National Institute for Health and Care Excellence

Cystic Fibrosis: diagnosis and management

Appendix 1

Main appendix document

Forest Plots

04 May 2017

Disclaimer

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

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Contents

Appendices

Appendix I: Forest plots

I.1 Diagnosis of cystic fibrosis

Not applicable for this review.

I.2 Information and support

Not applicable to this review.

I.3 Service delivery

I.3.1 Service configuration

I.3.1.1 Home-based care

Comparison 1.1: home *versus* hospital care for the administration of intravenous antibiotics (IV AB) in people with CF experiencing an acute pulmonary exacerbation

Figure 1: Lung function: Change in FEV_1 % predicted at 21 days follow-up (range of scores: 0-100)
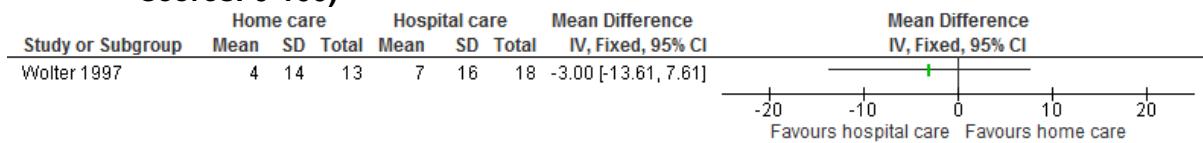
Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 2: Lung function: Change in FEV_1 % predicted at 18 days follow-up (range of scores: 0-100)
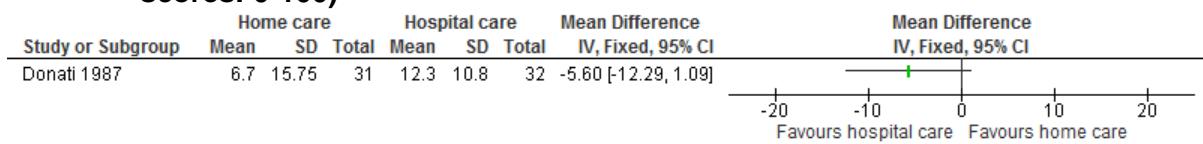
Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 3: Lung function: Change in FEV_1 % predicted at 15 days follow-up (range of scores: 0-100)
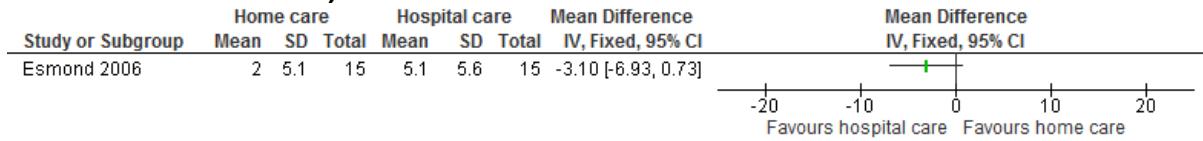
Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 4: People starting next course of AB more than 12 weeks after completing the previous course (proxy outcome for time to next exacerbation) at 18 days follow-up

Study or Subgroup	Home care Events	Total	Hospital care Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bosworth 1997	13	27	28	32	0.55 [0.36, 0.83]	

Abbreviations: AB: antibiotics; CI: confidence interval; M-H: Mantel Haenszel;

Figure 5: Nutritional status: Change in weight (kg) at 18 days follow-up
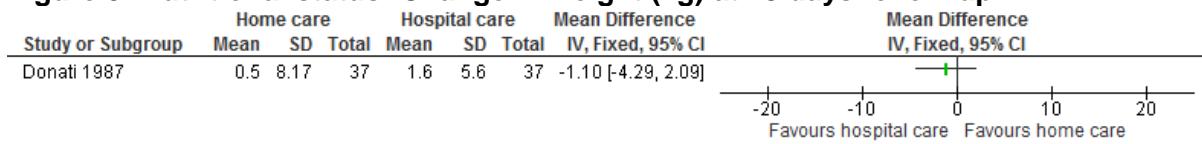
Study or Subgroup	Home care Mean	SD	Total	Hospital care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Donati 1987	0.5	8.17	37	1.6	5.6	37	-1.10 [-4.29, 2.09]	

Abbreviations: CI: confidence interval; kg: kilograms; IV: inverse variance; SD: standard deviation;

Figure 6: Nutritional status: Change in weight (kg) at 10 days post-treatment follow-up
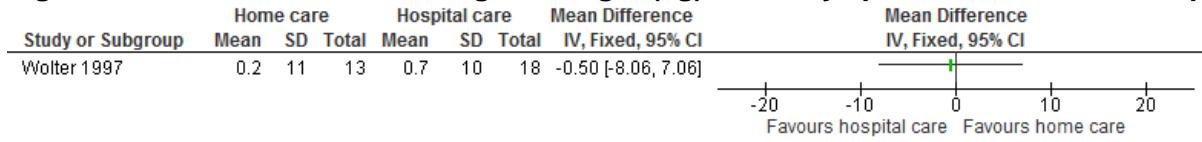
Study or Subgroup	Home care Mean	SD	Total	Hospital care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Wolter 1997	0.2	11	13	0.7	10	18	-0.50 [-8.06, 7.06]	

Abbreviations: CI: confidence interval; kg: kilograms; IV: inverse variance; SD: standard deviation;

Figure 7: Nutritional status: Change in BMI at 15 days follow-up
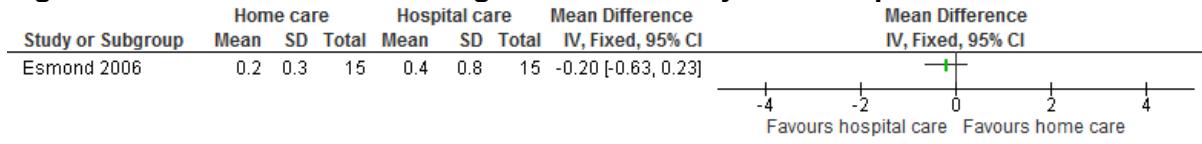
Study or Subgroup	Home care Mean	SD	Total	Hospital care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Esmond 2006	0.2	0.3	15	0.4	0.8	15	-0.20 [-0.63, 0.23]	

Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation;

Figure 8: Change in quality of life (CF-QOL) at 15 days follow-up (range of scores: 0-100)

Study or Subgroup	Home care Mean	SD	Total	Hospital care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.9.1 Physical							
Esmond 2006	10	11.6	15	12.2	18.4	15	-2.20 [-13.21, 8.81]
1.9.2 Social							
Esmond 2006	3	18.8	15	6.4	24.1	15	-3.40 [-18.87, 12.07]
1.9.3 Treatment							
Esmond 2006	6.2	22.8	15	8.2	19.4	15	-2.00 [-17.15, 13.15]
1.9.4 Symptoms							
Esmond 2006	6.2	22.8	15	23.3	16.2	15	-17.10 [-31.25, -2.95]
1.9.5 Emotional							
Esmond 2006	12.5	16.8	15	8.3	19.1	15	4.20 [-8.67, 17.07]
1.9.6 Future							
Esmond 2006	3.8	16.8	15	9.3	18	15	-5.50 [-17.96, 6.96]
1.9.7 Relationships							
Esmond 2006	6.9	18.8	15	-0.5	17.5	15	7.40 [-5.60, 20.40]
1.9.8 Body image							
Esmond 2006	2.7	23.4	15	1.8	17.6	15	0.90 [-13.92, 15.72]
1.9.9 Career							
Esmond 2006	10	21	15	1.7	18.2	15	8.30 [-5.76, 22.36]

Favours hospital care   Favours home care

Abbreviations: CI: confidence interval; CF-QOL: cystic fibrosis quality of life questionnaire; IV: inverse variance; SD: standard deviation

Comparison 1.2. Home *versus* hospital care for the administration of intravenous antibiotics (IV AB) in people with CF and chronic pulmonary infection with P. Aeruginosa

Figure 9: Change in FEV_1% predicted at 14 days follow-up (range of scores: 0-100)
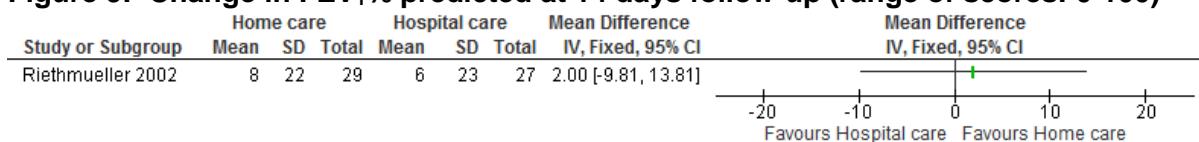
| Study or Subgroup	Home care Mean	SD	Total	Hospital care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Riethmueller 2002	8	22	29	6	23	27	2.00 [-9.81, 13.81]

Favours Hospital care   Favours Home care

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second ; IV: inverse variance; SD: standard deviation

Figure 10: Change in weight (kg) at 14 days follow-up

Study or Subgroup	Home care Mean	SD	Total	Hospital care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Riethmueller 2002	1.1	9.7	29	1.1	7	28	0.00 [-4.38, 4.38]

Favours Hospital care   Favours Home care
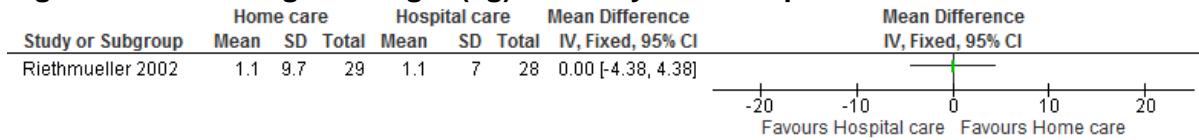
Abbreviations: CI: confidence interval; kg: kilograms ; SD: standard deviation; IV: inverse variance

Figure 11: Change in weight for height (%) at 14 days follow-up

Study or Subgroup	Home care Mean	SD	Total	Hospital care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Riethmueller 2002	3	7	29	4	7	28	-1.00 [-4.64, 2.64]

Favours Hospital care   Favours Home care
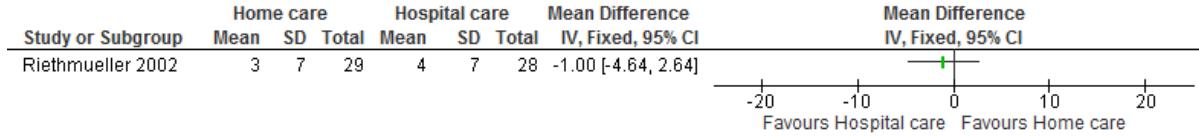
Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

I.3.1.2 CF centre care

Comparison 2.1. CF centre care *versus* shared care

Figure 12: Lung function: Change in FEV$_1$ % predicted at 1 year follow-up (range of scores: 0-100)
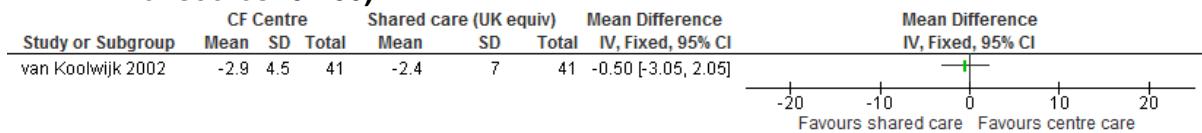
Study or Subgroup	CF Centre Mean	SD	Total	Shared care (UK equiv) Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
van Koolwijk 2002	-2.9	4.5	41	-2.4	7	41	-0.50 [-3.05, 2.05]

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 13: Lung function: Change from first to last FEV$_1$ % predicted per year at 3 years follow-up (range of scores: 0-100)

Study or Subgroup	CF Centre Mean	SD	Total	Local care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Thomas 2008	-1.4	6.2	67	1	8.3	30	-2.40 [-5.72, 0.92]
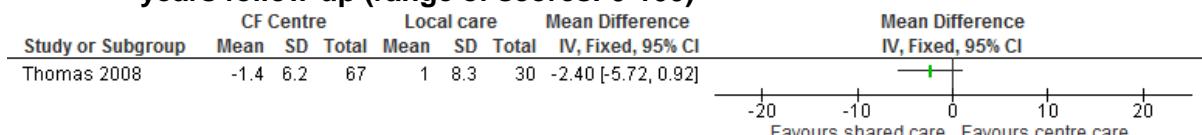
Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 14: Lung function: Slope FEV$_1$ % predicted per year at 3 years follow-up
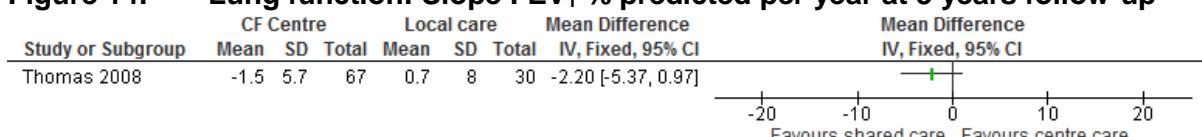
Study or Subgroup	CF Centre Mean	SD	Total	Local care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Thomas 2008	-1.5	5.7	67	0.7	8	30	-2.20 [-5.37, 0.97]

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 15: Nutritional status: Change in BMI at 1 year follow-up
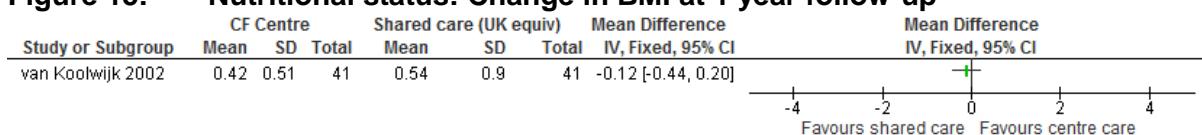
Study or Subgroup	CF Centre Mean	SD	Total	Shared care (UK equiv) Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
van Koolwijk 2002	0.42	0.51	41	0.54	0.9	41	-0.12 [-0.44, 0.20]

Abbreviations: BMI: body mass index ; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 16: **Quality of life: CFQ-R Teen (range of scores: 0-100)**

Study or Subgroup	CF Centre			Shared care			Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
3.7.1 Physical								
Thomas 2006	72.6	23.7	24	90.4	13.1	10	-17.80 [-30.28, -5.32]	
3.7.2 Role								
Thomas 2006	76.2	21.4	24	86.6	21.9	10	-10.40 [-26.45, 5.65]	
3.7.3 Vitality								
Thomas 2006	56	25.9	24	74.2	15.9	10	-18.20 [-32.50, -3.90]	
3.7.4 Emotional								
Thomas 2006	77.2	18.4	24	82.7	17	10	-5.50 [-18.35, 7.35]	
3.7.5 Social								
Thomas 2006	76.4	19.1	24	94	8	10	-17.60 [-26.71, -8.49]	
3.7.6 Body								
Thomas 2006	72.2	23.2	24	76.7	23.1	10	-4.50 [-21.56, 12.56]	
3.7.7 Eating								
Thomas 2006	72.2	23.2	24	76.7	23.1	10	-4.50 [-21.56, 12.56]	
3.7.8 Treatment burden								
Thomas 2006	56	21.1	24	65.6	26.4	10	-9.60 [-28.01, 8.81]	
3.7.9 Health								
Thomas 2006	57.4	21.4	24	72.2	23.6	10	-14.80 [-31.75, 2.15]	
3.7.10 Weight								
Thomas 2006	59.7	21.4	24	72.2	23.6	10	-12.50 [-29.45, 4.45]	
3.7.11 Respiratory								
Thomas 2006	68.3	18.3	24	72.8	12.7	10	-4.50 [-15.25, 6.25]	
3.7.12 Digestion								
Thomas 2006	84.3	16.4	24	92.2	10.5	10	-7.90 [-17.14, 1.34]	

-50   -25   0   25   50
Favours shared care   Favours centre care

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation.
Note: Cross-sectional study

Figure 17: Quality of life: CFQ-R Child (range of scores: 0-100)

Study or Subgroup	CF Centre			Shared care			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
3.6.1 Physical								
Thomas 2006	76	21.9	46	77.2	23.1	37	-1.20 [-10.97, 8.57]	
3.6.4 Emotional								
Thomas 2006	76.1	14.8	46	74.8	14.9	37	1.30 [-5.13, 7.73]	
3.6.5 Social								
Thomas 2006	70.2	15.9	46	71.9	19.4	37	-1.70 [-9.46, 6.06]	
3.6.6 Body								
Thomas 2006	78.3	24.6	46	81.1	25.4	37	-2.80 [-13.64, 8.04]	
3.6.7 Eating								
Thomas 2006	76.1	26.2	46	76.6	26.6	37	-0.50 [-11.94, 10.94]	
3.6.8 Treatment burden								
Thomas 2006	68.4	25.2	46	63.7	23.8	37	4.70 [-5.88, 15.28]	
3.6.11 Respiratory								
Thomas 2006	70.8	20.5	46	66.9	23.4	37	3.90 [-5.69, 13.49]	
3.6.12 Digestion								
Thomas 2006	76.1	26.9	46	72.1	29.9	37	4.00 [-8.38, 16.38]	

Favours shared care   Favours centre care

-50 -25 0 25 50

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation.
Note: Cross-sectional study

Figure 18: Quality of life: CFQ-R Parent (range of scores: 0-100)

Study or Subgroup	CF Centre			Shared care			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
3.8.1 Physical								
Thomas 2006	74.2	20.5	45	71.7	22.1	35	2.50 [-6.96, 11.96]	
3.8.3 Vitality								
Thomas 2006	64.3	15.4	45	65	16.5	35	-0.70 [-7.78, 6.38]	
3.8.4 Emotional								
Thomas 2006	76.1	16.8	45	75	21.4	35	1.10 [-7.52, 9.72]	
3.8.6 Body								
Thomas 2006	72.2	28.7	45	69.2	26.4	35	3.00 [-9.12, 15.12]	
3.8.7 Eating								
Thomas 2006	63	33.7	45	70.5	24.3	35	-7.50 [-20.22, 5.22]	
3.8.8 Treatment burden								
Thomas 2006	45.2	19.8	45	51.4	18.5	35	-6.20 [-14.63, 2.23]	
3.8.9 Health								
Thomas 2006	69.4	22.9	45	68.3	21.2	35	1.10 [-8.60, 10.80]	
3.8.10 Weight								
Thomas 2006	56.3	37.5	45	57.1	33.5	35	-0.80 [-16.40, 14.80]	
3.8.11 Respiratory								
Thomas 2006	74.3	21	45	74.8	23.2	35	-0.50 [-10.33, 9.33]	
3.8.12 Digestion								
Thomas 2006	76.5	16.3	45	77.1	20	35	-0.60 [-8.76, 7.56]	
3.8.13 School function								
Thomas 2006	64.5	27.7	45	65.1	22.6	35	-0.60 [-11.63, 10.43]	

Favours shared care   Favours centre care

-50 -25 0 25 50

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation.

Note: Cross-sectional study

Comparison 2.2. CF centre care *versus* local care (below CF Trust recommendations)

Figure 19: Lung function: Change in FEV₁ % predicted at 1 year follow-up (range of scores: 0-100)
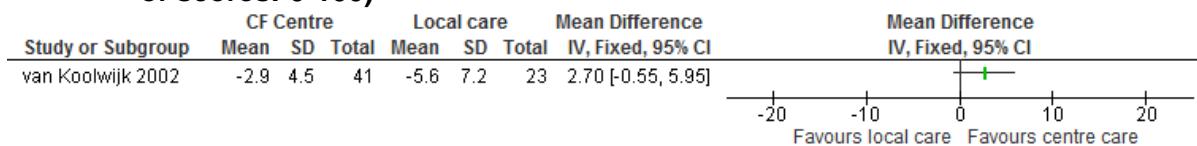
| Study or Subgroup	CF Centre			Local care			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
van Koolwijk 2002	-2.9	4.5	41	-5.6	7.2	23	2.70 [-0.55, 5.95]	

Favours local care Favours centre care

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 20: Lung function: Change from first to last FEV₁ % predicted per year at 3 years follow-up (range of scores: 0-100)

| Study or Subgroup	CF Centre			Local care			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Thomas 2008	-1.4	6.15	67	4.3	8.6	11	-5.70 [-10.99, -0.41]	

Favours local care Favours centre care
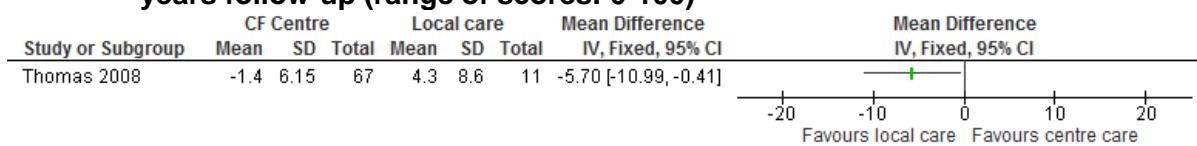
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 21: Lung function: Slope FEV₁ % predicted per year at 3 years follow-up (range of scores: 0-100)
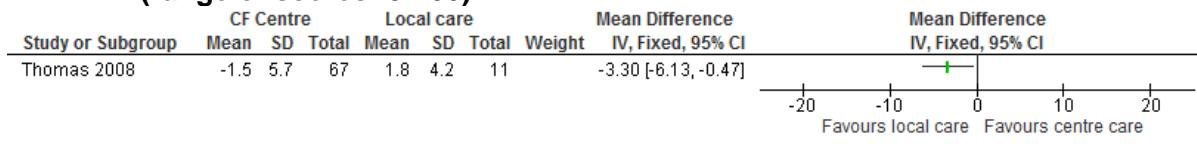
Study or Subgroup	CF Centre			Local care			Weight	Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI	IV, Fixed, 95% CI
Thomas 2008	-1.5	5.7	67	1.8	4.2	11		-3.30 [-6.13, -0.47]	

Favours local care Favours centre care

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 22: Nutritional status: Change in BMI at 1 year follow-up
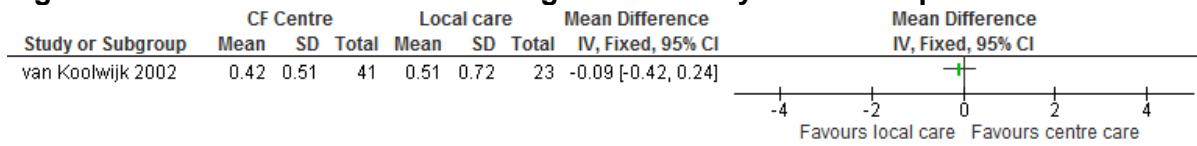
Study or Subgroup	CF Centre			Local care			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
van Koolwijk 2002	0.42	0.51	41	0.51	0.72	23	-0.09 [-0.42, 0.24]	

Favours local care Favours centre care

Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation;

Comparison 2.3. CF centre care *versus* general clinic (non-CF)

Data could not be plotted.

I.3.1.3   Shared care

## Comparison 3.1. Local care (below CF Trust Standards) *versus* shared care (UK equivalent)

Figure 23: Lung function: Change in FEV₁ % predicted at 1 year follow-up (range of scores: 0-100)
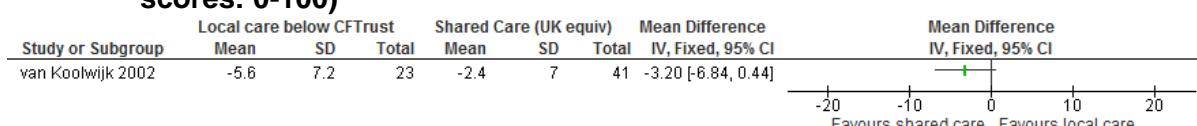
Study or Subgroup	Local care below CFTrust			Shared Care (UK equiv)			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
van Koolwijk 2002	-5.6	7.2	23	-2.4	7	41	-3.20 [-6.84, 0.44]	

Favours shared care Favours local care

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD:

standard deviation

Figure 24: **Lung function: Change from first to last FEV$_1$% predicted per year at 3 years follow-up (range of scores: 0-100)**

| Study or Subgroup	Local care below CFTrust			Shared Care (UK equiv)			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Thomas 2008	4.3	8.6	11	1	8.3	30	3.30 [-2.59, 9.19]	
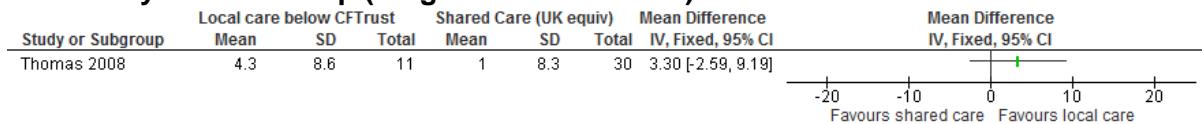
Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 25: Lung function: slope FEV$_1$ % predicted per year at 3 years follow-up
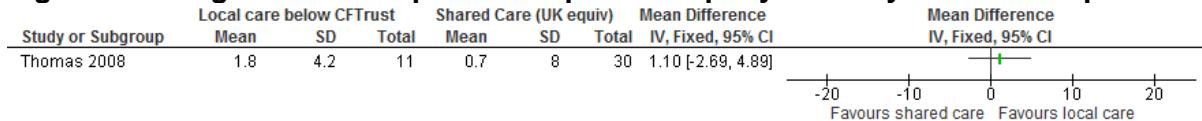
Study or Subgroup	Local care below CFTrust			Shared Care (UK equiv)			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Thomas 2008	1.8	4.2	11	0.7	8	30	1.10 [-2.69, 4.89]	

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 26: **Nutritional status: Change in BMI at 1 year follow-up**
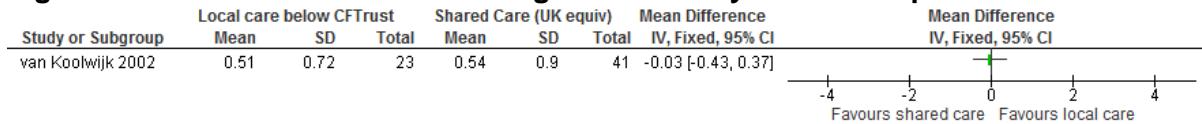
Study or Subgroup	Local care below CFTrust			Shared Care (UK equiv)			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
van Koolwijk 2002	0.51	0.72	23	0.54	0.9	41	-0.03 [-0.43, 0.37]	

*Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation*

Comparison 3.2 Shared care (above UK standards) *versus* shared care (UK equivalent)

Figure 27: **Lung function: Change from first to last FEV$_1$ % predicted per year at 3 years follow-up (range of scores: 0-100)**

Study or Subgroup	Shared Care (above UK)			Shared Care (UK equiv)			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Thomas 2008	0.5	9.3	19	1	8.3	30	-0.50 [-5.63, 4.63]	
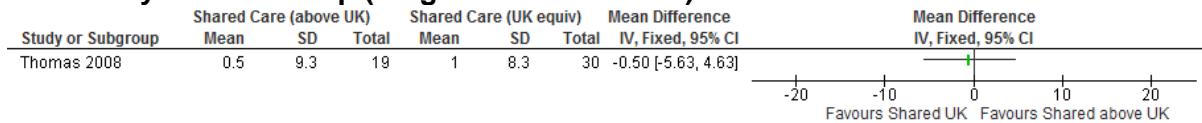
Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 28: **Lung function: slope FEV$_1$ % per year at 3 years follow-up**
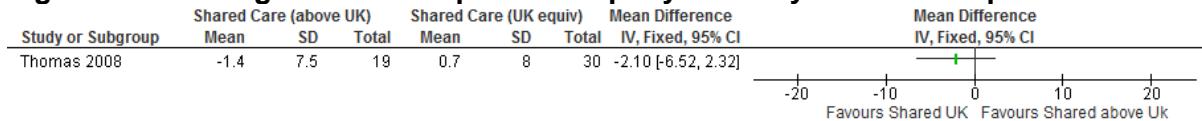
| Study or Subgroup	Shared Care (above UK)			Shared Care (UK equiv)			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Thomas 2008	-1.4	7.5	19	0.7	8	30	-2.10 [-6.52, 2.32]	

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

I.3.1.4 **Telemedicine**

Comparison 4.1. Home monitoring + diary recording *versus* usual care

Figure 29: **Lung function: Change in FEV$_1$ % predicted at 4 years follow-up (range of scores: 0-100)**
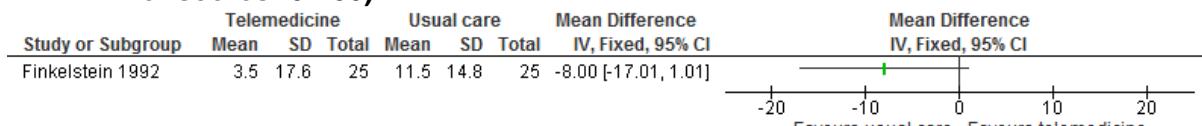
Study or Subgroup	Telemedicine			Usual care			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Finkelstein 1992	3.5	17.6	25	11.5	14.8	25	-8.00 [-17.01, 1.01]	

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD:

standard deviation

Comparison 4.2. Telemedicine *versus* usual care

Data could not be plotted.

