	NA	0.547722	558	0.481995	851	NA	#
2	10 Ravamaik	16	NA 2003	33.46	34.98	NA	0.394360	241	0.411889	7	NA	#
2	11 Holleboor	11	NA 1998	35.7	35.4	NA	0.308461	529	0.31	NA	#	
2	11 ALOo#an	16	NA	29.5	30.2	NA	0.434659	144	0.474692	883	NA	#
2	11 Cararach	16	NA	36.1	36.2	NA	0.384307	569	0.384307	569	NA	#
2	11 Panatson	16 (1007/2	NA 000)	32.1	33.4	NA	0.464233	584	0.461690	258	NA	#
2	11 Fan	16 2002	NA	34.07	34.71	NA	0.794197	708	0.495710	634	NA	#
2	11 Kale	16	NA	31.8	33.3	NA	0.656392	462	0.593295	879	NA	#
2	11 Lin	18 2009	NA	37.4	37.1	NA	0.511681	719	0.521286	035	NA	#

2	11 Shim	18 2006	NA	37.3	37.3	NA	0.390563289		0.440958552		NA	#
2	11 Moutquir	18	NA	35.2	35.1	NA	0.363636364		0.374165739		NA	#
2	11 2009	18	NA	30	35.1	NA	0.94	0.87276	8089	NA	#	Neri
2	12 Jannet	15 1997	NA	37.6	38.4	NA	0.320246998		0.25924757		NA	#
2	12 Trabelsi	15	NA	35.29	35.07	NA	0.43788	3027	0.64	NA	#	
2	12 French/A	18 ustralian	NA 2001	36.3	36.5	NA	0.33498226		0.2750	09549	NA	#
2	13 Weeraku	16	NA	34.89	35.67	NA	0.46281	9914	0.4323	06476	NA	#
2	13 Europea	18	NA 2001	35.2	35.8	NA	0.36978	89381	0.3806	75443	NA	#
2	16 Nassar	16	NA	36	34.7	NA	0.4	0.50823	34087	NA	#	
END	110.3.501	2000										

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