I.3.2 Multidisciplinary teams

Not applicable, as no studies were included in this review.

I.4 Transition

Not applicable to this review.

I.5 Complications of cystic fibrosis

Not applicable to this review.

I.6 Monitoring for pulmonary disease

I.6.1 Review 1. Monitoring for pulmonary disease onset in people with CF without clinical signs or symptoms of lung disease

Comparison 1. Lung function tests *versus* imaging tests

No forest plots available.

I.6.2 Review 2. Monitoring for evolving pulmonary disease in people with CF with established lung disease

Not applicable, as evidence was found for this review.

I.6.3 Review 3. Monitoring for evolving pulmonary disease in people with CF following an acute pulmonary exacerbation

Comparison 1. Monitoring using bronchoalveolar lavage (BAL) *versus* standard monitoring

Figure 30: Lung function – FEV_1% predicted (z-scores) at age 5 years
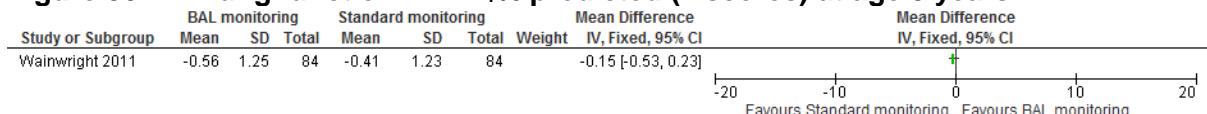
Study or Subgroup	BAL monitoring Mean	SD	Total	Standard monitoring Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Wainwright 2011	-0.56	1.25	84	-0.41	1.23	84		-0.15 [-0.53, 0.23]

Abbreviations. BAL: bronchoalveolar lavage; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation. Infants were recruited before age 6 months and followed until age 5 years.

Figure 31: Clearance of the organism from the cultures at age 5 years

Study or Subgroup	BAL monitoring Events	Total	Standard monitoring Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Wainwright 2011	38	39	39	43		1.07 [0.96, 1.20]
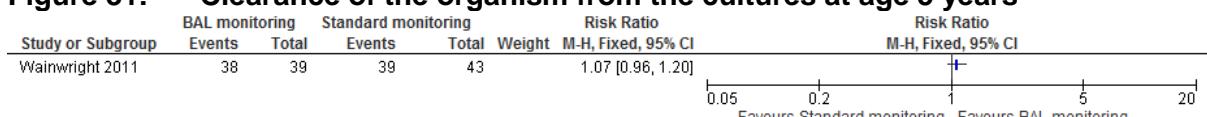
Abbreviations: BAL: bronchoalveolar lavage; M-H: Mantel-Haenszel; CI: confidence interval. Infants were

recruited before age 6 months and followed until age 5 years

Figure 32:   Weight (z-scores) at age 5 years

| Study or Subgroup	BAL monitoring Mean	SD	Total	Standard monitoring Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Wainwright 2011	-0.15	0.88	80	-0.21	0.82	77		0.06 [-0.21, 0.33]
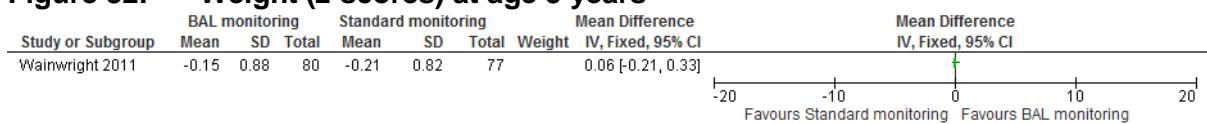
Abbreviations: BAL: bronchoalveolar lavage; SD: standard deviation; IV: inverse variance; CI: confidence interval. Infants were recruited before age 6 months and followed until age 5 years

Figure 33:   Height (z-scores) at age 5 years
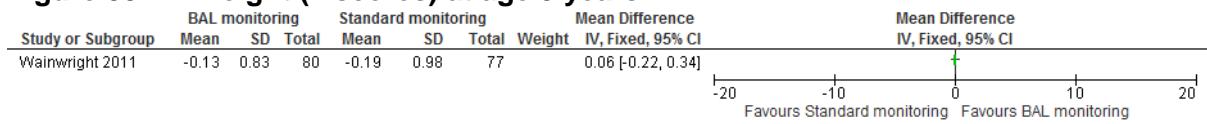
Study or Subgroup	BAL monitoring Mean	SD	Total	Standard monitoring Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Wainwright 2011	-0.13	0.83	80	-0.19	0.98	77		0.06 [-0.22, 0.34]

Abbreviations: BAL: bronchoalveolar lavage; CI: confidence interval; IV: inverse variance; SD: standard deviation. Infants were recruited before age 6 months and followed until age 5 years

Figure 34:   BMI (z-scores) at age 5 years

Study or Subgroup	BAL monitoring Mean	SD	Total	Standard monitoring Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Wainwright 2011	0.03	0.93	80	0.01	0.83	77		0.02 [-0.26, 0.30]
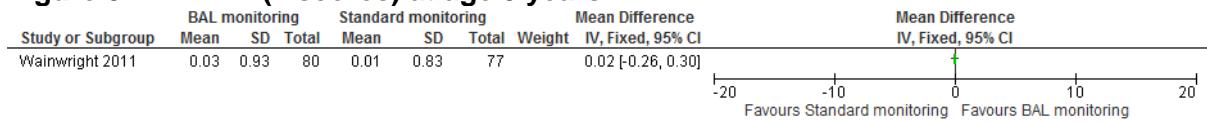
Abbreviations: BAL: bronchoalveolar lavage; BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation. Infants were recruited before age 6 months and followed until age 5 years

I.7   Airway clearance techniques

Comparison 1. Manual physiotherapy *versus* no airway clearance techniques

No evidence was found for this comparison.

Comparison 2. Manual physiotherapy techniques *versus* oscillating devices

Figure 35:   Change in FEV$_1$ % predicted after 8.8 days follow-up (range of scores: 0-100)
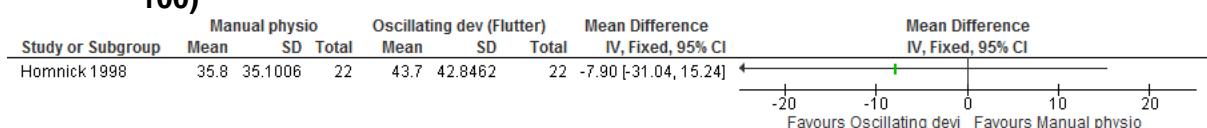
Study or Subgroup	Manual physio Mean	SD	Total	Oscillating dev (Flutter) Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Homnick 1998	35.8	35.1006	22	43.7	42.8462	22	-7.90 [-31.04, 15.24]

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 36:   Change in FEV$_1$ % predicted at 1 month follow-up (range of scores: 0-100)
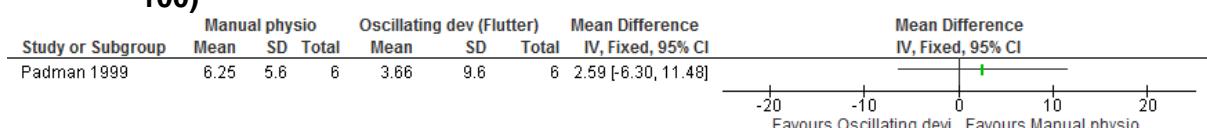
| Study or Subgroup	Manual physio Mean	SD	Total	Oscillating dev (Flutter) Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Padman 1999	6.25	5.6	6	3.66	9.6	6	2.59 [-6.30, 11.48]

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 37:   Change in FVC % predicted at 2 weeks follow-up (range of scores: 0-100)
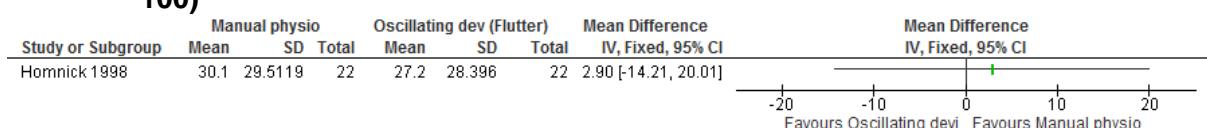
Study or Subgroup	Manual physio Mean	SD	Total	Oscillating dev (Flutter) Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Homnick 1998	30.1	29.5119	22	27.2	28.396	22	2.90 [-14.21, 20.01]

Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Comparison 3. Manual physiotherapy *versus* high frequency chest wall oscillation (HFCWO)

Figure 38: Wet sputum weight (g.) at 1 to 2 weeks follow-up
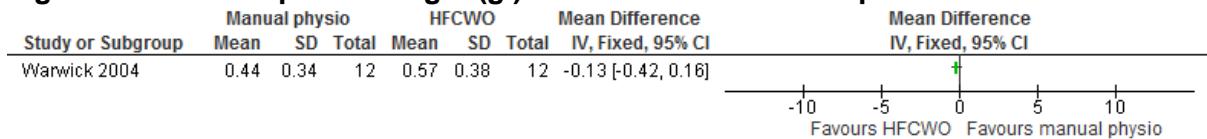
| Study or Subgroup | Manual physio | | | HFCWO | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Warwick 2004	0.44	0.34	12	0.57	0.38	12	-0.13 [-0.42, 0.16]	

Abbreviations: HFCWO: High Frequency Chest Wall Oscillation; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 39: Dry sputum weight (g.) at 1 to 2 weeks follow-up
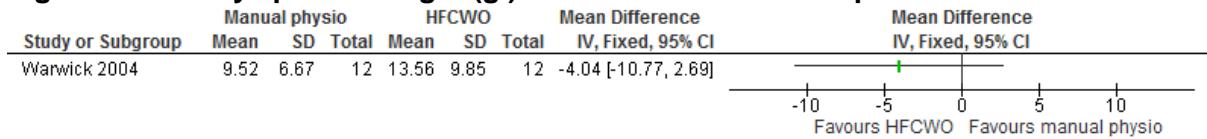
| Study or Subgroup | Manual physio | | | HFCWO | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Warwick 2004	9.52	6.67	12	13.56	9.85	12	-4.04 [-10.77, 2.69]	

Abbreviations: HFCWO: High Frequency Chest Wall Oscillation; SD: standard deviation; IV: inverse variance; CI: confidence interval

Comparison 4. Positive expiratory pressure mask (PEP) *versus* no airway clearance technique

Figure 40: Dry sputum weight (g.) at 2 days follow-up
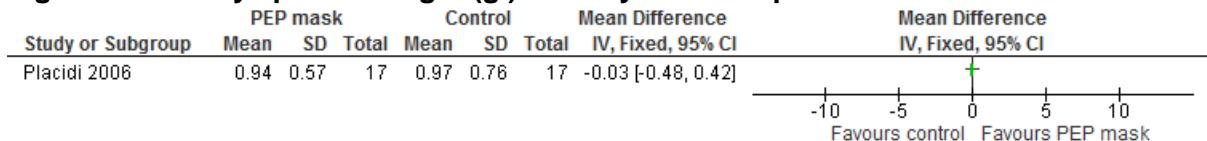
| Study or Subgroup | PEP mask | | | Control | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Placidi 2006	0.94	0.57	17	0.97	0.76	17	-0.03 [-0.48, 0.42]	

Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 41: Wet sputum weight (g.) at 2 days follow-up
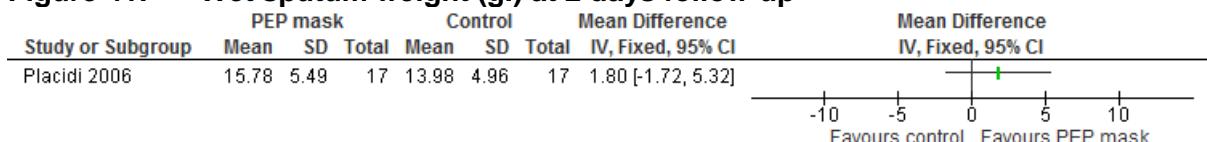
| Study or Subgroup | PEP mask | | | Control | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Placidi 2006	15.78	5.49	17	13.98	4.96	17	1.80 [-1.72, 5.32]	

Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 42: FEV$_1$ % predicted at 2 days follow-up (range of scores: 0-100)
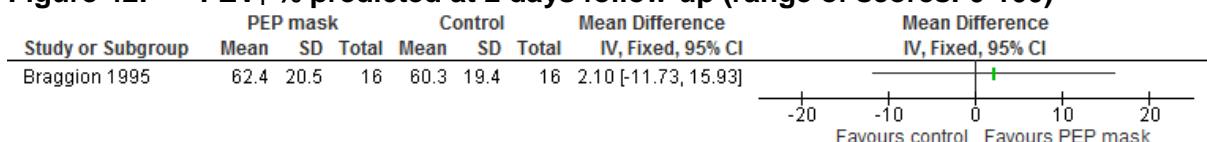
| Study or Subgroup | PEP mask | | | Control | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Braggion 1995	62.4	20.5	16	60.3	19.4	16	2.10 [-11.73, 15.93]	

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 43: Change in FEV$_1$ (litres) at 2 days follow-up
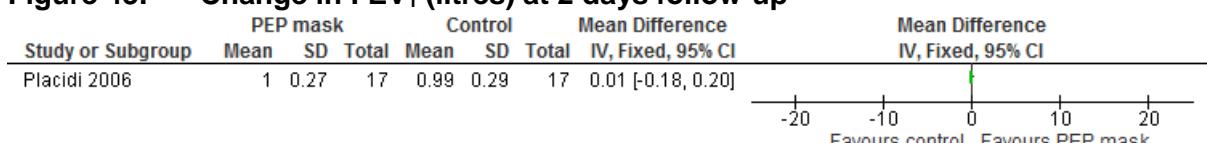
| Study or Subgroup | PEP mask | | | Control | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Placidi 2006	1	0.27	17	0.99	0.29	17	0.01 [-0.18, 0.20]	

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

## Figure 44: FVC % predicted at 2 days follow-up (range of scores: 0-100)
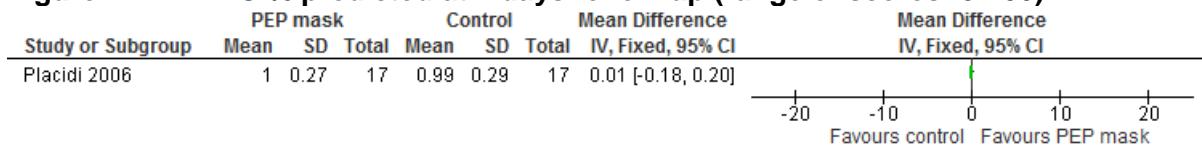
Study or Subgroup	PEP mask Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Placidi 2006	1	0.27	17	0.99	0.29	17	0.01 [-0.18, 0.20]	

Favours control Favours PEP mask

Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 45: Change in FVC (litres) at 2 days follow-up
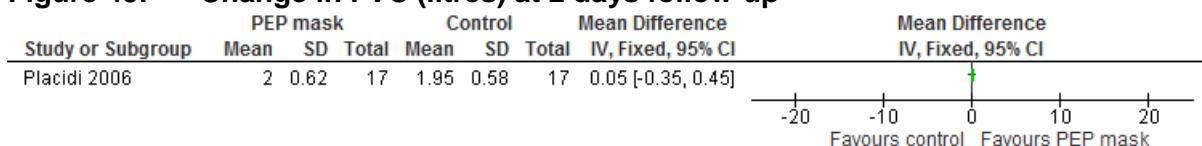
Study or Subgroup	PEP mask Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Placidi 2006	2	0.62	17	1.95	0.58	17	0.05 [-0.35, 0.45]	

Favours control Favours PEP mask

Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 46: Oxygen saturation (SpO2) at 2 days follow-up
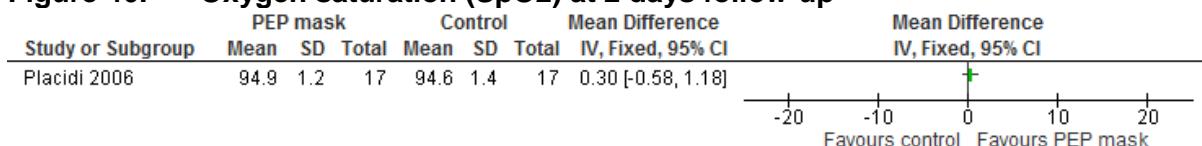
| Study or Subgroup	PEP mask Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Placidi 2006	94.9	1.2	17	94.6	1.4	17	0.30 [-0.58, 1.18]	

Favours control Favours PEP mask

Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Comparison 5. Positive expiratory pressure mask (PEP) *versus* active cycle of breathing techniques (ACBT)

No evidence was found for this comparison.

Comparison 6. Positive expiratory pressure mask (PEP) *versus* oscillating devices

Figure 47: Patient preference (measured as self-withdrawal due to lack of perceived effectiveness) at 1 year follow-up

Study or Subgroup	PEP Events	Total	Oscillating device Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
McIlwaine 2001	0	20	5	20	0.09 [0.01, 1.54]	

Favours Oscillating device Favours PEP
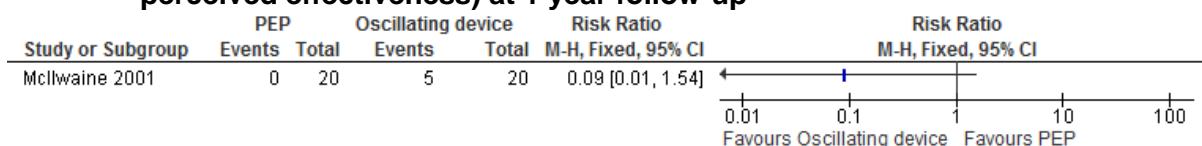
Abbreviations: PEP: positive expiratory pressure mask; M-H: Mantel-Haenszel; CI: confidence interval

Figure 48: Hospitalisations due to respiratory exacerbations (mean number per participant) at 13 months follow-up
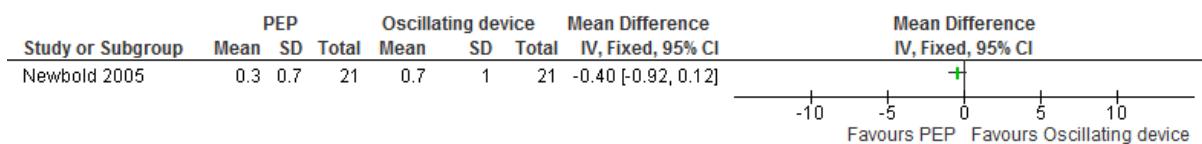
Study or Subgroup	PEP Mean	SD	Total	Oscillating device Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Newbold 2005	0.3	0.7	21	0.7	1	21	-0.40 [-0.92, 0.12]	

Favours PEP Favours Oscillating device

Abbreviations: PEP: positive expiratory pressure mask; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 49:   Change in FEV$_1$ % predicted at up to 2 years follow-up (range of scores: 0-100)
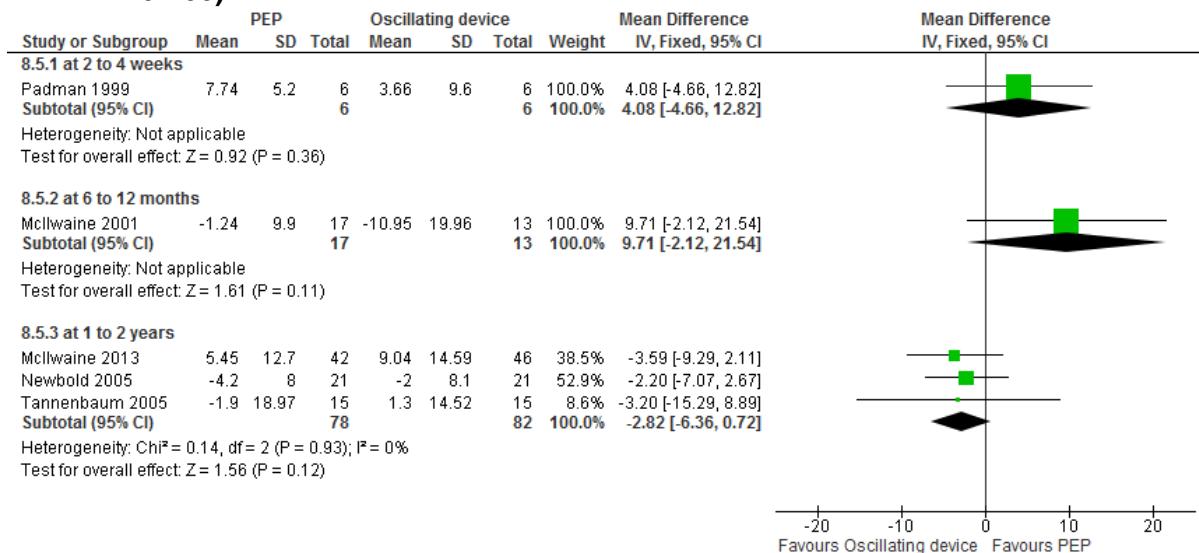
Abbreviations: CI: confidence interval; df: degrees of freedom; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; PEP: positive expiratory pressure mask; SD: standard deviation

Figure 50:   FVC % predicted at 2 to 4 weeks follow-up (range of scores: 0-100)
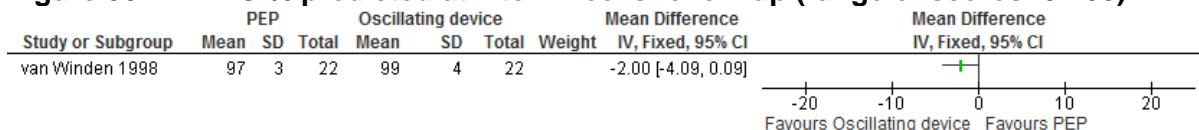
Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; PEP: positive expiratory pressure mask; SD: standard deviation

Figure 51:   Change in FVC % predicted at 1 year follow-up (range of scores: 0-100)
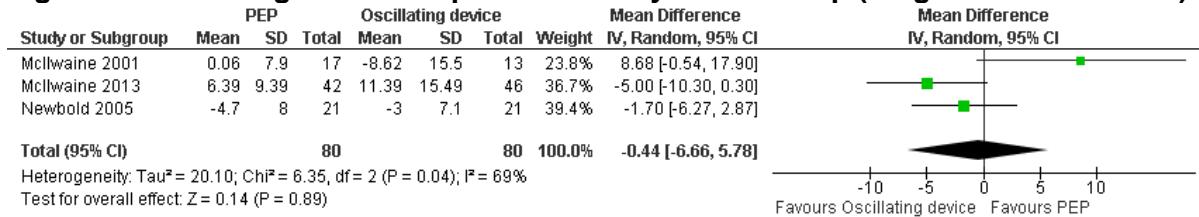
Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; PEP: positive expiratory pressure mask; SD: standard deviation

Figure 52:   Change in quality of life (measured with CF-QOL) at 1 year follow-up (range of scores: 0-100)
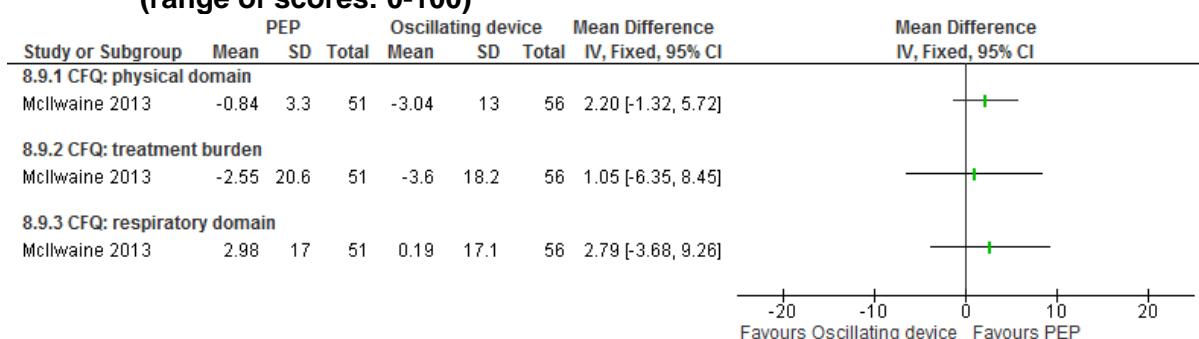
Abbreviations: CI: confidence interval; CF-QOL: cystic fibrosis quality of life questionnaire; IV: inverse variance; PEP: positive expiratory pressure mask; SD: standard deviation

Comparison 7. Positive expiratory pressure mask (PEP) *versus* high frequency chest wall oscillation (HFCWO)

Figure 53:   Sputum volume (ml.) at 1 week follow-up
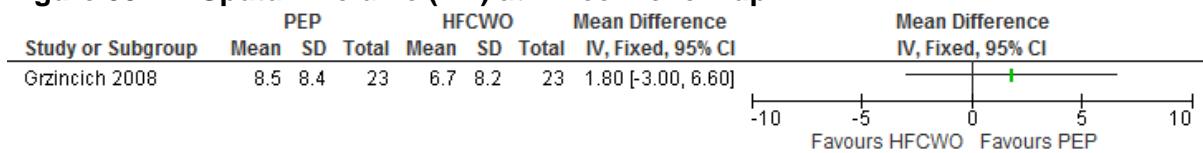
	PEP			HFCWO			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Grzincich 2008	8.5	8.4	23	6.7	8.2	23	1.80 [-3.00, 6.60]	

Abbreviations: PEP: positive expiratory pressure mask; HFCWO: high frequency chest wall oscillation; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 54:   Pulmonary exacerbations (number of patients) at 1 year follow-up
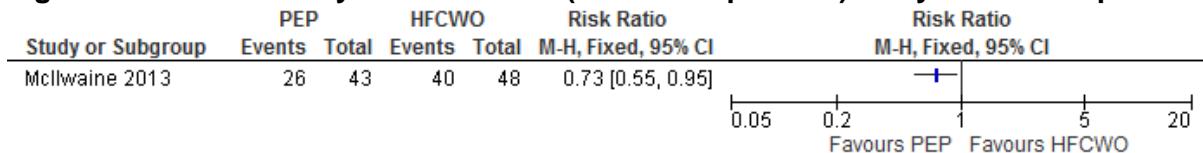
	PEP		HFCWO		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
McIlwaine 2013	26	43	40	48	0.73 [0.55, 0.95]	

Abbreviations: PEP: positive expiratory pressure mask; HFCWO: high frequency chest wall oscillation; M-H: Mantel-Haenszel; CI: confidence interval

Figure 55:   Pulmonary exacerbations (patients requiring antibiotics) at 1 year follow-up
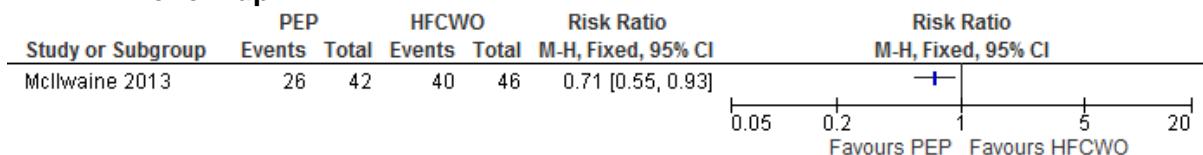
	PEP		HFCWO		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
McIlwaine 2013	26	42	40	46	0.71 [0.55, 0.93]	

Abbreviations: PEP: positive expiratory pressure mask; HFCWO: high frequency chest wall oscillation; M-H: Mantel-Haenszel; CI: confidence interval

Figure 56:   FEV$_1$ % predicted at 1 week follow-up (range of scores: 0-100)
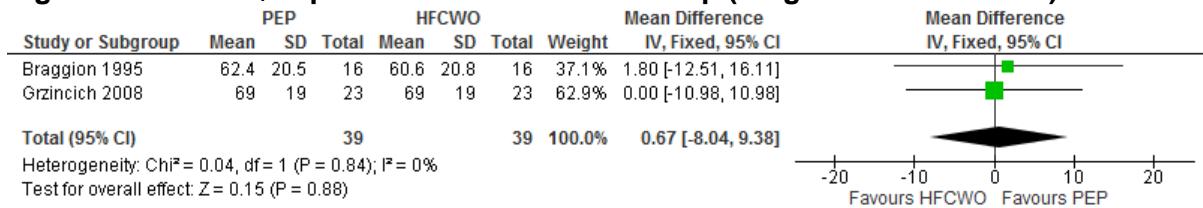
	PEP			HFCWO				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Braggion 1995	62.4	20.5	16	60.6	20.8	16	37.1%	1.80 [-12.51, 16.11]	
Grzincich 2008	69	19	23	69	19	23	62.9%	0.00 [-10.98, 10.98]	
Total (95% CI)			39			39	100.0%	0.67 [-8.04, 9.38]	

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)

Abbreviations: CI: confidence interval; df: degrees of freedom; FEV$_1$: forced expiratory volume in 1 second; HFCWO: high frequency chest wall oscillation; IV: inverse variance; PEP: positive expiratory pressure mask; SD: standard deviation

Figure 57:   FEV$_1$ % predicted at 1 to 2 weeks follow-up (range of scores: 0-100)
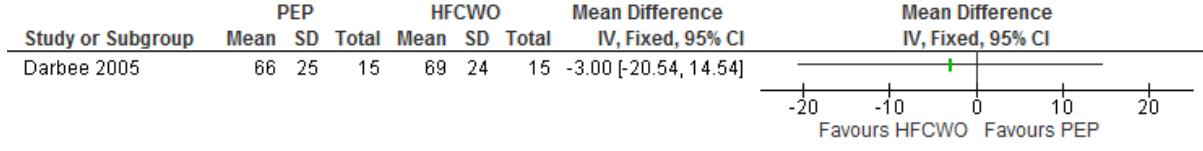
	PEP			HFCWO			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Darbee 2005	66	25	15	69	24	15	-3.00 [-20.54, 14.54]	

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; HFCWO: high frequency chest wall oscillation; IV: inverse variance; PEP: positive expiratory pressure mask; SD: standard deviation

Figure 58:   Change in FEV$_1$ % predicted at 1 year follow-up (range of scores: 0-100)
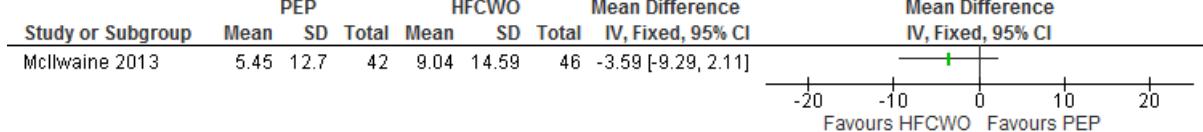
	PEP			HFCWO			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
McIlwaine 2013	5.45	12.7	42	9.04	14.59	46	-3.59 [-9.29, 2.11]	

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; HFCWO: high frequency

chest wall oscillation; IV: inverse variance; PEP: positive expiratory pressure mask; SD: standard deviation

**Figure 59:   FVC % predicted at 1 week follow-up (range of scores: 0-100)**
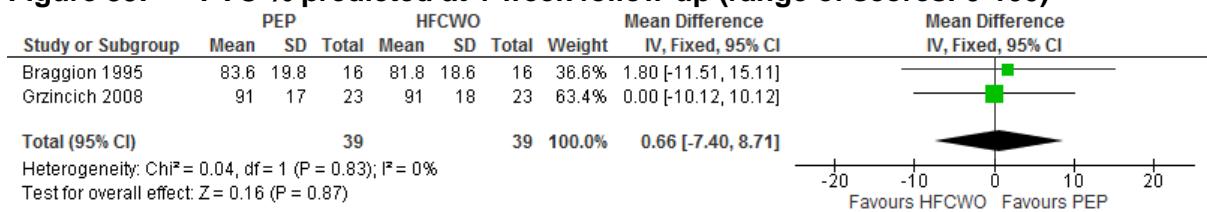
Study or Subgroup	PEP Mean	SD	Total	HFCWO Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Braggion 1995	83.6	19.8	16	81.8	18.6	16	36.6%	1.80 [-11.51, 15.11]
Grzincich 2008	91	17	23	91	18	23	63.4%	0.00 [-10.12, 10.12]
Total (95% CI)			**39**			**39**	**100.0%**	**0.66 [-7.40, 8.71]**

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.87)

*Abbreviations: CI: confidence interval; df: degrees of freedom; FVC: forced vital capacity; HFCWO: high frequency chest wall oscillation; IV: inverse variance; PEP: positive expiratory pressure mask; SD: standard deviation*

Figure 60:   FVC % predicted at 1 to 2 weeks follow-up (range of scores: 0-100)
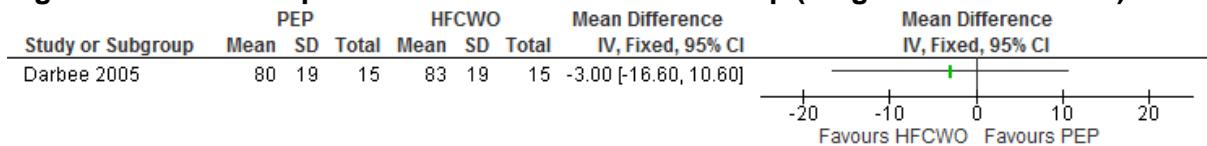
Study or Subgroup	PEP Mean	SD	Total	HFCWO Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Darbee 2005	80	19	15	83	19	15	-3.00 [-16.60, 10.60]

Abbreviations: CI: confidence interval; FVC: forced vital capacity; HFCWO: high frequency chest wall oscillation; IV: inverse variance; PEP: positive expiratory pressure mask; SD: standard deviation

Figure 61:   Change in FVC % predicted at 1 year follow-up (range of scores: 0-100)
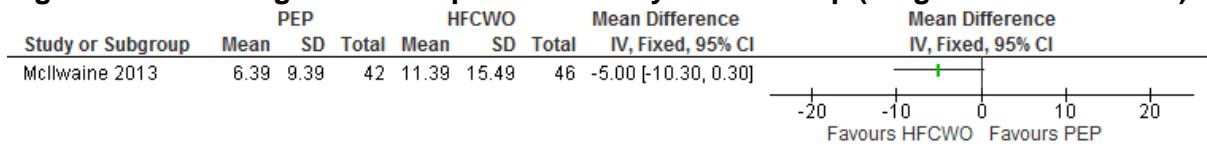
Study or Subgroup	PEP Mean	SD	Total	HFCWO Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
McIlwaine 2013	6.39	9.39	42	11.39	15.49	46	-5.00 [-10.30, 0.30]

Abbreviations: CI: confidence interval; FVC: forced vital capacity; HFCWO: high frequency chest wall oscillation; IV: inverse variance; PEP: positive expiratory pressure mask; SD: standard deviation

Comparison 8. Active cycle of breathing technique (ACBT) *versus* no airway clearance technique

No evidence was retrieved for this comparison.

Comparison 9. Active cycle breathing technique (ACBT) *versus* autogenic drainage (AD)

No evidence was retrieved for this comparison.

Comparison 10. Autogenic drainage (AD) *versus* no airway clearance technique

No evidence was retrieved for this comparison.

Comparison 11. Oscillating device *versus* no airway clearance technique

No evidence was retrieved for this comparison.

Comparison 12. Oscillating device *versus* high frequency chest wall oscillation (HFCWO)

Figure 62:   FEV$_1$ % predicted at 2 to 4 weeks follow-up (range of scores: 0-100)
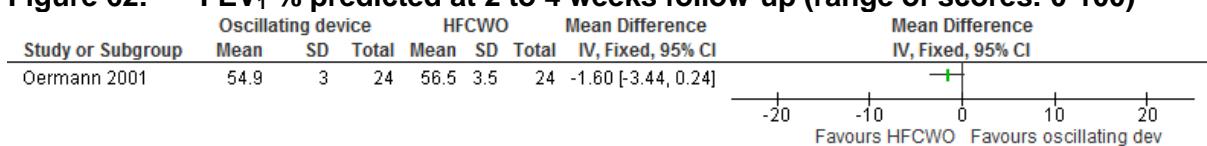
Study or Subgroup	Oscillating device Mean	SD	Total	HFCWO Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Oermann 2001	54.9	3	24	56.5	3.5	24	-1.60 [-3.44, 0.24]

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; HFCWO: high frequency chest wall oscillation; IV: inverse variance; SD: standard deviation

Figure 63: FVC % predicted at 2 to 4 weeks follow-up (range of scores: 0-100)
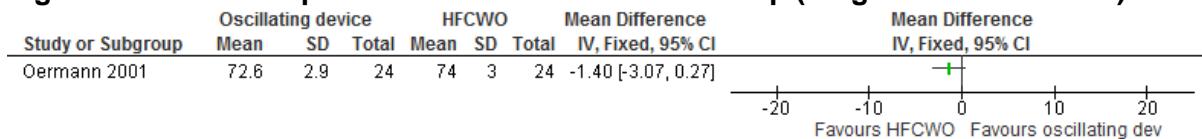
Study or Subgroup	Oscillating device Mean	SD	Total	HFCWO Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Oermann 2001	72.6	2.9	24	74	3	24	-1.40 [-3.07, 0.27]

Mean Difference IV, Fixed, 95% CI
-20 -10 0 10 20
Favours HFCWO Favours oscillating dev

Abbreviations: CI: confidence interval; FVC: forced vital capacity; HFCWO: high frequency chest wall oscillation; IV: inverse variance; SD: standard deviation

Comparison 13. High frequency chest wall oscillation (HFCWO) *versus* no airway clearance technique

No evidence was found for this comparison.

## Comparison 14. Non-invasive ventilation (NIV) *versus* no airway clearance technique

Figure 64: FEV$_1$ % predicted at 6 weeks follow-up (range of scores: 0-100)
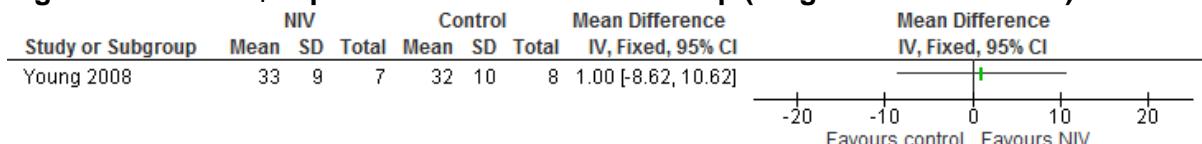
Study or Subgroup	NIV Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Young 2008	33	9	7	32	10	8	1.00 [-8.62, 10.62]

Mean Difference IV, Fixed, 95% CI
-20 -10 0 10 20
Favours control Favours NIV

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; NIV: non-invasive ventilation; SD: standard deviation;

Figure 65: FVC % predicted at 6 weeks follow-up (range of scores: 0-100)
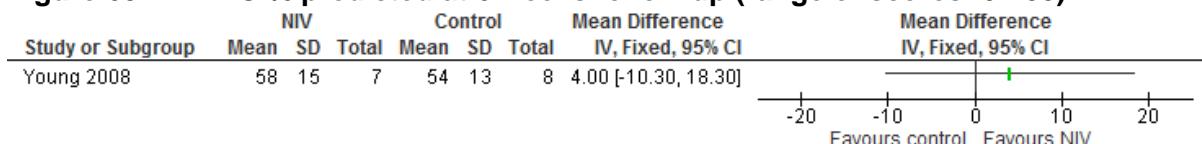
Study or Subgroup	NIV Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Young 2008	58	15	7	54	13	8	4.00 [-10.30, 18.30]

Mean Difference IV, Fixed, 95% CI
-20 -10 0 10 20
Favours control Favours NIV

Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; NIV: non-invasive ventilation; SD: standard deviation

Figure 66: Nocturnal oxygen saturation at 6 weeks follow-up
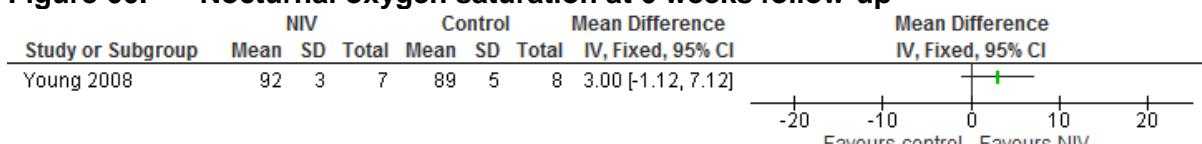
Study or Subgroup	NIV Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Young 2008	92	3	7	89	5	8	3.00 [-1.12, 7.12]

Mean Difference IV, Fixed, 95% CI
-20 -10 0 10 20
Favours control Favours NIV

Abbreviations: CI: confidence interval; IV: inverse variance; NIV: non-invasive ventilation; SD: standard deviation

Figure 67: Quality of life (CF-QOL questionnaire) at 6 weeks follow-up (range of scores: 0-100)
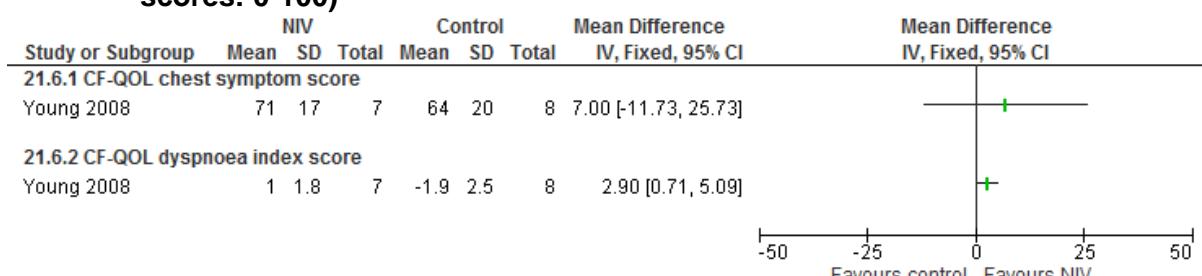
Study or Subgroup	NIV Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
21.6.1 CF-QOL chest symptom score							
Young 2008	71	17	7	64	20	8	7.00 [-11.73, 25.73]
21.6.2 CF-QOL dyspnoea index score							
Young 2008	1	1.8	7	-1.9	2.5	8	2.90 [0.71, 5.09]

Mean Difference IV, Fixed, 95% CI
-50 -25 0 25 50
Favours control Favours NIV

Abbreviations: CI: confidence interval; CF-QOL: cystic fibrosis quality of life questionnaire; IV: inverse variance; NIV: non-invasive ventilation; SD: standard deviation

I.8   Mucoactive agents

I.8.1   Mannitol

Comparison 1.1. Mannitol versus placebo

Figure 68:   Lung function: change in FEV$_1$ % predicted at 2 weeks and 2, 4 & 6 months follow-up (range of scores: 0-100)
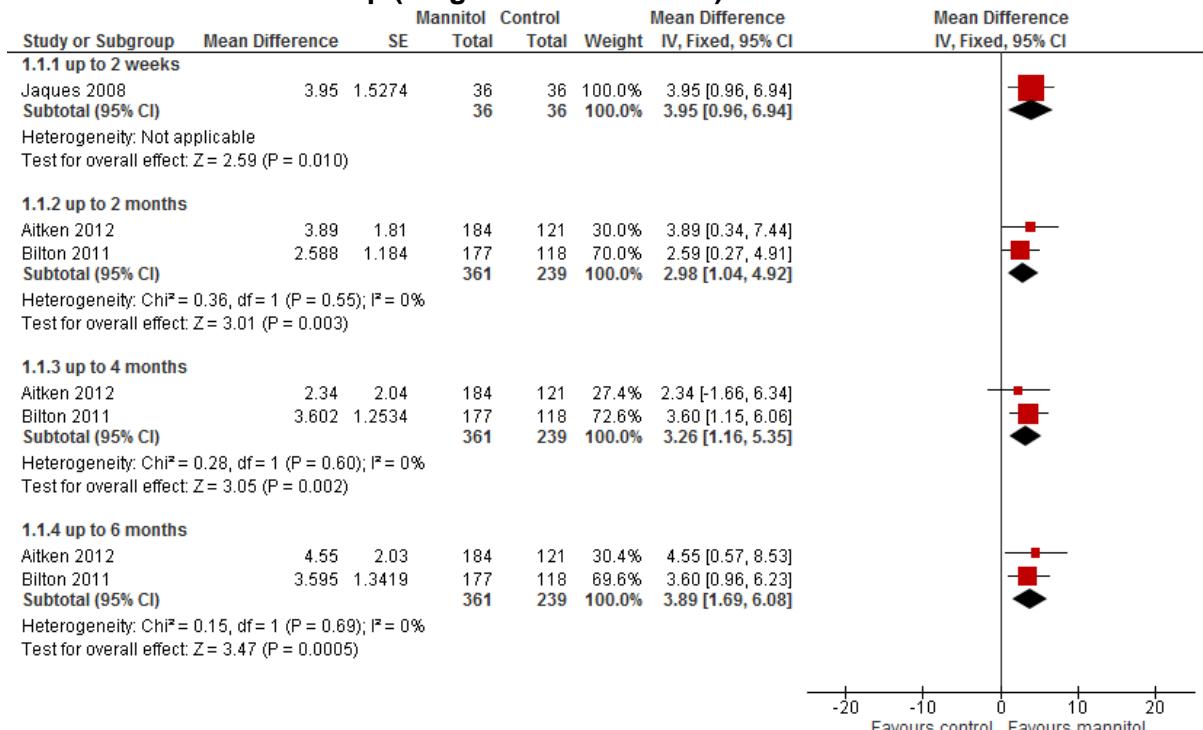
Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SE: standard error

Figure 69:   Time to first pulmonary exacerbation at 6 months follow-up
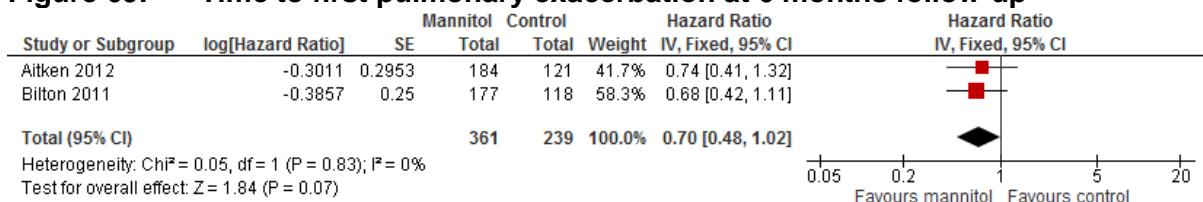
Abbreviations: CI: confidence interval; IV: inverse variance; SE: standard error

Figure 70:   Number of patients needing additional IV antibiotics at 6 months follow-up
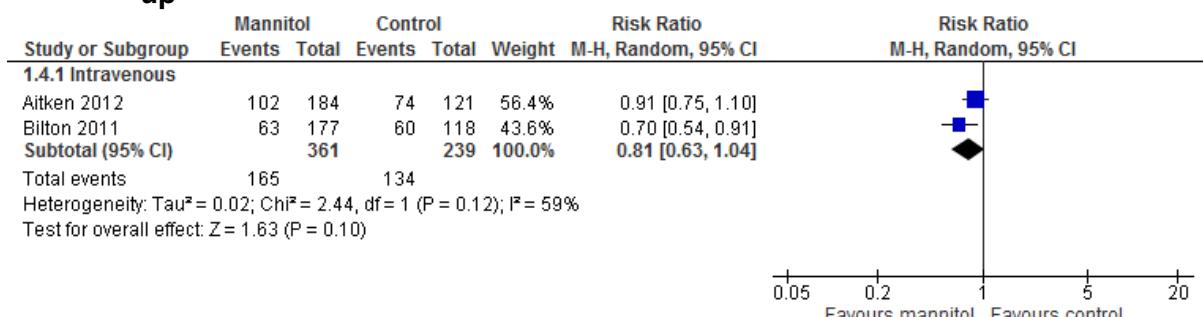
Abbreviations: CI: confidence interval; IV: intravenous; M-H: Mantel-Haenszel

Figure 71: Quality of life: change in CFQ-R respiratory at 4 & 6 months follow-up (range of scores: 0-100)
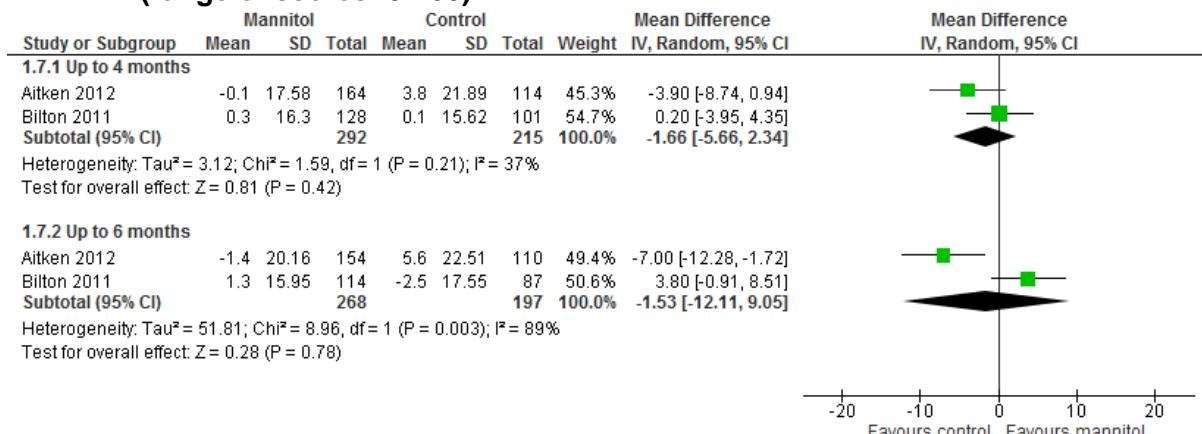
Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; df: degrees of freedom; IV: inverse variance; SD: standard deviation

Figure 72: Quality of life: change in CFQ-R vitality at 4 & 6 months follow-up (range of scores: 0-100)
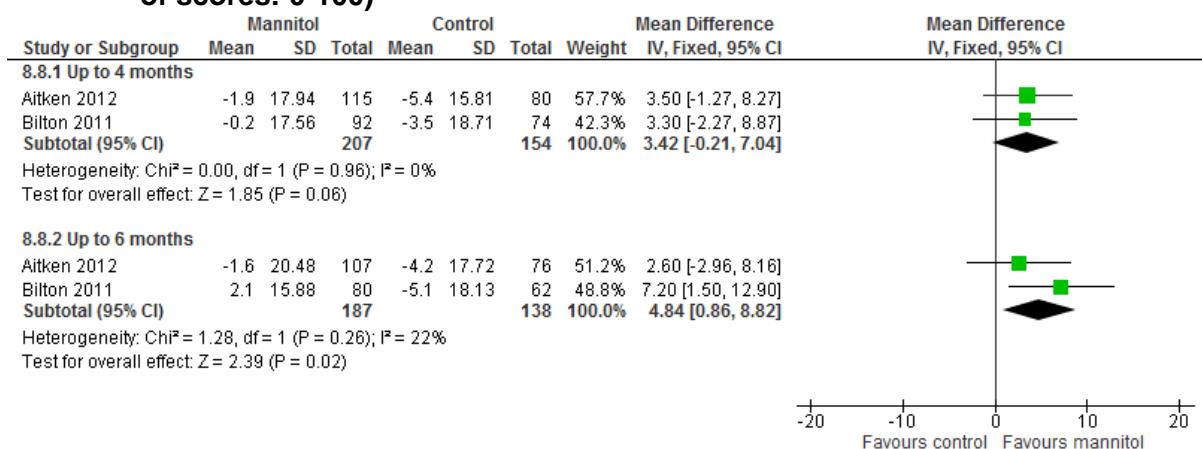
Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; df: degrees of freedom; IV: inverse variance; SD: standard deviation

Figure 73: Quality of life: change in CFQ-R physical at 4 & 6 months follow-up (range of scores: 0-100)
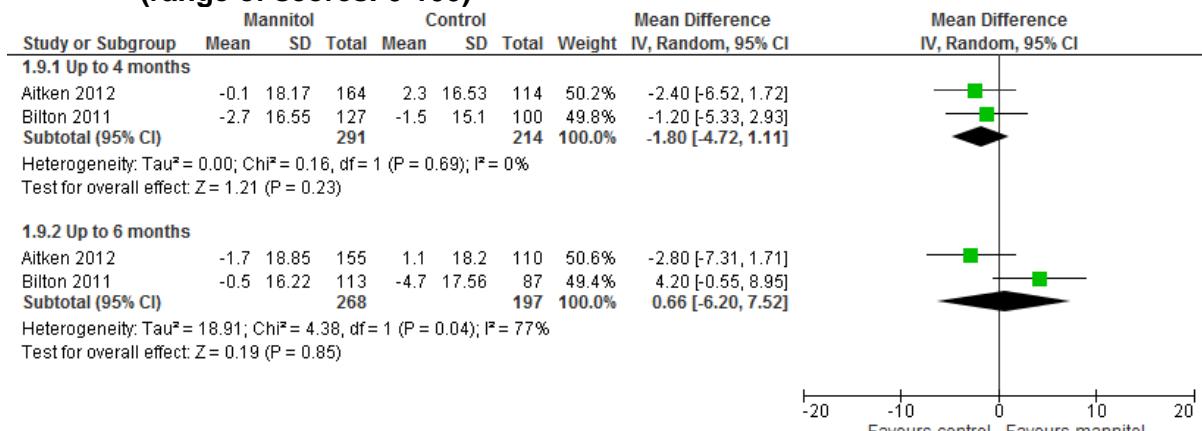
Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; df: degrees of freedom; IV: inverse variance; SD: standard deviation

Figure 74: **Quality of life: change in CFQ-R emotion at 4 & 6 months follow-up (range of scores: 0-100)**

	Mannitol			Control				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 Up to 4 months									
Aitken 2012	0.3	14.35	164	2.9	12.64	114	58.8%	-2.60 [-5.79, 0.59]	
Bilton 2011	-1.5	15.4	128	-0.1	13.94	100	41.2%	-1.40 [-5.22, 2.42]	
Subtotal (95% CI)			292			214	100.0%	-2.11 [-4.56, 0.34]	
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%									
Test for overall effect: Z = 1.68 (P = 0.09)									
1.10.2 Up to 6 months									
Aitken 2012	0.4	15.34	155	2.1	12.84	109	52.5%	-1.70 [-5.11, 1.71]	
Bilton 2011	-0.3	11.7	114	0.5	13.66	87	47.5%	-0.80 [-4.38, 2.78]	
Subtotal (95% CI)			269			196	100.0%	-1.27 [-3.74, 1.20]	
Heterogeneity: Chi² = 0.13, df = 1 (P = 0.72); I² = 0%									
Test for overall effect: Z = 1.01 (P = 0.31)									

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; df: degrees of freedom; IV: inverse variance; SD: standard deviation

Figure 75: **Quality of life: change in CFQ-R eating at 4 & 6 months follow-up (range of scores: 0-100)**

	Mannitol			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.11.1 Up to 4 months									
Aitken 2012	-1.6	17.29	164	-3.3	16.39	114	47.8%	1.70 [-2.31, 5.71]	
Bilton 2011	0.6	15.1	128	0.6	14.23	99	52.2%	0.00 [-3.83, 3.83]	
Subtotal (95% CI)			292			213	100.0%	0.81 [-1.96, 3.58]	
Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%									
Test for overall effect: Z = 0.57 (P = 0.57)									
1.11.2 Up to 6 months									
Aitken 2012	-0.4	18.37	155	-1.4	17.3	110	46.8%	1.00 [-3.34, 5.34]	
Bilton 2011	2.3	15.47	114	1.9	13.89	87	53.2%	0.40 [-3.67, 4.47]	
Subtotal (95% CI)			269			197	100.0%	0.68 [-2.29, 3.65]	
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%									
Test for overall effect: Z = 0.45 (P = 0.65)									

*Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; df: degrees of freedom; IV: inverse variance; SD: standard deviation*

Figure 76: **Quality of life: change in CFQ-R health at 4 & 6 months follow-up (range of scores: 0-100)**

|	Mannitol			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.12.1 Up to 4 months									
Aitken 2012	-0.1	16.22	115	-1	17.52	80	59.7%	0.90 [-3.95, 5.75]	
Bilton 2011	-0.1	18.45	93	2.3	19.73	72	40.3%	-2.40 [-8.30, 3.50]	
Subtotal (95% CI)			208			152	100.0%	-0.43 [-4.18, 3.32]	
Heterogeneity: Chi² = 0.72, df = 1 (P = 0.40); I² = 0%									
Test for overall effect: Z = 0.23 (P = 0.82)									
1.12.2 Up to 6 months									
Aitken 2012	-1.5	17.61	107	-0.9	18	77	56.6%	-0.60 [-5.82, 4.62]	
Bilton 2011	1.4	17.47	79	1.1	18.3	62	43.4%	0.30 [-5.67, 6.27]	
Subtotal (95% CI)			186			139	100.0%	-0.21 [-4.14, 3.72]	
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%									
Test for overall effect: Z = 0.10 (P = 0.92)									

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; df: degrees of freedom; IV: inverse variance; SD: standard deviation

Figure 77:   Quality of life: change in CFQ-R social at 4 & 6 months follow-up (range of scores: 0-100)
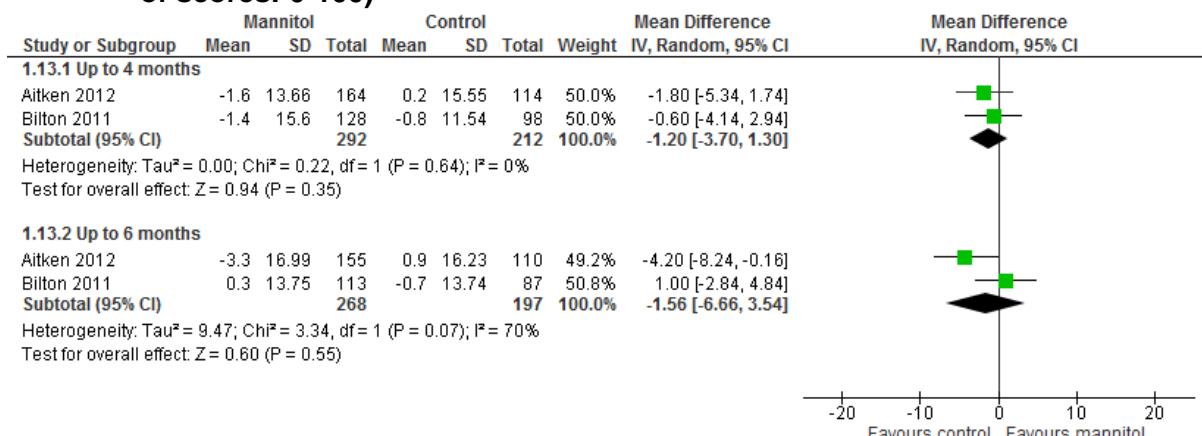

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; df: degrees of freedom; IV: inverse variance; SD: standard deviation

Figure 78:   Quality of life: change in CFQ-R body at 4 & 6 months follow-up (range of scores: 0-100)
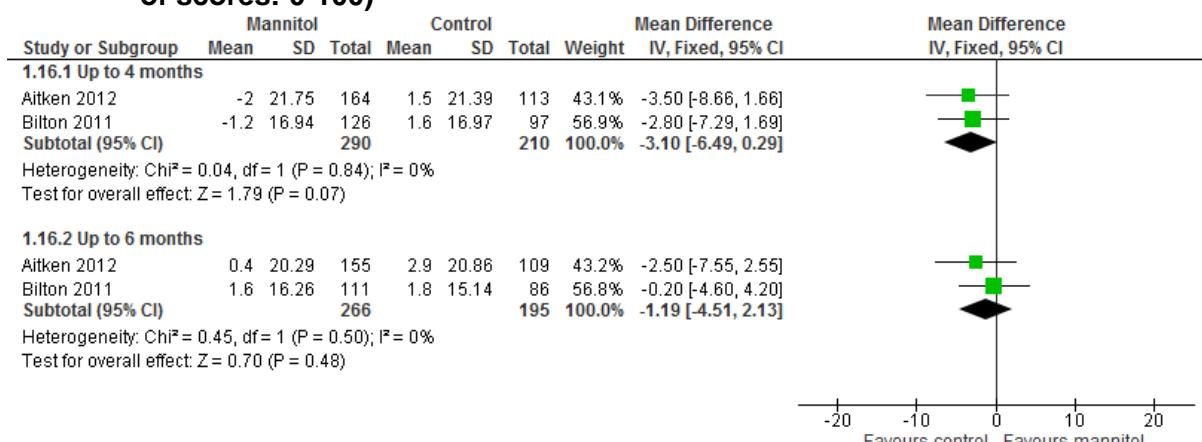
Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; df: degrees of freedom; IV: inverse variance; SD: standard deviation

Figure 79:   Quality of life: change in CFQ-R role at 4 & 6 months follow-up (range of scores: 0-100)
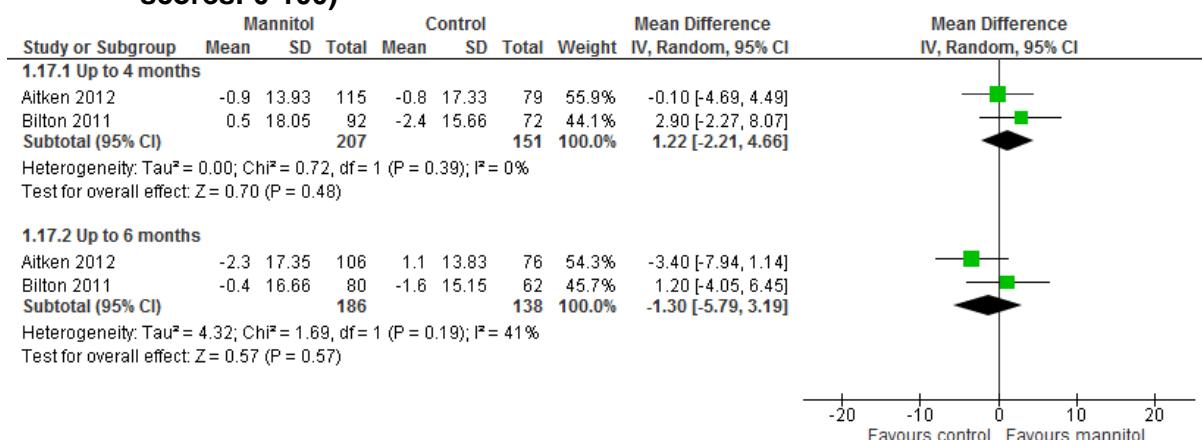
Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; df: degrees of freedom; IV: inverse variance; SD: standard deviation

Figure 80: Quality of life: change in CFQ-R digestion at 4 & 6 months follow-up (range of scores: 0-100)
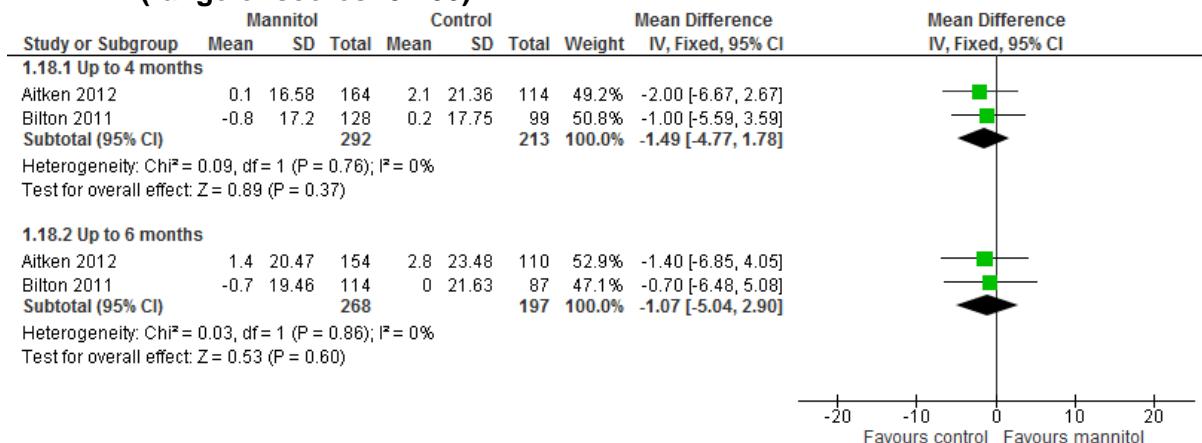

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; df: degrees of freedom; IV: inverse variance; SD: standard deviation

Figure 81: Quality of life: change in CFQ-R weight at 4 & 6 months follow-up (range of scores: 0-100)
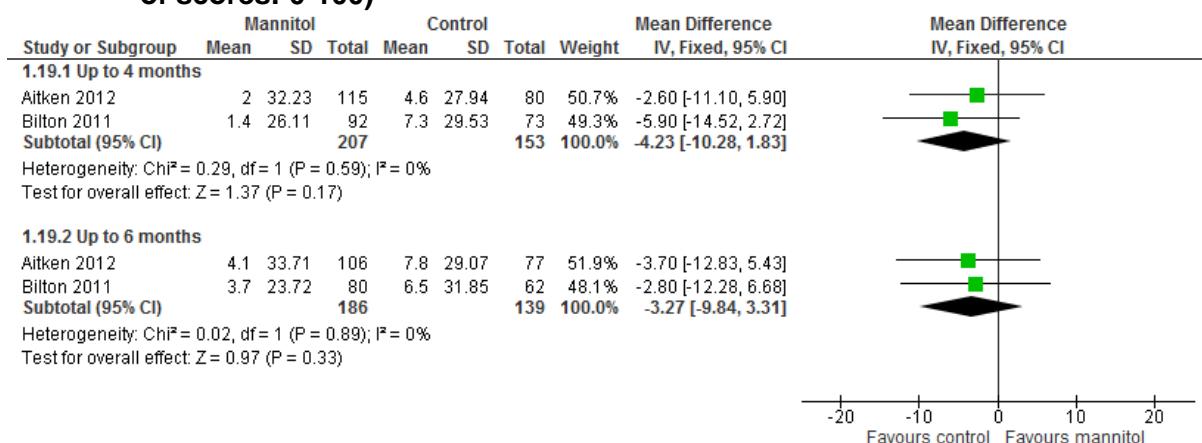

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; df: degrees of freedom; IV: inverse variance; SD: standard deviation

Figure 82: Adverse events at 2 weeks follow-up
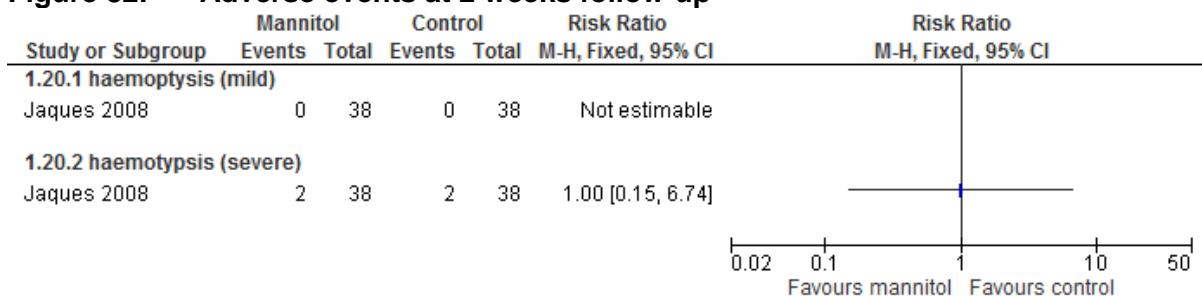
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 83:   Adverse events at up to 6 months follow-up

Study or Subgroup	Mannitol Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 99% CI
1.21.1 Bronchospasm (mild)						
Bilton 2011	0	177	0	118		Not estimable
Subtotal (99% CI)		**177**		**118**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.21.2 Haemoptysis (mild)						
Bilton 2011	3	177	2	118	79.9%	1.00 [0.10, 10.29]
Aitken 2012	3	184	0	121	20.1%	4.62 [0.10, 224.14]
Subtotal (99% CI)		**361**		**239**	**100.0%**	**1.73 [0.26, 11.62]**
Total events	6		2			
Heterogeneity: Chi² = 0.79, df = 1 (P = 0.37); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						
1.21.3 Bronchospasm (moderate)						
Bilton 2011	1	177	0	118	100.0%	2.01 [0.03, 133.11]
Subtotal (99% CI)		**177**		**118**	**100.0%**	**2.01 [0.03, 133.11]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
1.21.4 Haemoptysis (moderate)						
Aitken 2012	1	184	0	121	33.4%	1.98 [0.03, 131.35]
Bilton 2011	9	177	1	118	66.6%	6.00 [0.40, 89.09]
Subtotal (99% CI)		**361**		**239**	**100.0%**	**4.66 [0.50, 43.49]**
Total events	10		1			
Heterogeneity: Chi² = 0.33, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 1.77 (P = 0.08)						
1.21.5 Bronchospasm (severe)						
Bilton 2011	1	177	0	118	100.0%	2.01 [0.03, 133.11]
Subtotal (99% CI)		**177**		**118**	**100.0%**	**2.01 [0.03, 133.11]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
1.21.8 Haemoptysis (severe)						
Bilton 2011	1	177	1	118	66.6%	0.67 [0.02, 25.14]
Aitken 2012	2	184	0	121	33.4%	3.30 [0.06, 176.31]
Subtotal (99% CI)		**361**		**239**	**100.0%**	**1.55 [0.13, 18.99]**
Total events	3		1			
Heterogeneity: Chi² = 0.60, df = 1 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.45 (P = 0.65)						

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Comparison 1.2.1. Mannitol versus Dornase alfa

Figure 84: Lung function – FEV$_1$ % change from baseline up to 3 months (range of scores: 0-100)
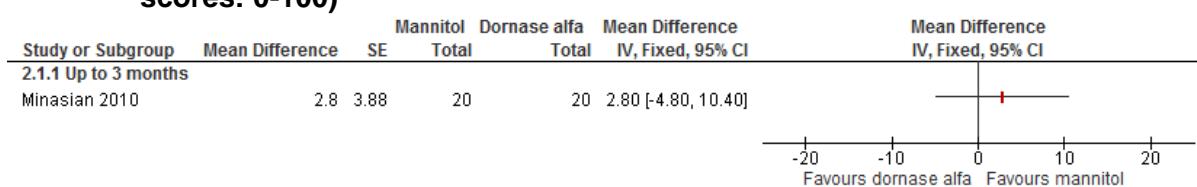
Study or Subgroup	Mannitol Mean Difference	SE	Total	Dornase alfa Total	Mean Difference IV, Fixed, 95% CI
2.1.1 Up to 3 months					
Minasian 2010	2.8	3.88	20	20	2.80 [-4.80, 10.40]

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SE: standard error

Comparison 1.2.2. Mannitol + Dornase alfa versus Dornase alfa alone

Figure 85: Lung function – FEV_1 % change from baseline up to 3 months (range of scores: 0-100)
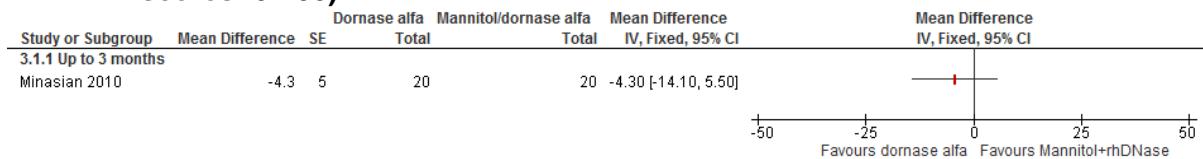
Study or Subgroup	Mean Difference	SE	Dornase alfa Total	Mannitol/dornase alfa Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
3.1.1 Up to 3 months						
Minasian 2010	-4.3	5	20	20	-4.30 [-14.10, 5.50]	

-50   -25   0   25   50
Favours dornase alfa   Favours Mannitol+rhDNase

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IV: inverse variance; SE: standard error

Comparison 1.3: Mannitol versus nebulised sodium chloride

No evidence was found for this comparison.

Comparison 1.4. Mannitol versus acetylcysteine

No evidence was found for this comparison.

### I.8.2   Dornase alfa

Comparison 2.1. Dornase alfa versus placebo

Figure 86: Lung function: relative mean % change in FEV_1 at 10 days; and at 1, 3 & 6 months follow-up (range of scores: 0-100)

Study or Subgroup	Dornase alfa Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
4.1.1 At 10 days									
Shah 1996	13.32	24.91	20	0.15	14.11	21	100.0%	13.17 [0.70, 25.64]	
Subtotal (95% CI)			20			21	100.0%	13.17 [0.70, 25.64]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.07 (P = 0.04)									
4.1.2 at 1 month									
Laube 1996	9.4	11.7	10	-1.9	5.38	10	23.4%	11.30 [3.32, 19.28]	
Ramsey 1993	13.8	13.27	44	-1.6	9	48	26.7%	15.40 [10.72, 20.08]	
Ranasinha 1993	12.8	18.6	36	-1.5	11.24	35	24.3%	14.30 [7.17, 21.43]	
Shah1995	1.4	11.7	31	4.2	12.8	34	25.5%	-2.80 [-8.76, 3.16]	
Subtotal (95% CI)			121			127	100.0%	9.52 [0.59, 18.46]	
Heterogeneity: Tau² = 72.12; Chi² = 24.36, df = 3 (P < 0.0001); I² = 88%									
Test for overall effect: Z = 2.09 (P = 0.04)									
4.1.3 at 3 months									
Amin 2011	5.63	6.5702	17	0.76	10.7073	17	24.9%	4.87 [-1.10, 10.84]	
McCoy 1996	9.4	16.3	158	2.1	13.3	127	75.1%	7.30 [3.86, 10.74]	
Subtotal (95% CI)			175			144	100.0%	6.70 [3.72, 9.67]	
Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%									
Test for overall effect: Z = 4.41 (P < 0.0001)									
4.1.4 at 6 months									
Fuchs 1994	5.8	12.56	322	0	1.82	325	100.0%	5.80 [4.41, 7.19]	
Subtotal (95% CI)			322			325	100.0%	5.80 [4.41, 7.19]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 8.20 (P < 0.00001)									

-20   -10   0   10   20
Favours placebo   Favours dornase alfa

Test for subgroup differences: Chi² = 2.13, df = 3 (P = 0.55), I² = 0%

Abbreviations: CI: confidence interval; df: degrees of freedom; FEV_1: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation.
*Note: See sensitivity analysis*

Figure 87: **Lung function: relative mean % change in FEV$_1$ at 1 month follow-up (range of scores: 0-100) (subgroup analysis based on disease severity)**

Study or Subgroup	Dornase alfa			Placebo			Weight	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
4.2.1 moderate								
Laube 1996	9.4	11.7	10	-1.8	5.38	10	19.3%	11.20 [3.22, 19.18]
Ramsey 1993	13.8	13.27	44	-1.6	9	48	56.4%	15.40 [10.72, 20.08]
Ranasinha 1993	12.8	18.6	36	-1.5	11.24	35	24.3%	14.30 [7.17, 21.43]
Subtotal (95% CI)			90			93	100.0%	14.32 [10.81, 17.83]

Heterogeneity: Chi² = 0.79, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 8.00 (P < 0.00001)

Study or Subgroup	Dornase alfa			Placebo			Weight	Mean Difference IV, Fixed, 95% CI
4.2.2 severe								
Shah1995	1.4	11.7	31	4.2	12.8	34	100.0%	-2.80 [-8.76, 3.16]
Subtotal (95% CI)			31			34	100.0%	-2.80 [-8.76, 3.16]

Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)

Test for subgroup differences: Chi² = 23.56, df = 1 (P < 0.00001), I² = 95.8%

Abbreviations: CI: confidence interval; df: degrees of freedom; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 88: **Lung function: mean % change in FEV$_1$ at 1 month follow-up (range of scores: 0-100) (subgroup analysis: participants with acute exacerbation)**
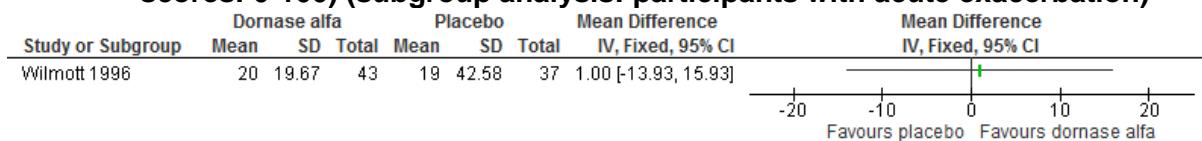
| Study or Subgroup	Dornase alfa			Placebo			Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total	
Wilmott 1996	20	19.67	43	19	42.58	37	1.00 [-13.93, 15.93]

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 89: **Lung function: absolute mean % change in FEV$_1$ at 2 years (range of scores: 0-100)**
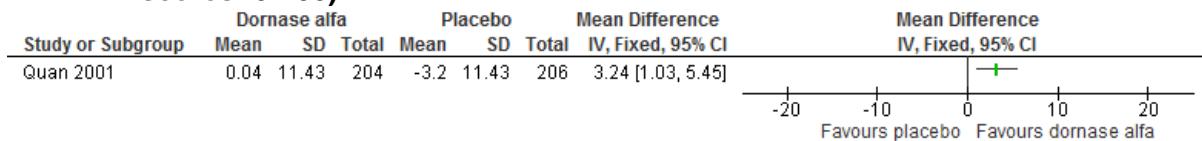
Study or Subgroup	Dornase alfa			Placebo			Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total	
Quan 2001	0.04	11.43	204	-3.2	11.43	206	3.24 [1.03, 5.45]

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

**Figure 90:** **Number of people experiencing exacerbations at 6 months & 2 years follow-up**

Study or Subgroup	Dornase alfa Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
4.5.1 at 6 months					
Fuchs 1994	71	322	89	325	0.81 [0.61, 1.06]
4.5.2 at 2 years					
Quan 2001	40	236	56	234	0.71 [0.49, 1.02]
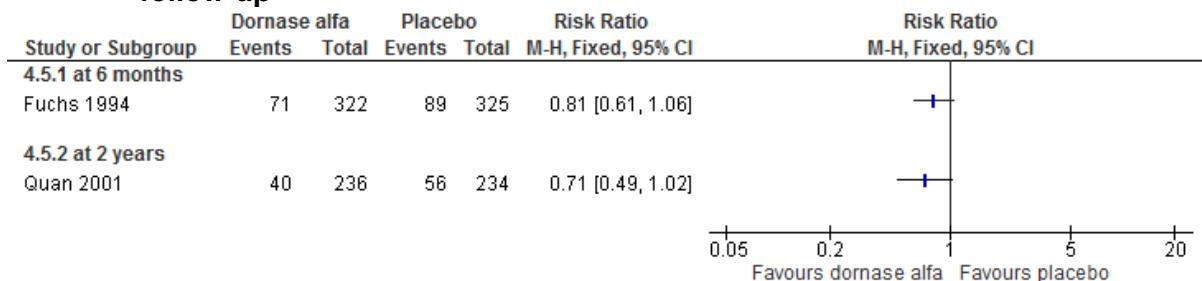
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 91: **Number of days of IV antibiotics use at 1 month follow-up**

| Study or Subgroup	Dornase alfa Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.6.1 at 3 months								
McCoy 1996	25.35	19.58	158	28.31	19.94	162	-2.96 [-7.29, 1.37]	

Favours dornase alfa Favours placebo
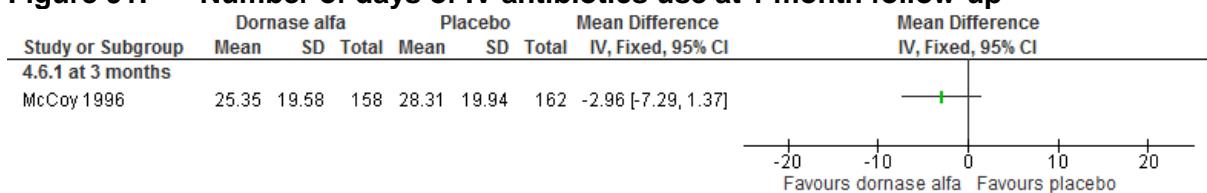
Abbreviations: CI: confidence interval; IV antibiotics: intravenous antibiotics; IV: inverse variance; SD: standard deviation

Figure 92: **Adverse events: haemoptysis at 1 & 6 months follow-up**

| Study or Subgroup	Dornase alfa Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
4.7.1 at 1 month							
Ranasinha 1993	2	36	0	35	30.8%	4.86 [0.24, 97.86]	
Shah1995	2	35	3	35	69.2%	0.67 [0.12, 3.75]	
Subtotal (95% CI)		71		70	100.0%	1.23 [0.20, 7.63]	
Total events	4		3				
Heterogeneity: Tau² = 0.48; Chi² = 1.31, df = 1 (P = 0.25); I² = 23%							
Test for overall effect: Z = 0.22 (P = 0.83)							
4.7.2 at 6 months							
Fuchs 1994	17	322	21	325	100.0%	0.82 [0.44, 1.52]	
Subtotal (95% CI)		322		325	100.0%	0.82 [0.44, 1.52]	
Total events	17		21				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.64 (P = 0.52)							

Favours dornase alfa Favours placebo

Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 93: **Adverse events: voice alteration at 1, 3, 6 months and 2 years follow-up**

Study or Subgroup	Dornase alpha Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
4.8.1 at 1 month							
Ramsey 1993	12	44	0	48	48.3%	27.22 [1.66, 446.58]	
Ranasinha 1993	0	36	0	35		Not estimable	
Shah1995	1	35	3	35	51.7%	0.33 [0.04, 3.05]	
Subtotal (95% CI)		115		118	100.0%	2.79 [0.03, 278.07]	
Total events	13		3				
Heterogeneity: Tau² = 9.38; Chi² = 6.66, df = 1 (P = 0.010); I² = 85%							
Test for overall effect: Z = 0.44 (P = 0.66)							
4.8.2 at 3 months							
McCoy 1996	28	158	10	162	100.0%	2.87 [1.44, 5.71]	
Subtotal (95% CI)		158		162	100.0%	2.87 [1.44, 5.71]	
Total events	28		10				
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.00 (P = 0.003)							
4.8.3 at 6 months							
Fuchs 1994	12	322	7	325	100.0%	1.73 [0.69, 4.34]	
Subtotal (95% CI)		322		325	100.0%	1.73 [0.69, 4.34]	
Total events	12		7				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.17 (P = 0.24)							
4.8.4 at 2 years							
Quan 2001	26	236	0	27	100.0%	6.26 [0.39, 99.96]	
Subtotal (95% CI)		236		27	100.0%	6.26 [0.39, 99.96]	
Total events	26		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.30 (P = 0.19)							

Favours dornase alfa Favours placebo

Test for subgroup differences: Chi² = 1.19, df = 3 (P = 0.75), I² = 0%
*Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel*

Figure 94:   Quality of life (measured with CFQ-R) at 3 months (range of scores: 0-100)
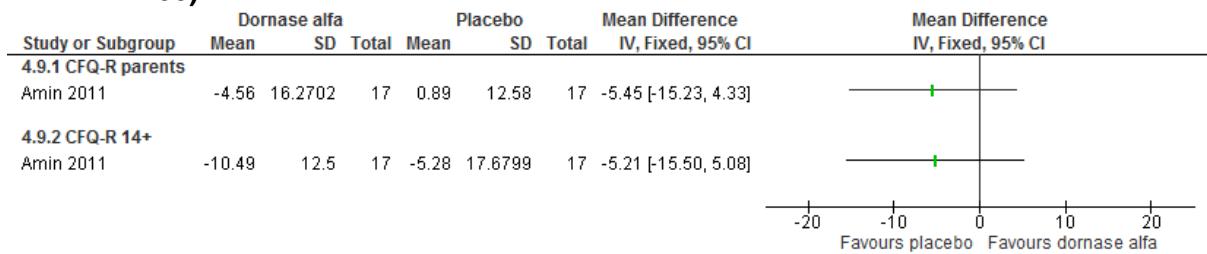
Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Comparison 2.2. Dornase alfa versus nebulized sodium chloride

Figure 95:   Lung function: mean % change in FEV$_1$ at 3 weeks and 3 months follow-up
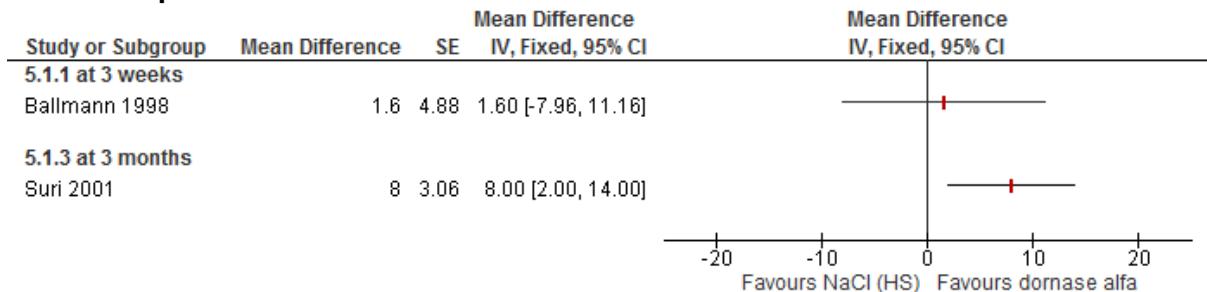
Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; NaCl (HS): sodium chloride (hypertonic saline); SE: standard error

Figure 96:   Number of days of inpatient treatment at 3 months follow-up
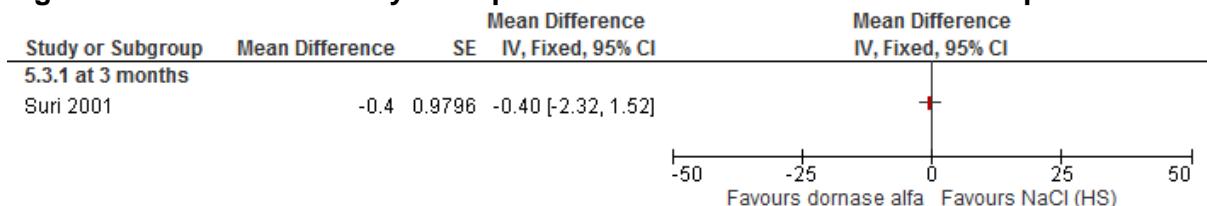
Abbreviations: CI: confidence interval; IV: inverse variance; NaCl (HS): sodium chloride (hypertonic saline); SE: standard error

Comparison 2.3. Dornase alfa versus acetylcysteine

No evidence was found for this comparison.

I.8.3   Nebulised sodium chloride

Comparison 3.1. Nebulised sodium chloride (> 3% concentration) versus placebo (0.9% to 0.12%) or low-concentration (≤ 3%)

Figure 97:   Failed to regain pre-exacerbation FEV$_1$% predicted at hospital discharge

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel. Note: Length of hospital stay was 12 days for the intervention group, and 13 days for the control group. Pre-exacerbation FEV$_1$% predicted was measured

≈ 6 months before.

Figure 98: **Lung function: % change in FEV$_1$ at 2, 4, 12, 24, 36 & 48 weeks follow-up (range of scores: 0-100)**
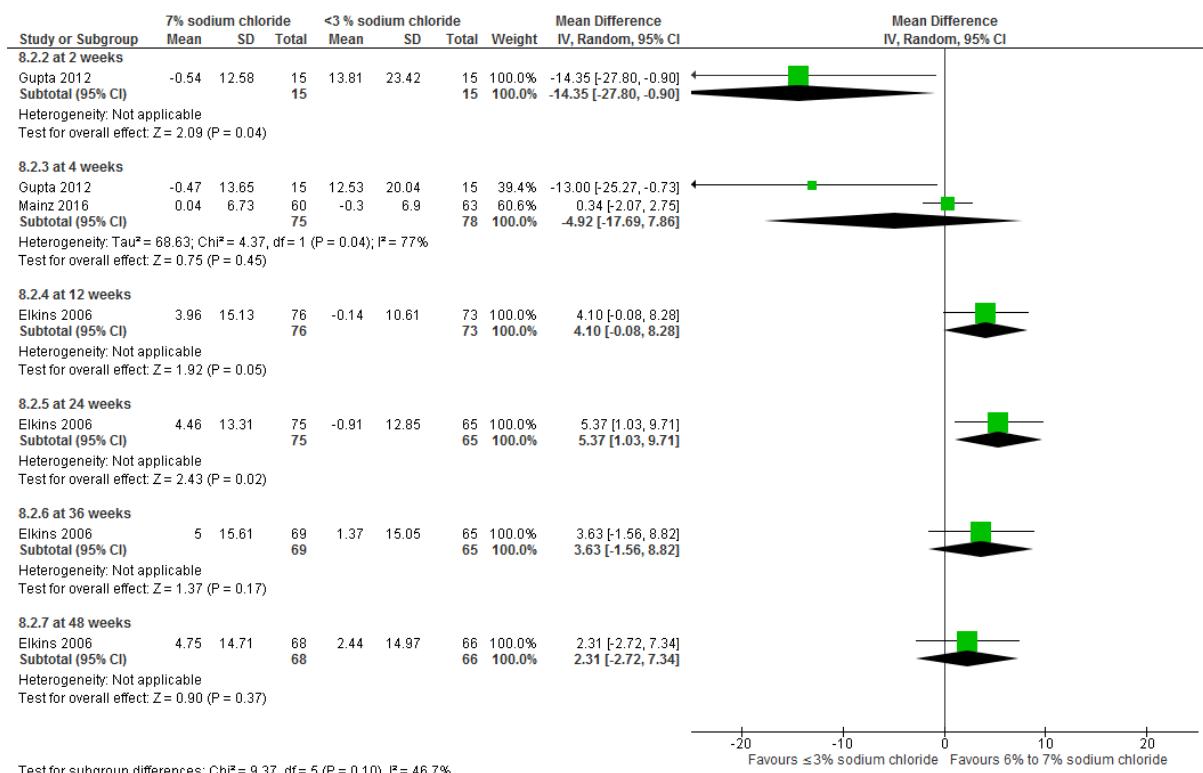

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

**Figure 99:** **Time to next pulmonary exacerbation at 1 year follow-up**
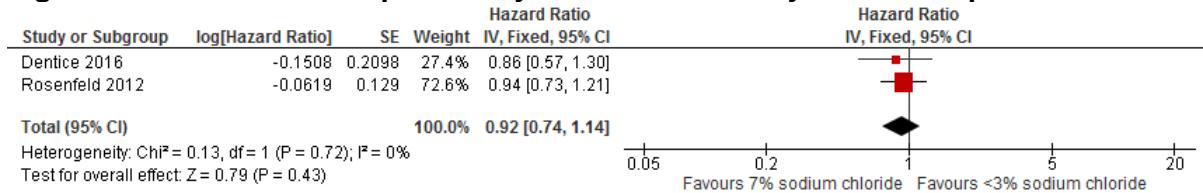
Abbreviations: CI: confidence interval; IV: inverse variance; SE: standard error

Figure 100: **Number of days of treatment for a pulmonary exacerbation at 48 weeks follow-up**
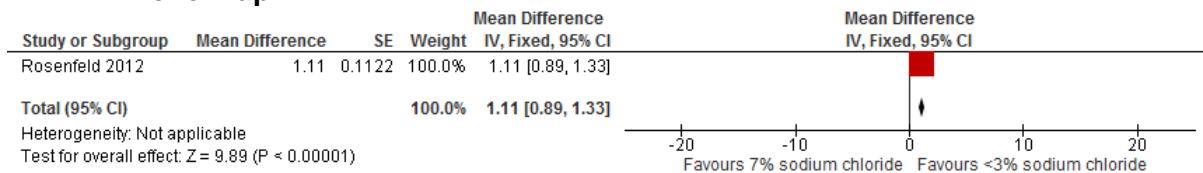

Abbreviations: CI: confidence interval; IV: inverse variance; SE: standard error

Figure 101:   Change in quality of life (CF-QOL) following treatment (range of scores: 0-100)

Study or Subgroup	7% sodium chloride			<3% sodium chloride			Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
8.6.1 CFQ - physical domain, change from hospital admision to day 7								
Dentice 2016	11	16	67	9	14	65	2.00 [-3.12, 7.12]	
8.6.2 CFQ - burden domain, change from hospital admision to day 7								
Dentice 2016	0	14	67	0	14	65	0.00 [-4.78, 4.78]	
8.6.3 CFQ - health domain, change from hospital admision to day 7								
Dentice 2016	12	19	67	14	17	65	-2.00 [-8.15, 4.15]	
8.6.4 CFQ - respiratory domain, change from hospital admision to day 7								
Dentice 2016	13	19	67	12	16	65	1.00 [-4.99, 6.99]	
8.6.5 CFQ - physical domain, change from hospital admision to discharge								
Dentice 2016	16	19	67	14	17	65	2.00 [-4.15, 8.15]	
8.6.6 CFQ - burden domain, change from hospital admision to discharge								
Dentice 2016	1	15	67	-1	20	65	2.00 [-4.04, 8.04]	
8.6.7 CFQ - health domain, change from hospital admision to discharge								
Dentice 2016	20	21	67	18	20	65	2.00 [-4.99, 8.99]	
8.6.8 CFQ - respiratory domain, change from hospital admision to discharge								
Dentice 2016	19	21	67	21	18	65	-2.00 [-8.67, 4.67]	

Favours <3% sodium chloride   Favours 7% sodium chloride

Abbreviations: CI: confidence interval; CF-QOL:: cystic fibrosis quality of life questionnaire; IV: inverse variance; SD: standard deviation

Figure 102:   Change in quality of life (CFQ-R), at 4 weeks follow-up (range of scores: 0-100)
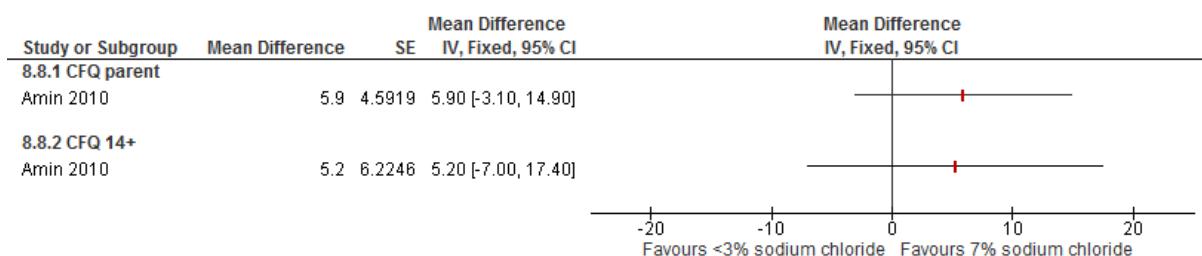
Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
8.8.1 CFQ parent				
Amin 2010	5.9	4.5919	5.90 [-3.10, 14.90]	
8.8.2 CFQ 14+				
Amin 2010	5.2	6.2246	5.20 [-7.00, 17.40]	

Favours <3% sodium chloride   Favours 7% sodium chloride

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SE: standard error

**Figure 103:   Change in quality of life (CFQ-R) at 48 weeks follow-up (range of scores: 0-100)**
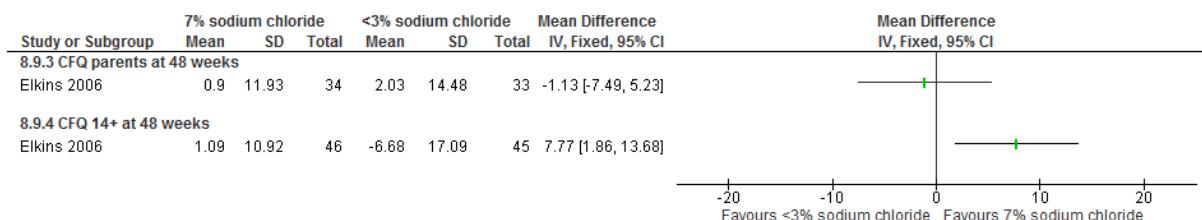
Study or Subgroup	7% sodium chloride			<3% sodium chloride			Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
8.9.3 CFQ parents at 48 weeks								
Elkins 2006	0.9	11.93	34	2.03	14.48	33	-1.13 [-7.49, 5.23]	
8.9.4 CFQ 14+ at 48 weeks								
Elkins 2006	1.09	10.92	46	-6.68	17.09	45	7.77 [1.86, 13.68]	

Favours <3% sodium chloride   Favours 7% sodium chloride

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Figure 104:   Change in quality of life: CFQ-R respiratory domain, at 48 weeks follow-up (range of scores: 0-100)
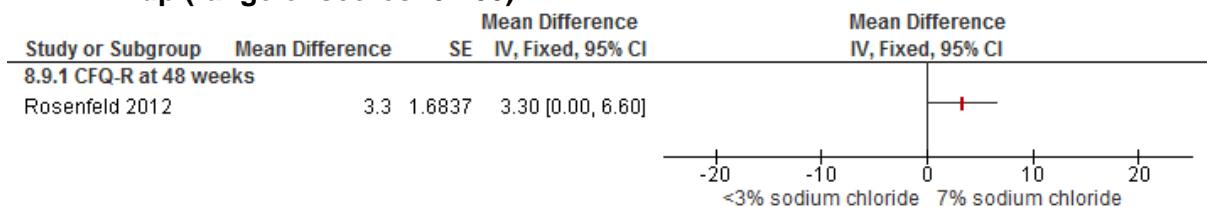
| | | | Mean Difference | Mean Difference |
Study or Subgroup	Mean Difference	SE	IV, Fixed, 95% CI	IV, Fixed, 95% CI
8.9.1 CFQ-R at 48 weeks				
Rosenfeld 2012	3.3	1.6837	3.30 [0.00, 6.60]	

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SE: standard error

Comparison 3.2. Nebulised sodium chloride versus acetylcysteine

No evidence was found for this comparison.

I.8.4   Acetylcysteine

Comparison 4. Acetylcysteine versus placebo

Figure 105:   Lung function: change in FEV$_1$ % predicted at 4 weeks (range of scores: 0-100)

| | Acetylcysteine | | | Placebo | | | Mean Difference | Mean Difference |
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
10.1.1 at 4 weeks								
Skov 2015	2.11	4.9626	10	-1.4	4.2931	9	3.51 [-0.65, 7.67]	
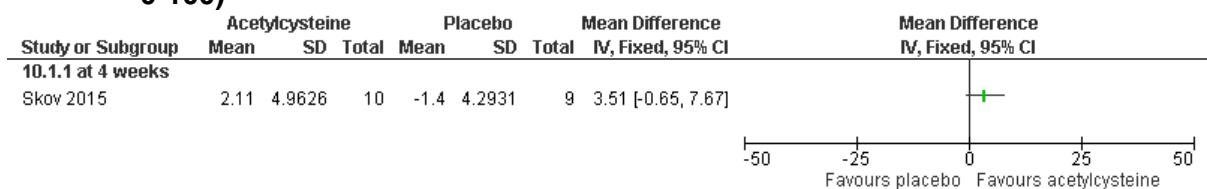
Abbreviations: CI: confidence interval; IV: inverse variance; SE: standard error

Figure 106:   Lung function: change in FEV$_1$ % predicted at 12 and 24 weeks (range of scores: 0-100)

| | | | Mean Difference | Mean Difference |
Study or Subgroup	Mean Difference	SE	IV, Fixed, 95% CI	IV, Fixed, 95% CI
10.1.1 at 12 weeks				
Ratjen 1985	5	8.0813	5.00 [-10.84, 20.84]	
10.1.2 at 24 weeks				
Conrad 2015	4.4	1.8215	4.40 [0.83, 7.97]	
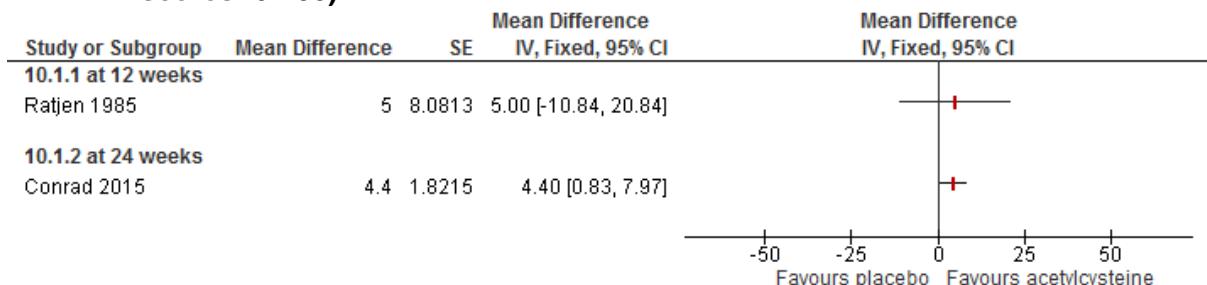
Abbreviations: CI: confidence interval; IV: inverse variance; SE: standard error

Figure 107:   Inflammatory markers: IL-8 at 24 weeks

| | | | Mean Difference | Mean Difference |
Study or Subgroup	Mean Difference	SE	IV, Fixed, 95% CI	IV, Fixed, 95% CI
10.2.1 at 24 weeks				
Conrad 2015	0.19	1.12	0.19 [-2.01, 2.39]	
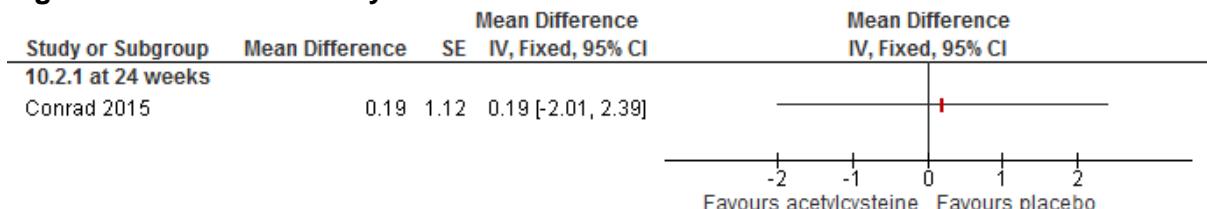
Abbreviations: CI: confidence interval; IV: inverse variance; SE: standard error

Figure 108:   Incidence of pulmonary exacerbations at 24 weeks
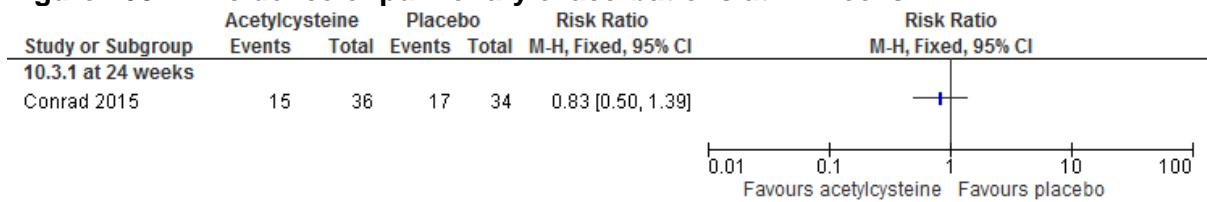
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

**Figure 109:   Quality of life: QFQ-R respiratory at 24 weeks (range of scores: 0-100)**
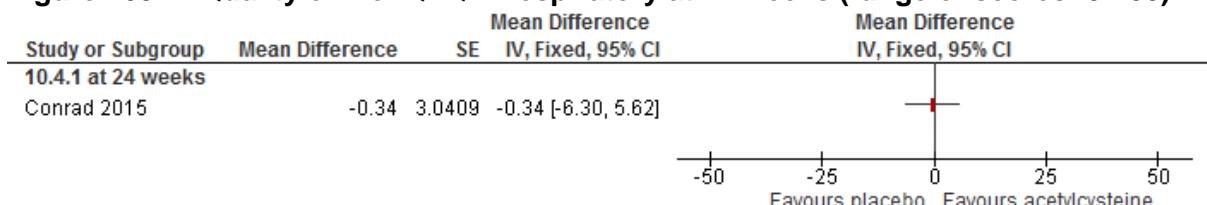
Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SE: standard error

I.9   Pulmonary infection – prophylaxis

Comparison 1. Continuous oral flucloxacillin *versus* antibiotics as required

Figure 110:   Number of children from whom *S. Aureus* was identified at least once during 3 years follow-up
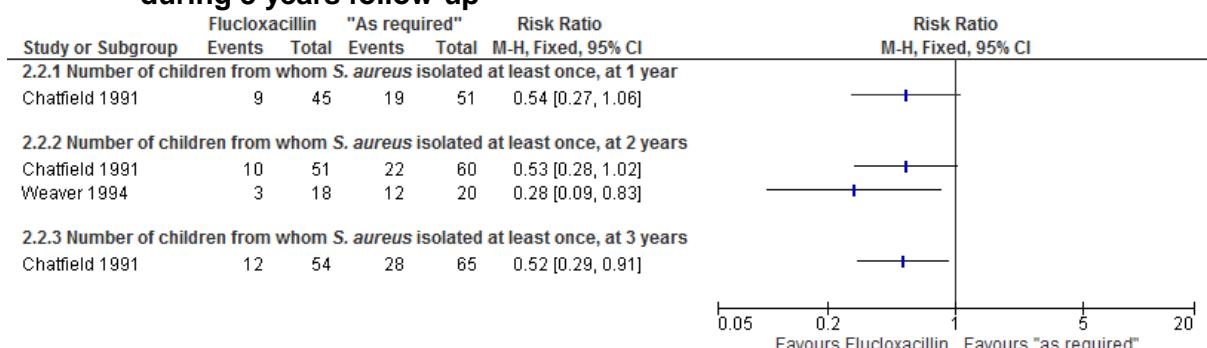
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 111:   Number of children admitted to hospital due to pulmonary exacerbations (annualised rates) during 3 years follow-up
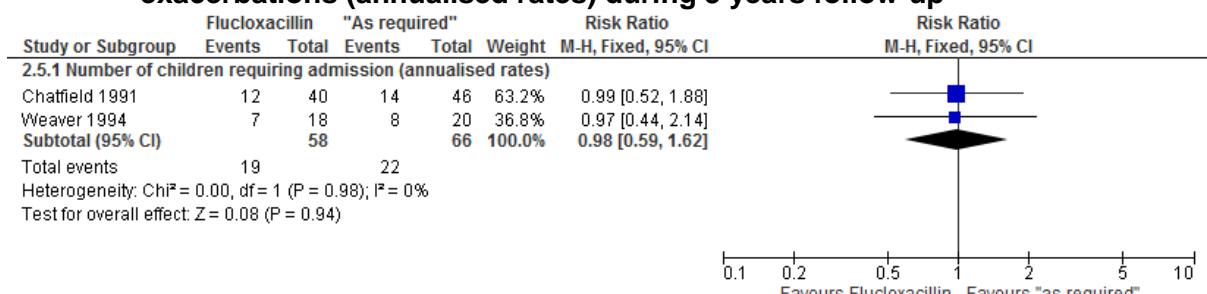
Abbreviations: CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel

Figure 112: Number of children in whom *P. aeruginosa* was identified during 3 years follow-up
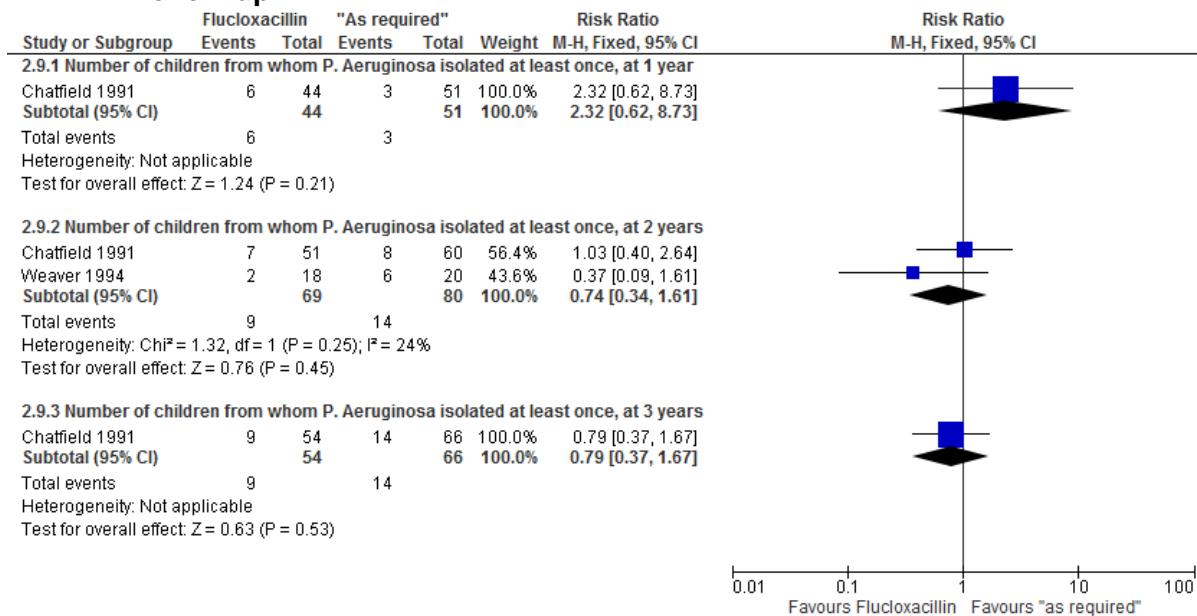
Abbreviations: CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel

Comparison 2. Continuous oral Cephalexin *versus* antibiotics as required

**Figure 113: Number of children from whom *S. aureus* was identified at least once during 6 years follow-up**
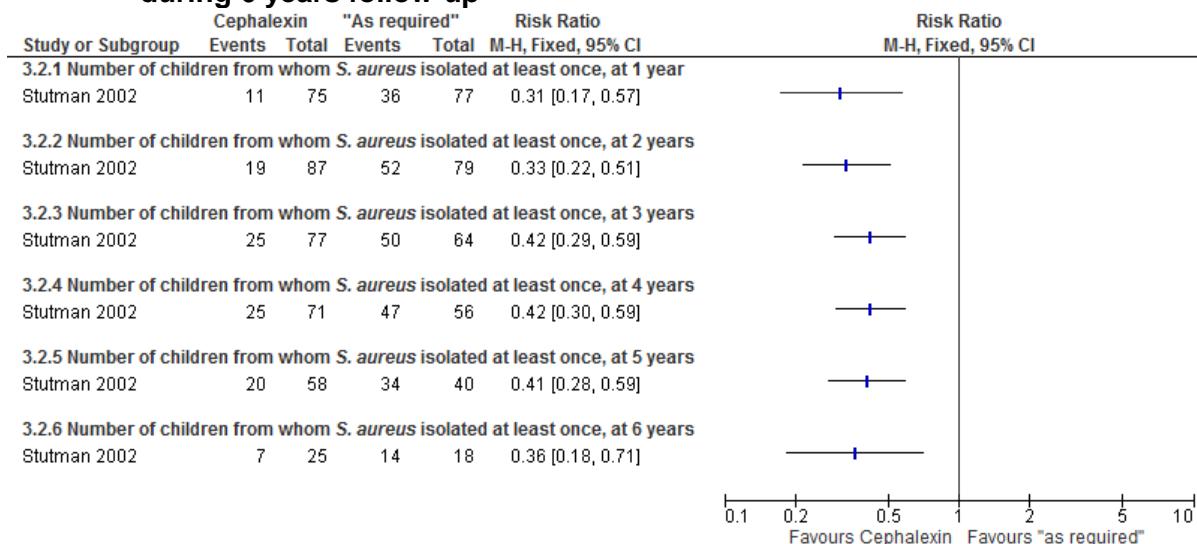
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

**Figure 114: FEV$_1$ (litres) at 6 years follow-up**
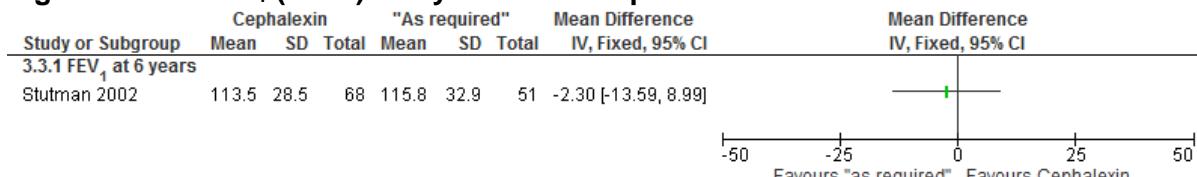
Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

## Figure 115: Pulmonary exacerbations (%) during 6 years follow-up
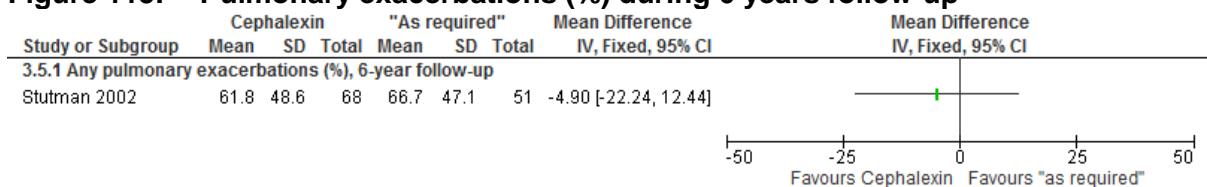
Study or Subgroup	Cephalexin Mean	SD	Total	"As required" Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
3.5.1 Any pulmonary exacerbations (%), 6-year follow-up								
Stutman 2002	61.8	48.6	68	66.7	47.1	51	-4.90 [-22.24, 12.44]	

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation;

Figure 116: Number of children admitted to hospital due to pulmonary exacerbations (annualised rates) during 6 years follow-up

Study or Subgroup	Cephalexin Events	Total	"As required" Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
3.4.1 Number of children requiring admission (annualised rates)						
Stutman 2002	5	68	4	51	0.94 [0.26, 3.32]	

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 117: Minor adverse events during 6 years follow-up
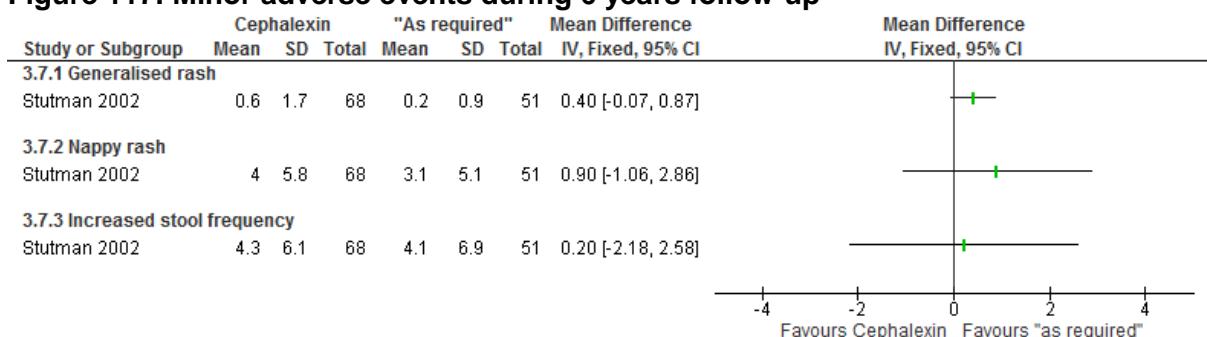
Study or Subgroup	Cephalexin Mean	SD	Total	"As required" Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
3.7.1 Generalised rash								
Stutman 2002	0.6	1.7	68	0.2	0.9	51	0.40 [-0.07, 0.87]	
3.7.2 Nappy rash								
Stutman 2002	4	5.8	68	3.1	5.1	51	0.90 [-1.06, 2.86]	
3.7.3 Increased stool frequency								
Stutman 2002	4.3	6.1	68	4.1	6.9	51	0.20 [-2.18, 2.58]	

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 118: Number of children in whom *P. Aeruginosa* was identified at 1 to 6 years follow-up

Study or Subgroup	Cephalexin Events	Total	"As required" Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
3.9.1 Number of children from whom P. aeruginosa identified at least once, at 1 year						
Stutman 2002	27	75	24	77	1.16 [0.74, 1.81]	
3.9.2 Number of children from whom P. aeruginosa identified at least once, at 2 years						
Stutman 2002	38	87	40	79	0.86 [0.62, 1.19]	
3.9.3 Number of children from whom P. aeruginosa identified at least once, at 3 years						
Stutman 2002	45	77	38	64	0.98 [0.75, 1.30]	
3.9.4 Number of children from whom P. aeruginosa identified at least once, at 4 years						
Stutman 2002	46	71	33	56	1.10 [0.83, 1.45]	
3.9.5 Number of children from whom P. aeruginosa identified at least once, at 5 years						
Stutman 2002	41	58	22	40	1.29 [0.93, 1.78]	
3.9.6 Number of children from whom P. aeruginosa identified at least once, at 6 years						
Stutman 2002	22	25	12	18	1.32 [0.92, 1.89]	

*Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel*

I.10 Pulmonary infection – acute

I.10.1 Pseudomonas aeruginosa

I.10.1.1 Antimicrobial treatment for pulmonary exacerbations due to P. aeruginosa

**Comparison 1. Single IV antibiotic *versus* single IV antibiotic**

Figure 119: FEV$_1$ litres (absolute change) at end of 2 week course [ceftazidime *versus* aztreonam]
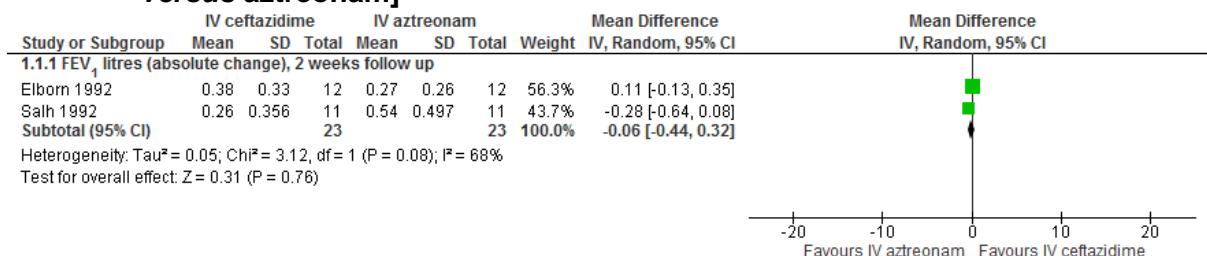
Abbreviations: CI: confidence interval; df: degrees of freedom; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Comparison 2. Single IV antibiotic (with placebo) *versus* combination IV

Figure 120: FEV$_1$ % predicted (absolute change) at 10 days follow-up (range of scores: 0-100) [Tobramycin + placebo *versus* tobramycin + ceftazidime]
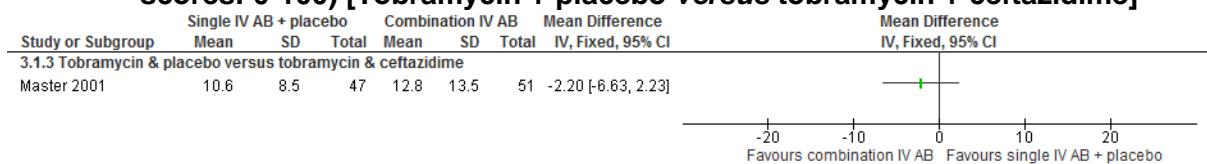

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance (at the top of the plot) or intravenous (at the bottom of the plot); SD: standard deviation

Figure 121: FEV$_1$ % predicted (relative change) at end of 2 weeks course (range of scores: 0-100) [tobramycin + placebo *versus* tobramycin + piperacillin (different regimens)]
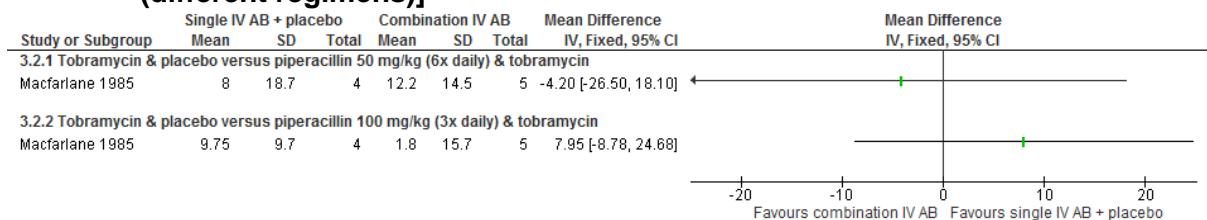

Abbreviations: AB: antibiotics; CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance (at the top of the plot) or intravenous (at the bottom of the plot); SD: standard deviation

Figure 122: Adverse effects: sensitivity reaction at end of 2 weeks course [tobramycin + placebo *versus* tobramycin + piperacillin (all regimens)]
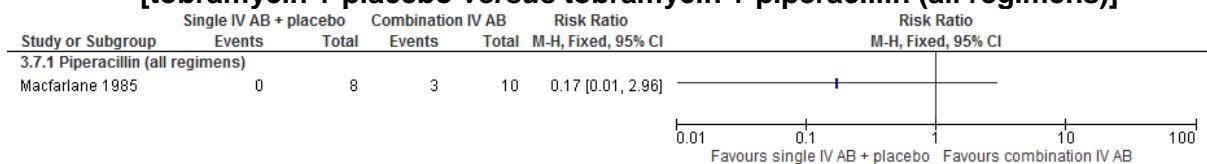

Abbreviations: AB: antibiotics; CI: confidence interval; IV: intravenous; M-H: Mantel-Haenszel

Figure 123:   Adverse effects: number of hospital admissions due to tinnitus during 10 day course [tobramycin + placebo *versus* ceftazidime + tobramycin]

Study or Subgroup	Single IV AB + placebo Events	Total	Combination IV AB Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
3.8.6 Number of hospital admissions due to Tinnitus						
Master 2001	2	47	2	51	1.09 [0.16, 7.40]	

0.01 0.1 1 10 100
Favours single IV AB + placebo Favours combination IV AB

*Abbreviations: AB: antibiotics; CI: confidence interval; IV: intravenous; M-H: Mantel-Haenszel;*
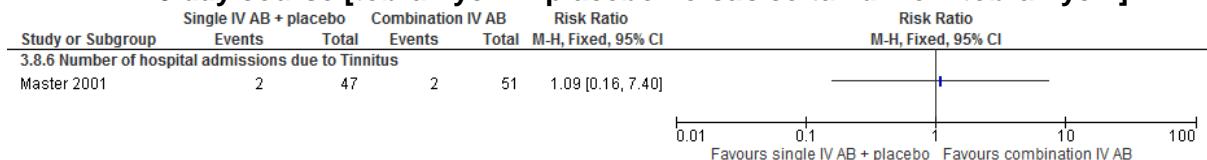
Figure 124:   Adverse effects: adverse effects (serum concentrations) during 10 day course [tobramycin + placebo *versus* ceftazidime + tobramycin]

Study or Subgroup	Single IV AB + placebo Mean	SD	Total	Combination IV AB Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
3.9.1 Creatinine								
Master 2001	0	8	23	4	10	21	-4.00 [-9.38, 1.38]	
3.9.2 NAG								
Master 2001	1.5	1.1	23	3.6	3	21	-2.10 [-3.46, -0.74]	

-100 -50 0 50 100
Favours single IV AB + placebo Favours combination IV AB

Abbreviations: AB: antibiotics; CI: confidence interval; IV: inverse variance; IV AB: intravenous antibiotics; SD: standard deviation

Comparison 3. Single IV antibiotic *versus* combination IV antibiotic for pulmonary exacerbations with PA

Figure 125:   FEV₁ (relative change) at 10 to 14 days follow-up (range of scores: 0-100) [ceftazidime *versus* tobramycin & ticarcillin]

Study or Subgroup	Single IV AB Mean	SD	Total	Combination IV AB Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.1.1 Ceftazidime versus tobramycin & ticarcillin								
Gold 1985	13.7	23.09	17	33.3	27.76	13	-19.60 [-38.26, -0.94]	

-20 -10 0 10 20
Favours combination IV AB Favours single IV AB

Abbreviations: AB: antibiotics; CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; IV AB: intravenous antibiotics; SD: standard deviation

Figure 126:   FEV₁ ml (absolute change) at 12 days follow-up [colistin *versus* colistin + "other"]

Study or Subgroup	Single IV AB Mean	SD	Total	Combination IV AB Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.2.1 Colstin versus colistin & "other", 12 days follow up								
Conway 1997	140	312.5	36	300	330.6	35	-160.00 [-309.72, -10.28]	

-100 -50 0 50 100
Favours combination IV AB Favours single IV AB

Abbreviations: AB: antibiotics; CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; IV AB: intravenous antibiotics; SD: standard deviation

Figure 127:   FEV₁ % predicted (absolute change) at 14 days follow-up (range of scores: 0-100) [ceftazidime *versus* tobramycin + piperacillin]

Study or Subgroup	Single IV AB Mean	SD	Total	Combination IV AB Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.3.2 Ceftazidime versus tobramycin & piperacillin								
De Boeck 1989	16	11.75	11	15	11.28	10	1.00 [-8.85, 10.85]	

-20 -10 0 10 20
Favours combination IV AB Favours single IV AB

Abbreviations: AB: antibiotics; CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; IV AB: intravenous antibiotics; SD: standard deviation

Figure 128: Eradication: number of people in whom pseudomonas isolates were eradicated at end of course at 10 days follow-up [piperacillin *versus* piperacillin & tobramycin]
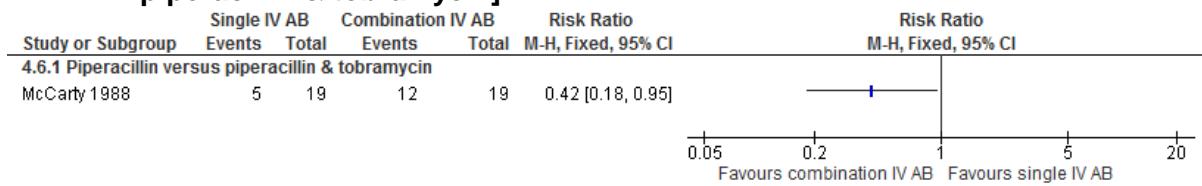
	Single IV AB		Combination IV AB		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
4.6.1 Piperacillin versus piperacillin & tobramycin						
McCarty 1988	5	19	12	19	0.42 [0.18, 0.95]	

0.05 0.2 1 5 20
Favours combination IV AB Favours single IV AB

Abbreviations: AB: antibiotics; CI: confidence interval; IV: intravenous; M-H: Mantel-Haenszel;

Figure 129: Time to readmission (in months) at 24 to 26 months follow-up [ceftazidime *versus* tobramycin + piperacillin]
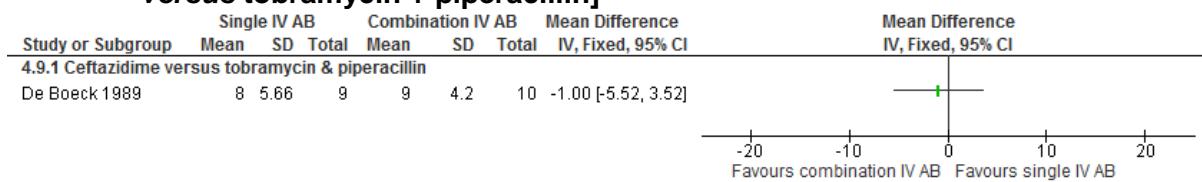
	Single IV AB			Combination IV AB			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
4.9.1 Ceftazidime versus tobramycin & piperacillin								
De Boeck 1989	8	5.66	9	9	4.2	10	-1.00 [-5.52, 3.52]	

-20 -10 0 10 20
Favours combination IV AB Favours single IV AB

Abbreviations: AB: antibiotics; CI: confidence interval; IV: inverse variance; IV AB: intravenous antibiotics; SD: standard deviation

Figure 130: Number of admissions requiring IV antibiotics or death at 3 months follow-up [ceftazidime *versus* tobramycin & ticarcillin] (follow-up 3 months)
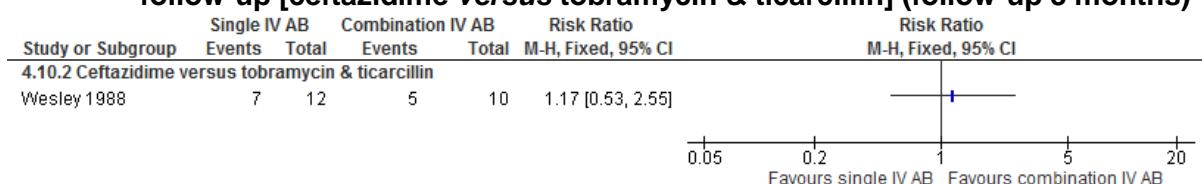
	Single IV AB		Combination IV AB		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
4.10.2 Ceftazidime versus tobramycin & ticarcillin						
Wesley 1988	7	12	5	10	1.17 [0.53, 2.55]	

0.05 0.2 1 5 20
Favours single IV AB Favours combination IV AB

Abbreviations: AB: antibiotics; CI: confidence interval; IV: intravenous; M-H: Mantel-Haenszel

Figure 131: Mortality at 4 months follow-up [Single IV AB *versus* combination IV AB]
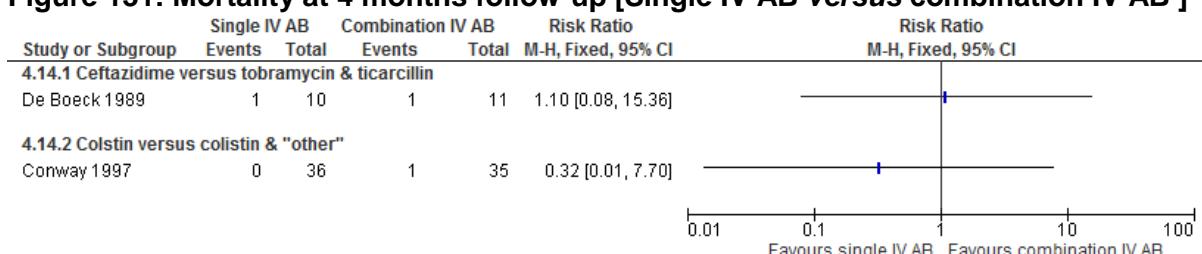
	Single IV AB		Combination IV AB		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
4.14.1 Ceftazidime versus tobramycin & ticarcillin						
De Boeck 1989	1	10	1	11	1.10 [0.08, 15.36]	
4.14.2 Colstin versus colistin & "other"						
Conway 1997	0	36	1	35	0.32 [0.01, 7.70]	

0.01 0.1 1 10 100
Favours single IV AB Favours combination IV AB

Abbreviations: AB: antibiotics; CI: confidence interval; IV: intravenous; M-H: Mantel-Haenszel;

Figure 132:   Adverse events at 14 days follow-up [single IV *versus* combination IV AB]

Study or Subgroup	Single IV AB Events	Total	Combination IV AB Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
4.12.1 Ceftazidime versus tobramycin & ticarcillin: liver transaminase enzyme elevation at 12 to 14 days						
Gold 1987	4	17	2	13	1.53 [0.33, 7.11]	
Wesley 1988	0	12	0	10	Not estimable	
4.12.2 Colistin versus combination anti-pseudo: neurological adverse effects at 12 days						
Conway 1997	33	35	36	36	0.94 [0.86, 1.04]	
4.12.3 Piperacillin versus piperacillin & tobramycin: rash at 10 days						
McCarty 1988	0	8	1	9	0.37 [0.02, 7.99]	
4.12.5 Piperacillin versus piperacillin & tobramycin: fever at 10 days						
McCarty 1988	1	8	1	9	1.13 [0.08, 15.19]	
4.12.6 Ceftazidime versus tobramycin & ticarcillin: proteinuria at 10 to 14 days						
Gold 1985	1	17	1	17	1.00 [0.07, 14.72]	

Favours single IV AB   Favours combination IV AB

Abbreviations: AB: antibiotics; CI: confidence interval; IV: intravenous; M-H: Mantel-Haenszel

**Figure 133:   Adverse events: renal toxicity at 12 days follow-up [colistin *versus* combination other anti-pseudomonal antibiotic]**
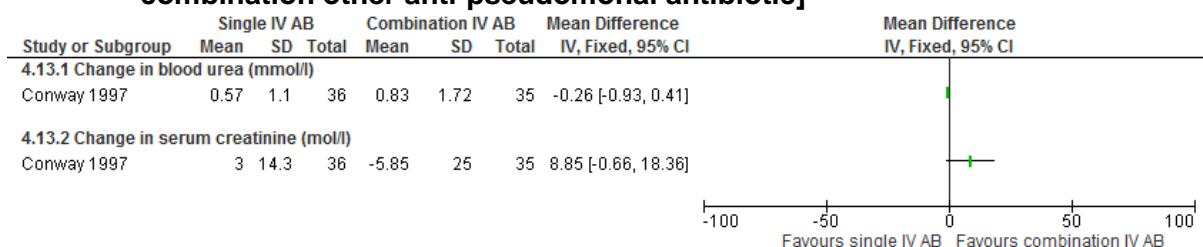
Study or Subgroup	Single IV AB Mean	SD	Total	Combination IV AB Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.13.1 Change in blood urea (mmol/l)								
Conway 1997	0.57	1.1	36	0.83	1.72	35	-0.26 [-0.93, 0.41]	
4.13.2 Change in serum creatinine (mol/l)								
Conway 1997	3	14.3	36	-5.85	25	35	8.85 [-0.66, 18.36]	

Favours single IV AB   Favours combination IV AB

Abbreviations: AB: antibiotics; CI: confidence interval; IV: inverse variance; IV AB: intravenous antibiotics; SD: standard deviation

Comparison 4. Combination IV antibiotics *versus* combination IV antibiotics for pulmonary exacerbations

**Figure 134:   Eradication of pathogen at 2 weeks follow-up [aztreonam + amikacin *versus* ceftazidime + amikacin]**

Study or Subgroup	IV aztreonam & IV amikaci Events	Total	IV ceft & IV amikacin Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Schaad 1989	17	28	16	28	1.06 [0.69, 1.65]	

Favours IV ceft/amika   Favours IV aztreo/amika

Abbreviations: aztreo: aztreonam; amika: amikacin; M-H: Mantel-Haenszel; CI: confidence interval

Figure 135:   FEV$_1$ % predicted (absolute change) at 2 weeks follow-up (range of scores: 0-100) [IV combination A vs IV combination B]

| Study or Subgroup	Combination A Mean	SD	Total	Combination B Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
6.2.1 aztreonam & IV amikacin (combination A) versus IV ceftazidime & IV amikacin (combination B), at 2 weeks								
Schaad 1989	13	6.8	24	9	8.33546639	25	4.00 [-0.25, 8.25]	
6.2.2 IV meropenem & IV tobramycin (combination A) versus IV ceftazidime & IV tobramycin (combination B), at 2 weeks								
Blumer 2005	13.8	9.52	47	11.1	7.68	50	2.70 [-0.76, 6.16]	

Favours combination B   Favours combination A

Abbreviations: amika: amikacin; ceft: ceftazidime; CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 136: FEV$_1$ % predicted (relative change) at 2 weeks follow-up (range of scores: 0-100) [meropenem + obramycin *versus* ceftazidime + tobramycin]
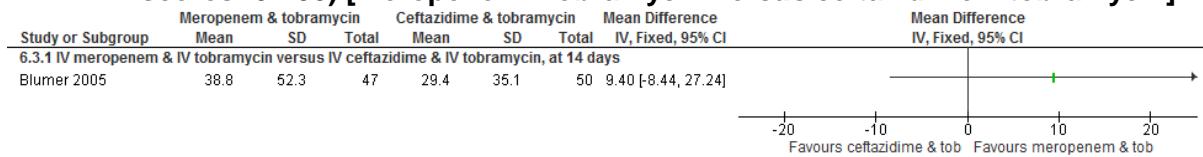
Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation; tob: tobramycin

Figure 137: Adverse effects at 2 weeks follow-up [aztreonam + amikacin *versus* ceftazidime + amikacin
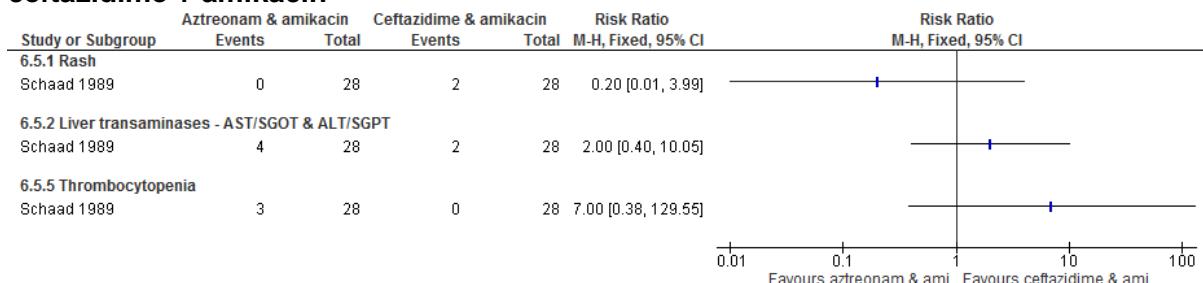
Abbreviations: ami: amikacin; CI: confidence interval; M-H: Mantel-Haenszel;

Comparison 5. Two IV antibiotics + inhaled antibiotic *versus* 2 IV without inhaled antibiotic

Figure 138: Eradication of P. aeruginosa at 15 days follow-up [IV ceftazidime + IV amikacin + inhaled amikacin *versus* IV ceftazidime + IV amikacin]
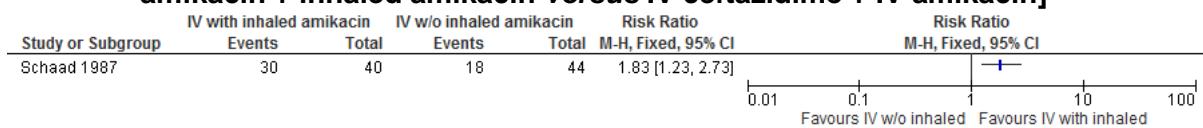
*Abbreviations: CI: confidence interval; IV: intravenous; M-H: Mantel-Haenszel; w/o: without*

Figure 139: Adverse effects: raised liver transaminases at 4 to 6 weeks follow-up [IV ceftazidime + IV amikacin + inhaled amikacin *versus* IV ceftazidime + IV amikacin]
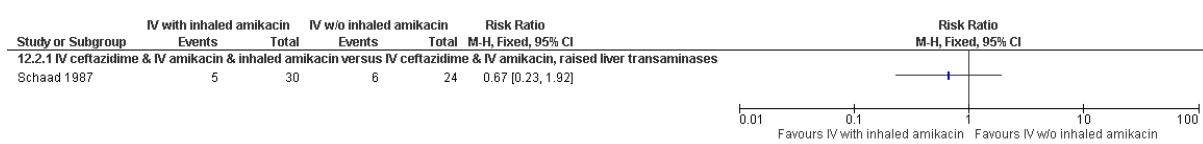
Abbreviations: CI: confidence interval; IV: intravenous; M-H: Mantel-Haenszel; w/o: without

Comparison 6. IV ceftazidime + IV tobramycin *versus* oral ciprofloxacin

Figure 140: Eradication of P. aeruginosa at 2 weeks follow-up
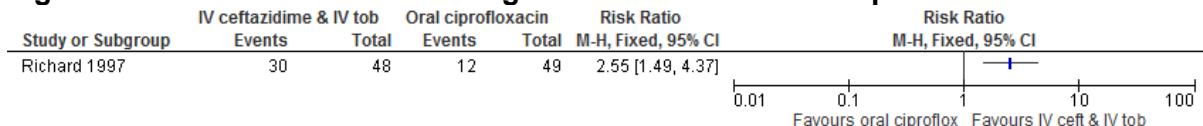
Abbreviations: ceft: ceftazidime; CI: confidence interval; IV: intravenous; M-H: Mantel-Haenszel; tob: tobramycin

Figure 141:   Adverse effects - Treatment-related events at 2 weeks follow-up

	IV ceftazidime & IV tob		Oral ciprofloxacin		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
15.2.1 Treatment-related events						
Richard 1997	10	53	9	55	1.15 [0.51, 2.61]	
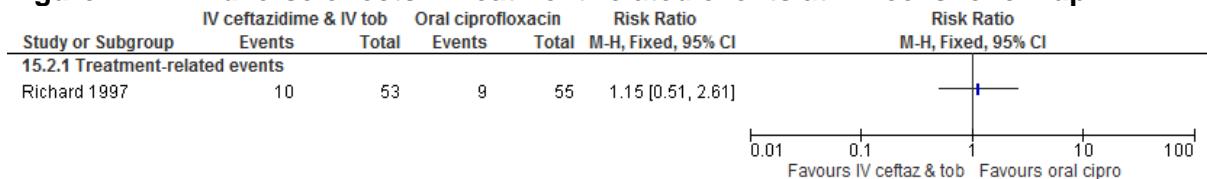
Abbreviations: ceft: ceftazidime; CI: confidence interval; cipro: ciprofloxacin; IV: intravenous; M-H: Mantel-Haenszel; tob: tobramycin

I.10.1.2   Antimicrobial treatment for acute infection with P. aeruginosa

**Comparison 7. Oral ciprofloxacin + inhaled colistin *versus* inhaled tobramycin**

Figure 142:   Adverse events: severe cough at 3 months follow-up

	Ciprofloxacin & Inhaled colistin		Inhaled tobramycin		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
3.2.1 Severe cough						
Proesmans 2013	0	29	1	29	0.33 [0.01, 7.86]	
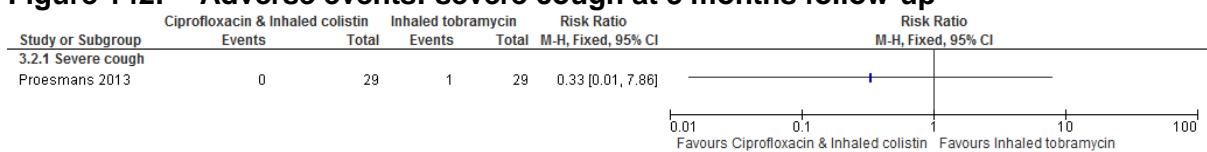
*Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel*

Comparison 8. Inhaled colistin + oral ciprofloxacin *versus* inhaled tobramycin + oral ciprofloxacin

Figure 143:   Relative change in % predicted FEV$_1$ from baseline at 54 days follow-up (range of scores: 0-100)

	Colistin/ciprofloxacin			Tobramycin/ciprofloxacin			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Taccetti 2012	2.15	8.5	60	4.55	11.54	68	-2.40 [-5.89, 1.09]	
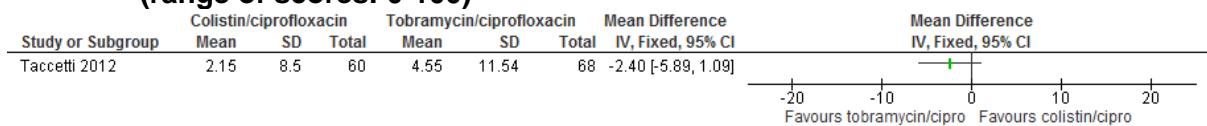
*Abbreviations: CI: confidence interval; cipro: ciprofloxacin; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation*

Figure 144: Treatment failure - trial discontinuation due to lack of compliance at 28 days follow-up

	Colistin/ciprofloxacin		Tobramycin/ciprofloxacin		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
5.2.4 Pulmonary exacerbation during early eradication treatment						
Taccetti 2012	4	105	5	118	0.90 [0.25, 3.26]	
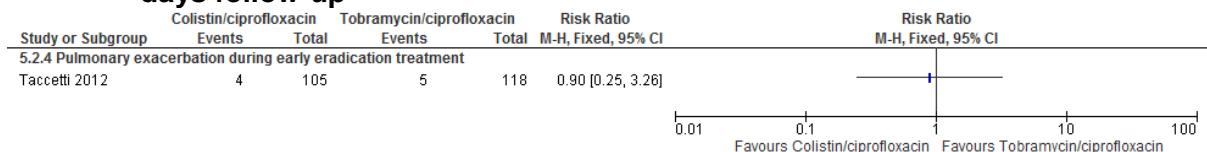
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel;

Figure 145:   Adverse effects at 28 days follow-up

	Colistin/ciprofloxacin		Tobramycin/ciprofloxacin		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
5.4.1 Vomiting						
Taccetti 2012	1	105	2	118	0.56 [0.05, 6.11]	
5.4.2 Photosensitivity						
Taccetti 2012	1	105	0	118	3.37 [0.14, 81.79]	
5.4.3 Wheeze						
Taccetti 2012	0	105	1	118	0.37 [0.02, 9.09]	
5.4.5 Lack of compliance						
Taccetti 2012	11	105	13	118	0.95 [0.45, 2.03]	
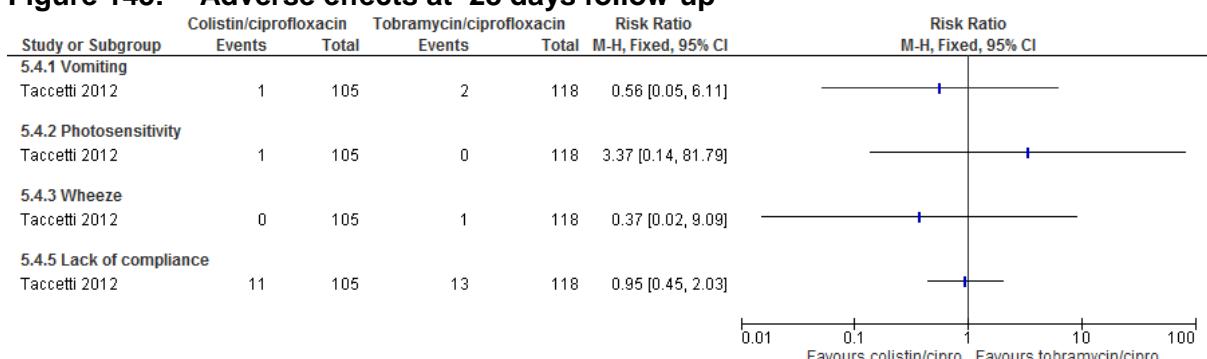
Abbreviations: CI: confidence interval; cipro: ciprofloxacin; M-H: Mantel-Haenszel

I.10.2 Staphylococcus aureus

Not applicable, as no studies were identified for inclusion.

I.10.3 Burkholderia cepacia complex

Not applicable, as no studies were identified for inclusion.

I.10.4 Non-tuberculous mycobacteria

Not applicable, as no studies were identified for inclusion.

I.10.5 Non-identified pathogen

Not applicable, as no studies were identified for inclusion.

I.11 Pulmonary infection – chronic

I.11.1 Pseudomonas Aeruginosa

I.11.1.1 NMA outcomes

Outcome 1: NMA FEV$_1$ % predicted (range of scores: 0-100)

Figure 146: Forest plot showing mean differences (with their 95% CI) of study estimates for interventions *versus* placebo
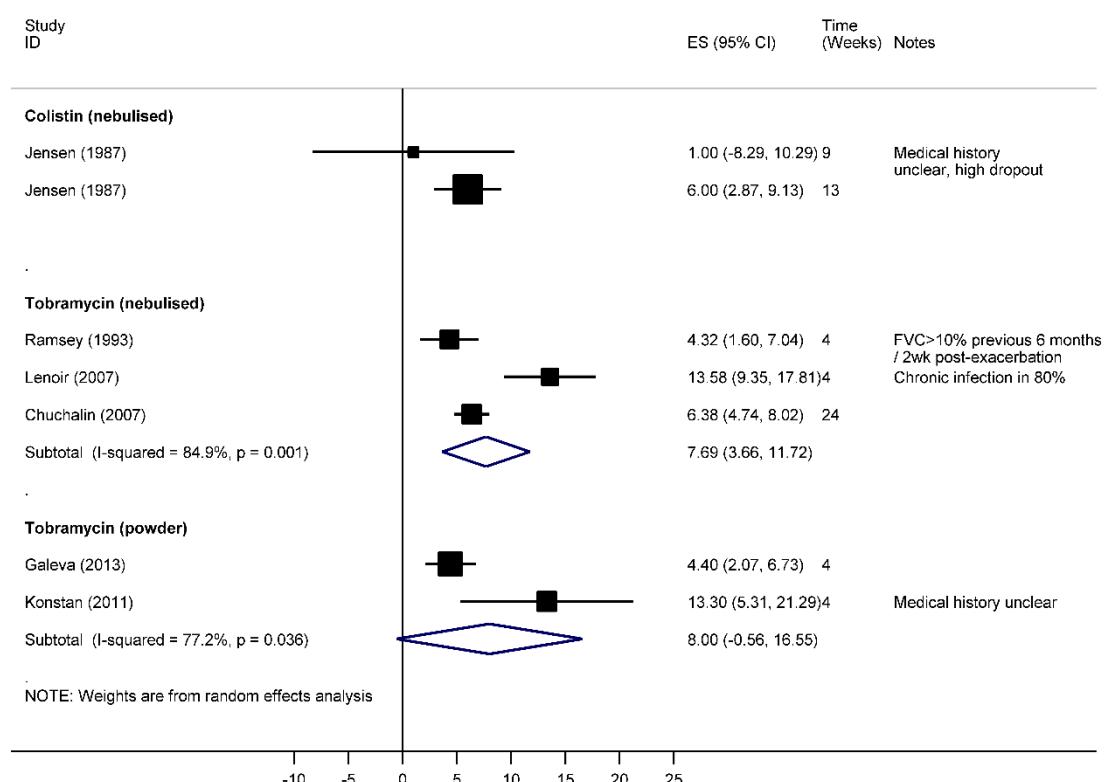
*Abbreviations: CI: confidence interval; ES: effect size*

Figure 147: **Forest plot showing mean differences (with their 95% CI) of study estimates for interventions *versus* tobramycin (nebulised)**
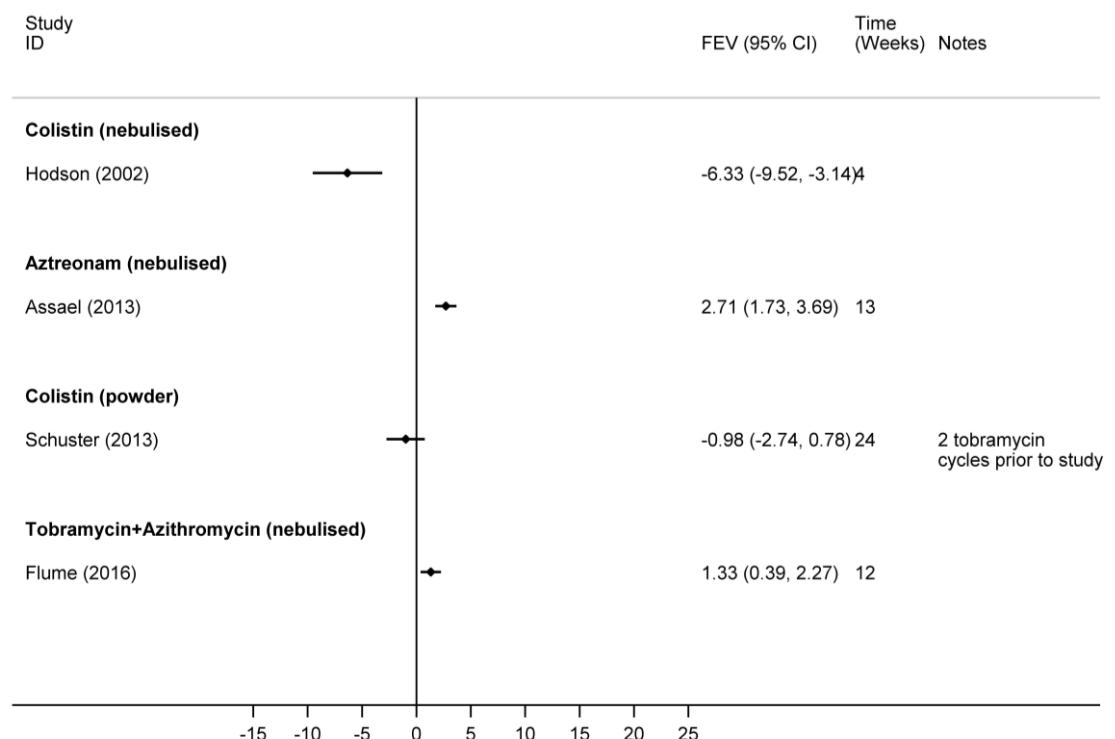
*Abbreviations: CI: confidence interval; FEV: forced expiratory volume*

Outcome 2: NMA number of patients experiencing at last one exacerbation

Figure 148: **Forest plot showing odds ratios (with their 95% CI) of NMA estimates for each intervention *versus* placebo for the number of people experiencing at least one exacerbation with short-term (4-10 weeks) treatment**
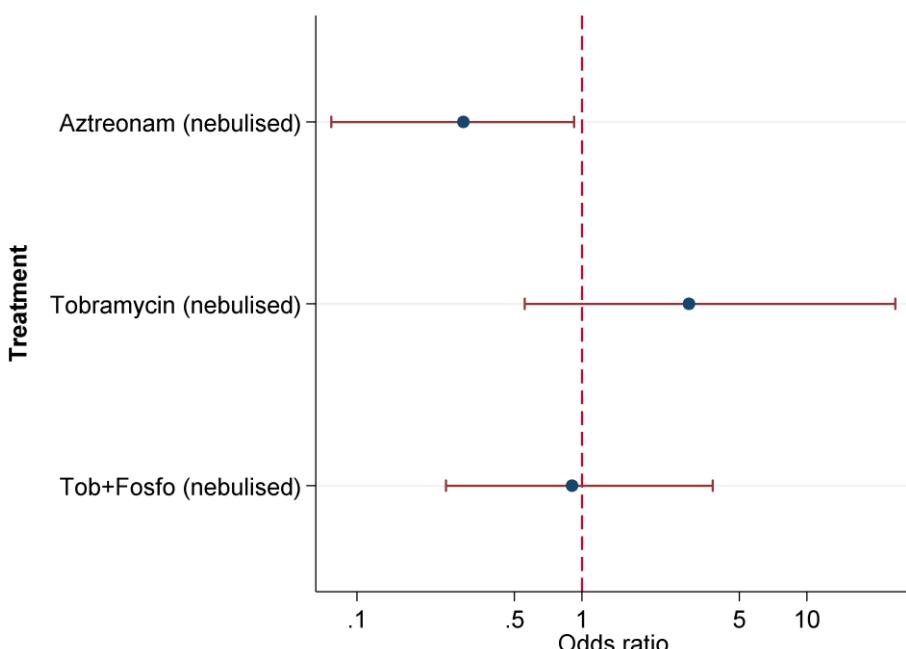
Abbreviations: CI: confidence interval; Fosfo: fosfomycin; Tob: tobramycin. Note: Vertical dashed line shows line of no effect.

Figure 149:   Forest plot showing odds ratios (with their 95% CI) of NMA estimates for each intervention *versus* placebo for the number of people experiencing at least one exacerbation with long-term (>10 weeks) treatment
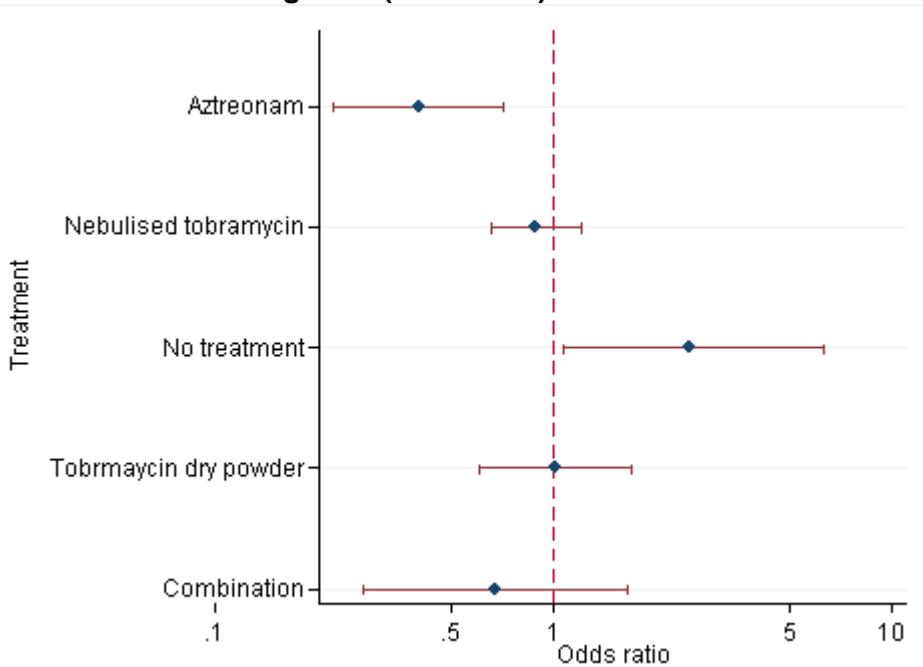

Combination: 28 days aztreonam lysine (nebulised) alternating with 28 days tobramycin (nebulised). Vertical dashed line shows the line of no effect

### I.11.1.2   Non-NMA outcomes (pairwise comparisons)

Pairwise comparison 1: Aztreonam lysine *versus* placebo

Figure 150:   Lung function: relative change in FEV$_1$% predicted at 28 days follow-up (range of scores: 0-100)
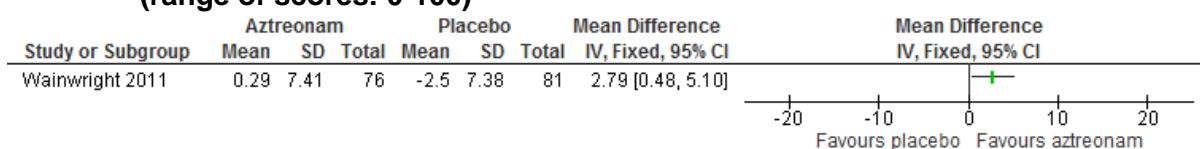
Study or Subgroup	Aztreonam Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Wainwright 2011	0.29	7.41	76	-2.5	7.38	81	2.79 [0.48, 5.10]

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 151:   Suppression of the organism: adjusted mean change in P. aeruginosa sputum density (log10), at 4 weeks follow-up
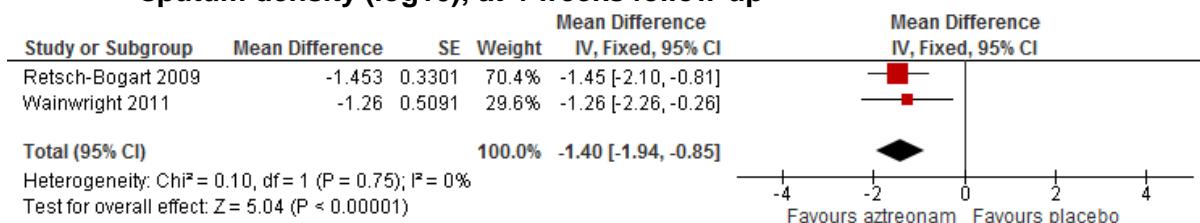
Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Retsch-Bogart 2009	-1.453	0.3301	70.4%	-1.45 [-2.10, -0.81]
Wainwright 2011	-1.26	0.5091	29.6%	-1.26 [-2.26, -0.26]
Total (95% CI)			100.0%	**-1.40 [-1.94, -0.85]**

Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 5.04 (P < 0.00001)

Abbreviations: CI: confidence interval; df: degrees of freedom; IV: inverse variance; SE: standard error

Figure 152:   Nutritional status: % weight change (kg), at 4 weeks follow-up

*Abbreviations: CI: confidence interval; IV: inverse variance; kg: kilograms; SD: standard deviation*

Figure 153:   Quality of life: CFQ-R, at 4 weeks follow-up (range of scores: 0-100)

Study or Subgroup	AZLI Mean	AZLI SD	AZLI Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
1.6.1 CFQ-R body image								
Retsch-Bogart 2009	3.2	14.3703	80	1	14.3703	84	40.3%	2.20 [-2.20, 6.60]
Wainwright 2011	3.7	10.4614	76	1.1	12.522	80	59.7%	2.60 [-1.01, 6.21]
Subtotal (95% CI)			156			164	100.0%	2.44 [-0.35, 5.23]

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 1.71 (P = 0.09)

1.6.2 CFQ-R digestion								
Retsch-Bogart 2009	2.2	12.4108	80	1.9	12.4108	84	65.8%	0.30 [-3.50, 4.10]
Wainwright 2011	3.6	16.5638	76	5.5	17.1	81	34.2%	-1.90 [-7.17, 3.37]
Subtotal (95% CI)			156			165	100.0%	-0.45 [-3.53, 2.63]

Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.29 (P = 0.77)

1.6.3 CFQ-R eating								
Retsch-Bogart 2009	3.6	13.7172	80	-4.7	13.7172	84	49.9%	8.30 [4.10, 12.50]
Wainwright 2011	0.5	13.0767	76	-1.2	13.5	81	50.1%	1.70 [-2.46, 5.86]
Subtotal (95% CI)			156			165	100.0%	4.99 [-1.47, 11.46]

Heterogeneity: Tau² = 17.23; Chi² = 4.79, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 1.51 (P = 0.13)

1.6.4 CFQ-R emotional functioning								
Retsch-Bogart 2009	3.9	11.7576	80	-1.3	11.7576	84	49.2%	5.20 [1.60, 8.80]
Wainwright 2011	3.3	10.4614	76	3.7	10.7331	80	50.8%	-0.40 [-3.73, 2.93]
Subtotal (95% CI)			156			164	100.0%	2.36 [-3.13, 7.84]

Heterogeneity: Tau² = 12.55; Chi² = 5.01, df = 1 (P = 0.03); I² = 80%
Test for overall effect: Z = 0.84 (P = 0.40)

1.6.5 CFQ-R health perceptions								
Retsch-Bogart 2009	5	16.3299	80	-4.8	16.3299	84	51.9%	9.80 [4.80, 14.80]
Wainwright 2011	1.8	14.6969	54	-1.8	14.6969	54	48.1%	3.60 [-1.94, 9.14]
Subtotal (95% CI)			134			138	100.0%	6.82 [0.75, 12.89]

Heterogeneity: Tau² = 11.97; Chi² = 2.65, df = 1 (P = 0.10); I² = 62%
Test for overall effect: Z = 2.20 (P = 0.03)

1.6.6 CFQ-R physical functioning								
Retsch-Bogart 2009	2.3	18.2895	80	-6.9	18.2895	84	46.3%	9.20 [3.60, 14.80]
Wainwright 2011	1.8	13.9485	76	-0.69	13.4164	80	53.7%	2.49 [-1.81, 6.79]
Subtotal (95% CI)			156			164	100.0%	5.60 [-0.96, 12.15]

Heterogeneity: Tau² = 16.03; Chi² = 3.47, df = 1 (P = 0.06); I² = 71%
Test for overall effect: Z = 1.67 (P = 0.09)

1.6.7 CFQ-R respiratory symptoms								
Retsch-Bogart 2009	7.1	17.6363	80	-2.6	17.6363	84	49.0%	9.70 [4.30, 15.10]
Wainwright 2011	3	14.8203	76	2.9	15.3	81	51.0%	0.10 [-4.61, 4.81]
Subtotal (95% CI)			156			165	100.0%	4.81 [-4.60, 14.21]

Heterogeneity: Tau² = 39.39; Chi² = 6.89, df = 1 (P = 0.009); I² = 85%
Test for overall effect: Z = 1.00 (P = 0.32)

1.6.8 CFQ-R role/school								
Retsch-Bogart 2009	2.1	16.3299	80	-4.2	16.3299	84	47.1%	6.30 [1.30, 11.30]
Wainwright 2011	0.29	10.9202	53	0.29	10.3827	55	52.9%	0.00 [-4.02, 4.02]
Subtotal (95% CI)			133			139	100.0%	2.97 [-3.20, 9.13]

Heterogeneity: Tau² = 14.49; Chi² = 3.70, df = 1 (P = 0.05); I² = 73%
Test for overall effect: Z = 0.94 (P = 0.35)

1.6.9 CFQ-R social functioning								
Retsch-Bogart 2009	-1.2	13.3906	80	-3.6	13.3906	84	45.5%	2.40 [-1.70, 6.50]
Wainwright 2011	1.9	12.1244	75	-2.6	11.6276	80	54.5%	4.50 [0.76, 8.24]
Subtotal (95% CI)			155			164	100.0%	3.54 [0.78, 6.31]

Heterogeneity: Tau² = 0.00; Chi² = 0.55, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 2.51 (P = 0.01)

1.6.10 CFQ-R treatment burden								
Retsch-Bogart 2009	0.2	15.6767	80	-3.1	15.6767	84	49.2%	3.30 [-1.50, 8.10]
Wainwright 2011	1.2	13.9485	76	5.1	14.4	81	50.8%	-3.90 [-8.33, 0.53]
Subtotal (95% CI)			156			165	100.0%	-0.36 [-7.42, 6.69]

Heterogeneity: Tau² = 20.36; Chi² = 4.66, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 0.10 (P = 0.92)

1.6.11 CFQ-R vitality								
Retsch-Bogart 2009	3.6	17.9629	80	-4.4	17.9629	84	53.1%	8.00 [2.50, 13.50]
Wainwright 2011	0.38	16.1666	54	-2.2	16.1666	54	46.9%	2.58 [-3.52, 8.68]
Subtotal (95% CI)			134			138	100.0%	5.46 [0.16, 10.76]

Heterogeneity: Tau² = 5.91; Chi² = 1.67, df = 1 (P = 0.20); I² = 40%
Test for overall effect: Z = 2.02 (P = 0.04)

1.6.12 CFQ-R weight								
Retsch-Bogart 2009	4.7	23.8417	80	1.4	23.8417	84	54.8%	3.30 [-4.00, 10.60]
Wainwright 2011	4.3	21.1123	53	2.6	21.507	55	45.2%	1.70 [-6.34, 9.74]
Subtotal (95% CI)			133			139	100.0%	2.58 [-2.83, 7.98]

Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.93 (P = 0.35)

Favours placebo   Favours aztreonam

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; df: degrees of freedom; IV: inverse variance; SD: standard deviation

Figure 154: Mild adverse events, at 4 weeks follow-up

Abbreviations: CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel

Figure 155: Serious adverse events, at 4 weeks follow-up

Abbreviations: CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel

Figure 156: Mortality, at 4 weeks follow-up
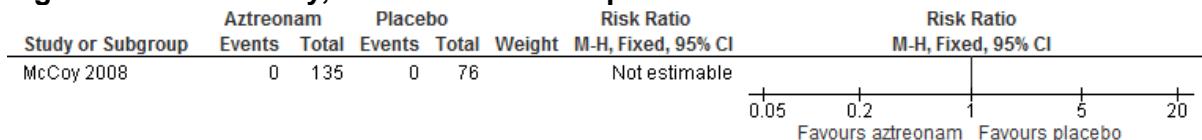
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel. Not estimable as no deaths were recorded in either group.

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Figure 157:   Emergence of resistant organisms, at 42 weeks follow-up
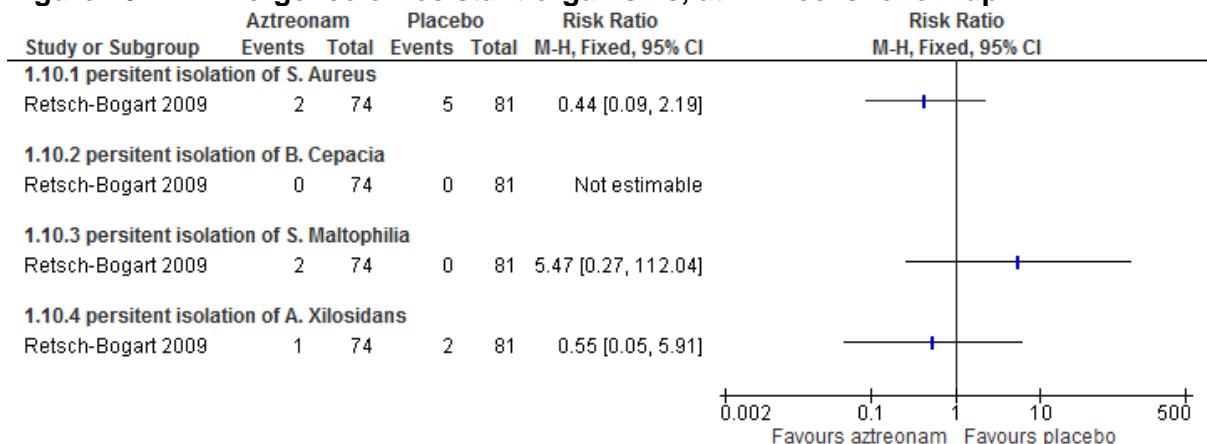
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel.

Pairwise comparison 2: Ciprofloxacin *versus* placebo

Figure 158:   Nutritional status: weight (kg), at 6 to 12 months follow-up
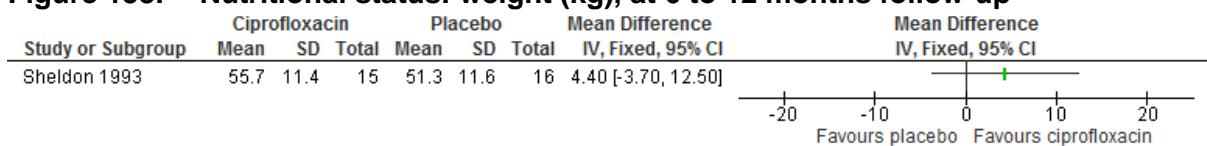
Abbreviations: CI: confidence interval; kg: kilograms; IV: inverse variance; SD: standard deviation

Figure 159: Mild adverse events, at 12 months follow-up
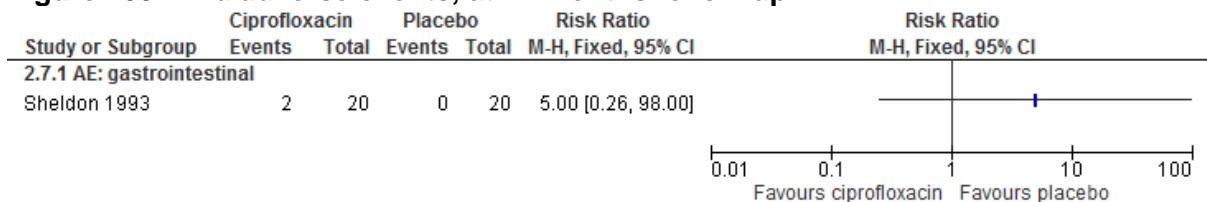
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel.

Figure 160: Mortality, at 12 months follow-up
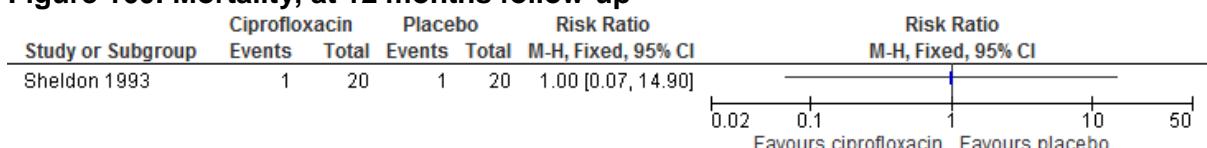
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 161: Emergence of resistant organisms, at 12 months follow-up
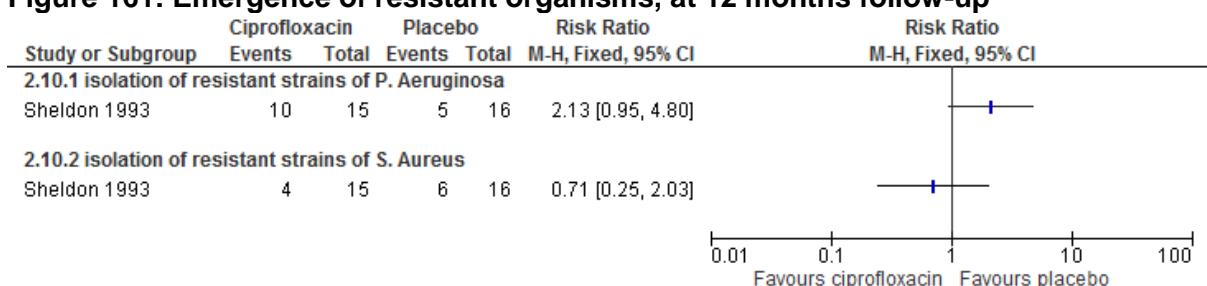
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Pairwise comparison 3.1. Colistin *versus* placebo

Figure 162: Lung function: change in FEV$_1$ % predicted at 3 months follow-up (range of scores: 0-100)
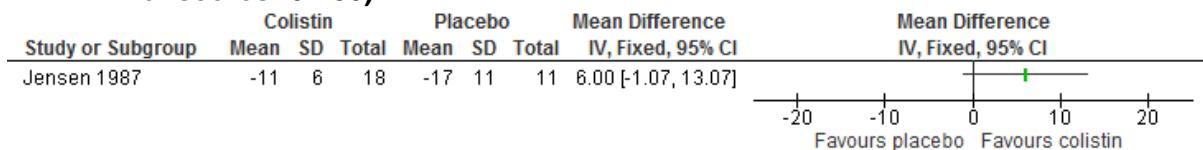
Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 163: Suppression of the organism: eradication of the organism from sputum, at 3 months follow-up
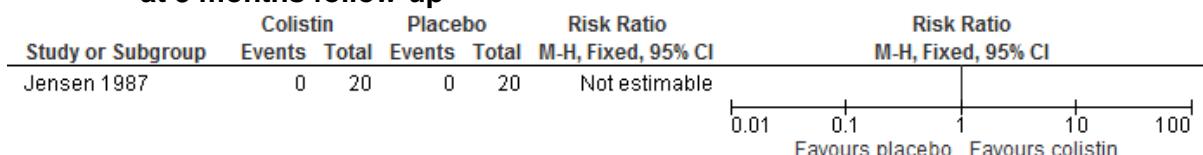
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel. Data cannot be plotted as there were 0 events in each group.

Figure 164: Emergence of resistant organisms, at 3 months follow-up
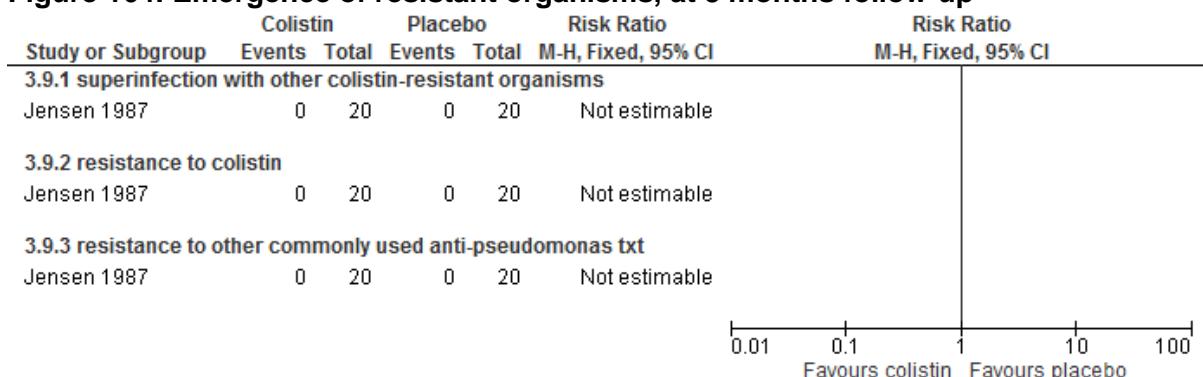
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel. Data cannot be plotted as there were 0 events in each group.

Pairwise comparison 3.2. Colistin inhalation powder (COLO DPI) *versus* colistin inhalation solution (COLI nebulised)

Figure 165: Lung function: % mean change in FEV$_1$% predicted at 4 weeks follow-up (range of scores: 0-100)
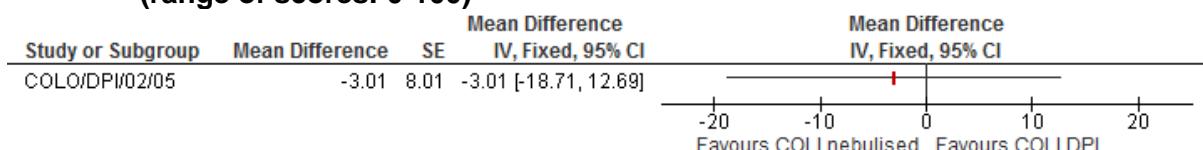

Abbreviations: CI: confidence interval; COLI: colistin; DPI: dry powder inhalation; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SE: standard error

Figure 166: Mild adverse events, at 8 weeks follow-up

Study or Subgroup	COLI DPI Events	Total	COLI nebulised Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
4.7.2 AE: vomiting						
COLO/DPI/02/05	2	16	0	15	4.71 [0.24, 90.69]	
4.7.3 AE: productive cough						
COLO/DPI/02/05	2	16	1	15	1.88 [0.19, 18.60]	
4.7.4 AE: chest discomfort						
COLO/DPI/02/05	4	16	2	15	1.88 [0.40, 8.78]	

0.01   0.1   1   10   100
Favours COLI DPI   Favours COLI nebulised

Abbreviations: CI: confidence interval; COLI: colistin; DPI: dry powder inhalation; M-H: Mantel-Haenszel

Figure 167: Serious adverse events, at 8 weeks follow-up

Study or Subgroup	COLI DPI Events	Total	COLI nebulised Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
4.8.1 AE: dyspnea						
COLO/DPI/02/05	3	16	4	15	0.70 [0.19, 2.63]	

0.01   0.1   1   10   100
Favours COLI DPI   Favours COLI nebulised

Abbreviations: CI: confidence interval; COLI: colistin; DPI: dry powder inhalation; M-H: Mantel-Haenszel
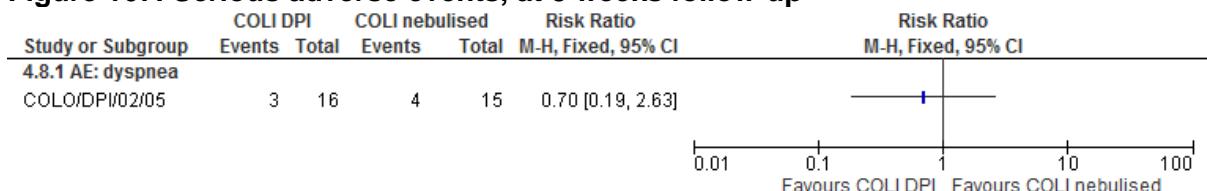
Pairwise comparison 3.3. Colistin *versus* tobramycin

Figure 168: Lung function: mean % change in FEV$_1$% predicted at 1 to 3 months follow-up (range of scores: 0-100)

Study or Subgroup	Colistin Mean	SD	Total	Tobramycin Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
5.1.2 COLI neb vs TOBI neb								
Hodson 2002	0.37	18.78	59	6.7	15.12	50	-6.33 [-12.70, 0.04]	

-20   -10   0   10   20
Favours tobramycin   Favours colistin

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; Neb: nebulised; SD: standard deviation
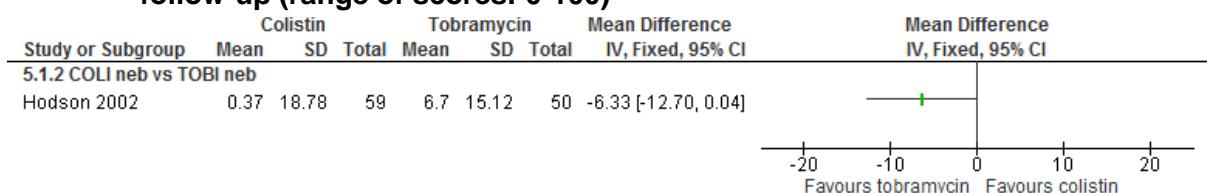
### Figure 169: Lung function: mean % change in FEV$_1$% predicted at 4 weeks follow-up (range of scores: 0-100)

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
5.2.1 COLI DPI vs TOBI neb				
COLO/DPI/02/06	-1.67	1.92	-1.67 [-5.43, 2.09]	

-20   -10   0   10   20
Favours tobramycin   Favours colistin

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; Neb: nebulised; SE: standard error
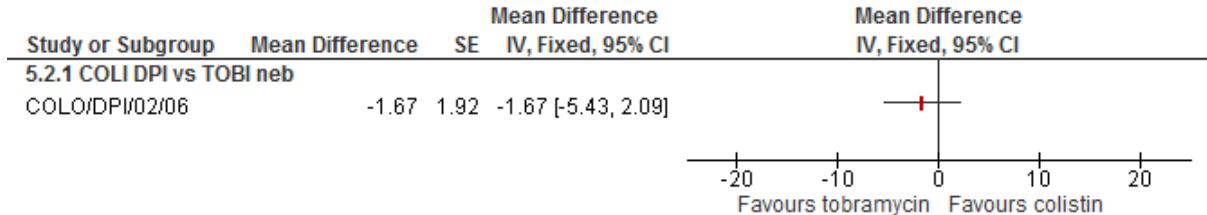
**Figure 170: Lung function: mean % change in FEV₁% predicted at 12 weeks follow-up (range of scores: 0-100)**
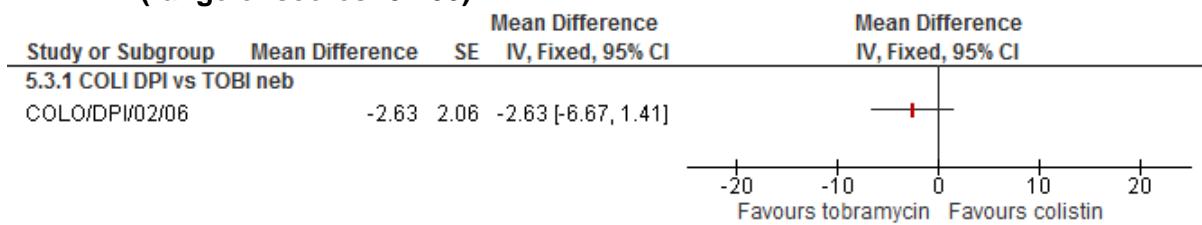
			Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	IV, Fixed, 95% CI	IV, Fixed, 95% CI
5.3.1 COLI DPI vs TOBI neb				
COLO/DPI/02/06	-2.63	2.06	-2.63 [-6.67, 1.41]	

Favours tobramycin   Favours colistin

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; Neb: nebulised; SE: standard error

Figure 171: Lung function: mean % change in FEV₁% predicted at 24 weeks follow-up (range of scores: 0-100)

			Colistin	Tobramycin		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
5.4.1 COLI DPI vs TOBI neb							
COLO/DPI/02/06	-0.59	2.23	153	181	0.0%	-0.59 [-4.96, 3.78]	
Schuster2013	0.99	0.02	153	171	100.0%	0.99 [0.95, 1.03]	
Subtotal (95% CI)			306	352	100.0%	0.99 [0.95, 1.03]	
Heterogeneity: Chi² = 0.50, df = 1 (P = 0.48); I² = 0%							
Test for overall effect: Z = 49.50 (P < 0.00001)							
Total (95% CI)			306	352	100.0%	0.99 [0.95, 1.03]	
Heterogeneity: Chi² = 0.50, df = 1 (P = 0.48); I² = 0%							
Test for overall effect: Z = 49.50 (P < 0.00001)							
Test for subgroup differences: Not applicable							

Favours tobramycin   Favours colistin

Abbreviations: CI: confidence interval; df: degrees of freedom; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; Neb: nebulised; SE: standard error

Figure 172: Time to next pulmonary exacerbation: time to first additional anti-pseudomonal treatment (days), at 24 weeks follow-up
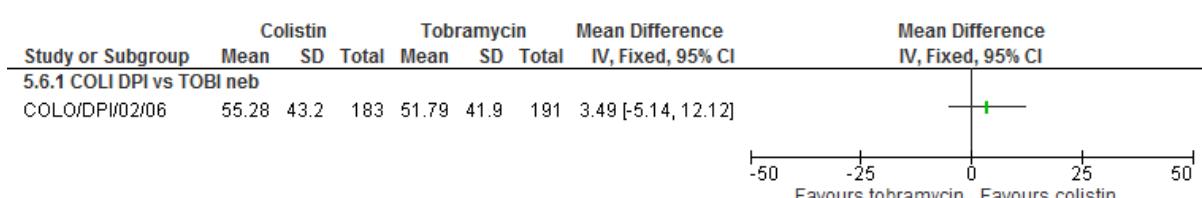
	Colistin			Tobramycin			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
5.6.1 COLI DPI vs TOBI neb								
COLO/DPI/02/06	55.28	43.2	183	51.79	41.9	191	3.49 [-5.14, 12.12]	

Favours tobramycin   Favours colistin

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 173: Suppression of the organism: change in sputum P. aeruginosa density Log10 CFU/ml, at 4 weeks follow-up
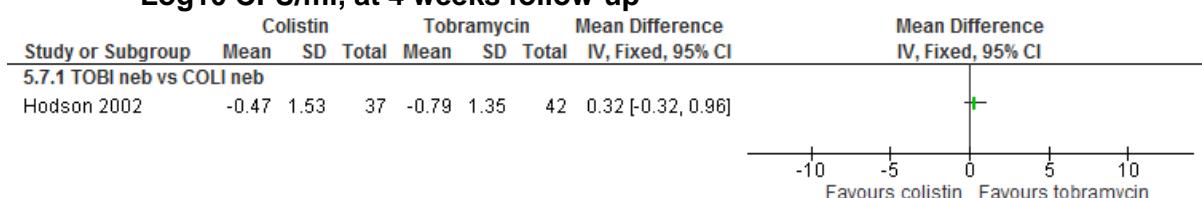
	Colistin			Tobramycin			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
5.7.1 TOBI neb vs COLI neb								
Hodson 2002	-0.47	1.53	37	-0.79	1.35	42	0.32 [-0.32, 0.96]	

Favours colistin   Favours tobramycin

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 174: Nutritional status: BMI change at 24 weeks follow-up
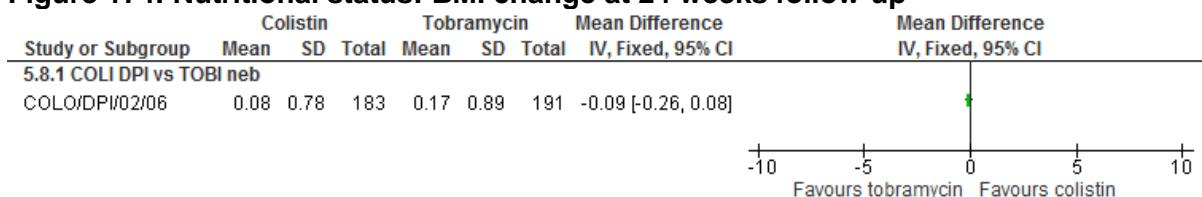
|	Colistin			Tobramycin			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
5.8.1 COLI DPI vs TOBI neb								
COLO/DPI/02/06	0.08	0.78	183	0.17	0.89	191	-0.09 [-0.26, 0.08]	

Favours tobramycin   Favours colistin

Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 175: Quality of life: CFQ-R all domains, at 24 weeks follow-up (range of scores: 0-100)

Data cannot be presented in forest plots, as SD are not reported.

Abbreviations: CFQ-R: cystic fibrosis questionnaire revised

**Figure 176: Mild adverse events: change in sputum, at 4 weeks follow-up**
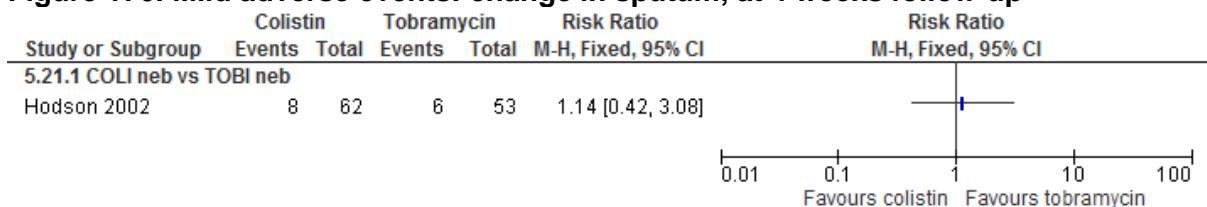
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

**Figure 177: Mild adverse events: pharyngitis, at 4 weeks follow-up**
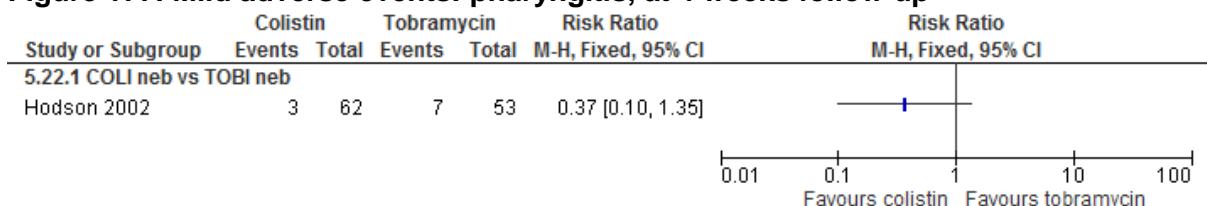
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

**Figure 178: Mild adverse events: cough, at 4 weeks follow-up**
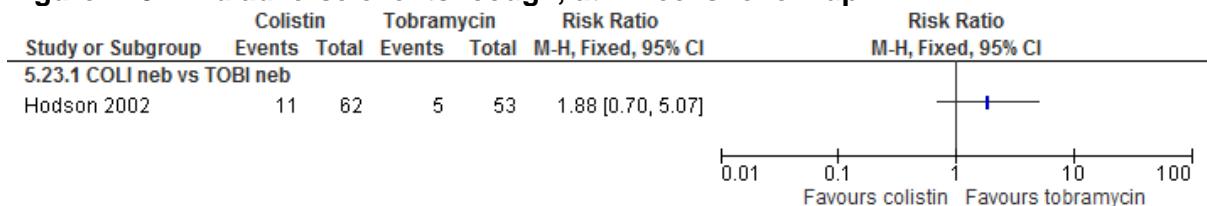

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 179: Mild adverse events: cough, at 24 weeks follow-up
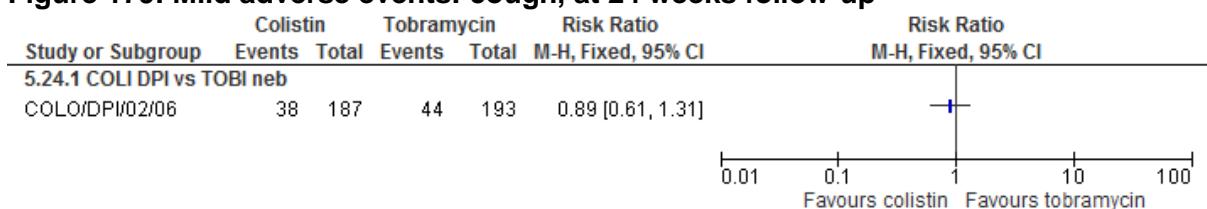
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 180: Mild adverse events: chest discomfort, at 24 weeks follow-up
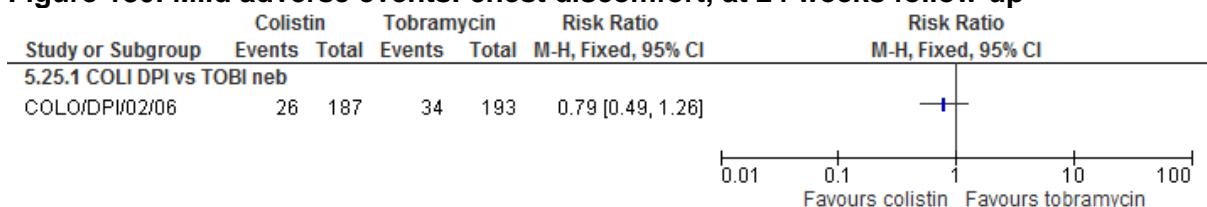
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 181: Mild adverse events: vomiting, at 24 weeks follow-up

Study or Subgroup	Colistin Events	Total	Tobramycin Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
5.26.1 COLI DPI vs TOBI neb						
COLO/DPI/02/06	6	187	8	193	0.77 [0.27, 2.19]	
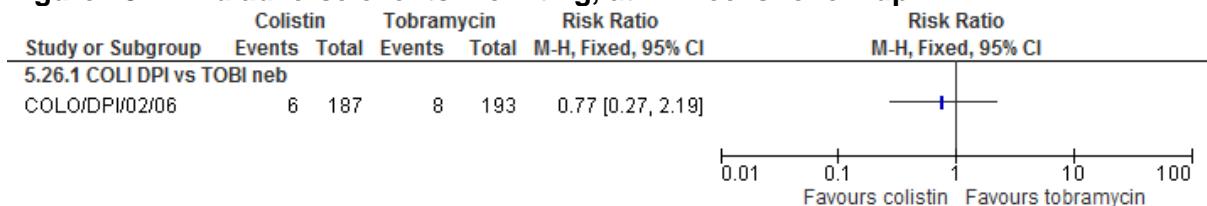
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 182: Serious adverse events: patients with > 1 serious AE, at 4 weeks follow-up

Study or Subgroup	Colistin Events	Total	Tobramycin Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
5.27.1 COLI neb vs TOBI neb						
Hodson 2002	7	62	8	53	0.75 [0.29, 1.93]	
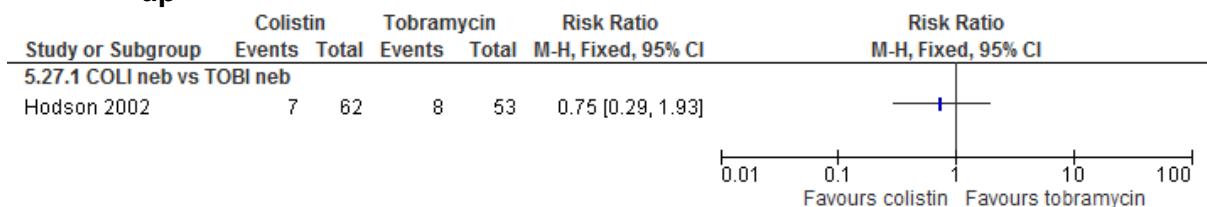
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 183: Serious adverse events: dyspnoea, at 4 weeks follow-up

Study or Subgroup	Colistin Events	Total	Tobramycin Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
5.28.1 COLI neb vs TOBI neb						
Hodson 2002	7	62	5	53	1.20 [0.40, 3.55]	
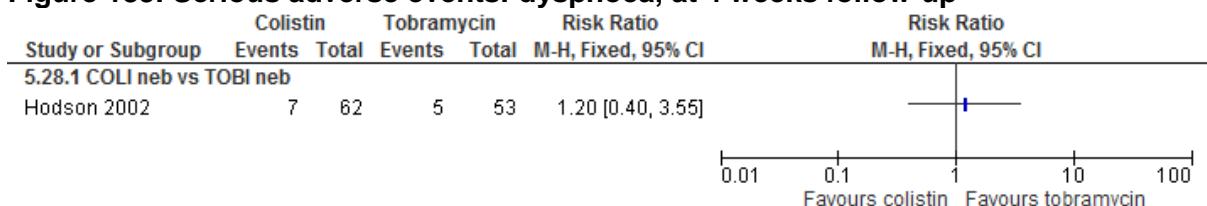
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 184: Serious adverse events: dyspnoea, at 24 weeks follow-up

| Study or Subgroup	Colistin Events	Total	Tobramycin Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
5.29.1 COLI DPI vs TOBI neb						
COLO/DPI/02/06	49	187	52	193	0.97 [0.70, 1.36]	
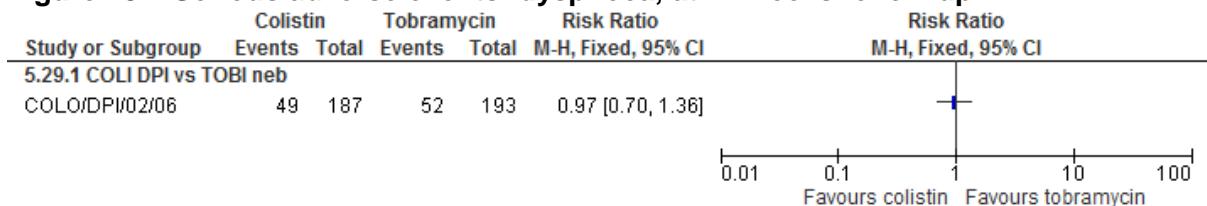
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 185: Serious adverse events: patients withdrawn, at 24 weeks follow-up

| Study or Subgroup	Colistin Events	Total	Tobramycin Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
5.30.1 COLI DPI vs TOBI neb						
COLO/DPI/02/06	22	187	5	193	4.54 [1.76, 11.74]	
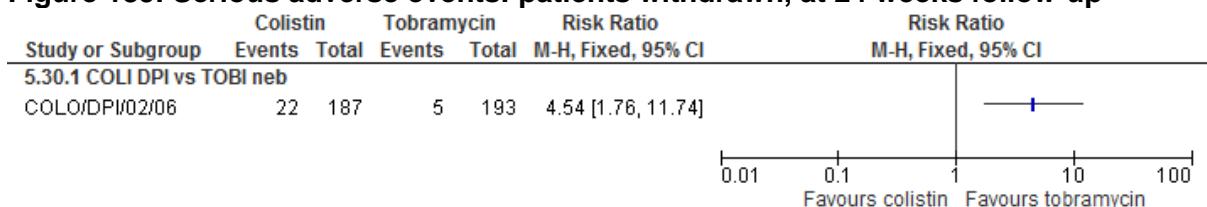
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 186: Serious adverse events: haemoptysis, at 24 weeks follow-up
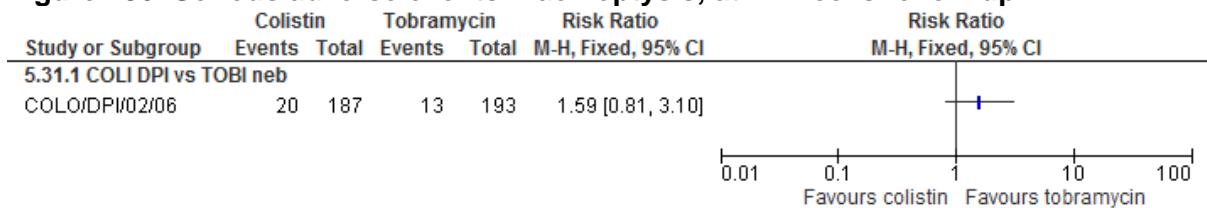
*Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel*

Figure 187: Emergence of resistant organisms: emergence of highly tobramycin-resistant P. Aeruginosa at 4 weeks follow-up
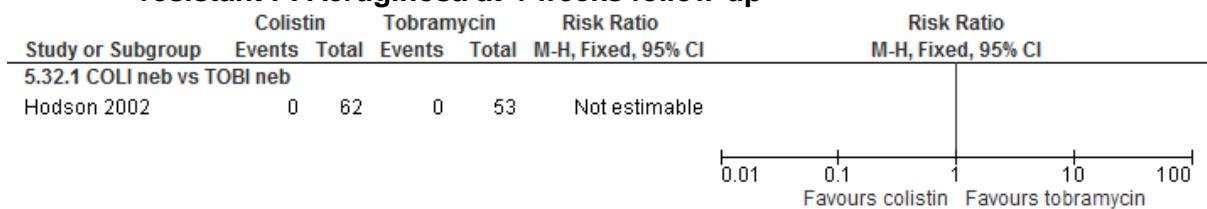
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel. Data cannot be plotted, as there were 0 events in each group.

Pairwise comparison 4.1. Tobramycin *versus* placebo

Figure 188: Lung function: mean % change in FEV$_1$% predicted at 1 to 3 months follow-up (range of scores: 0-100)
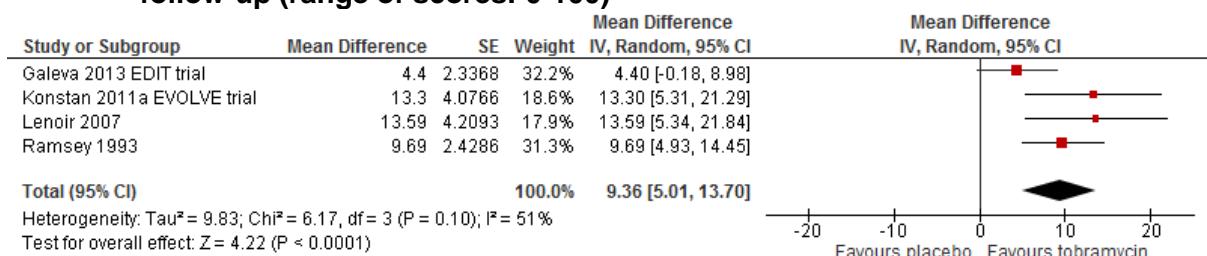

Abbreviations: CI: confidence interval; df: degrees of freedom; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SE: standard error

Figure 189: Suppression of the organism: eradication of the organism at 4, 6, 12, 8, 20 and 24 weeks follow-up
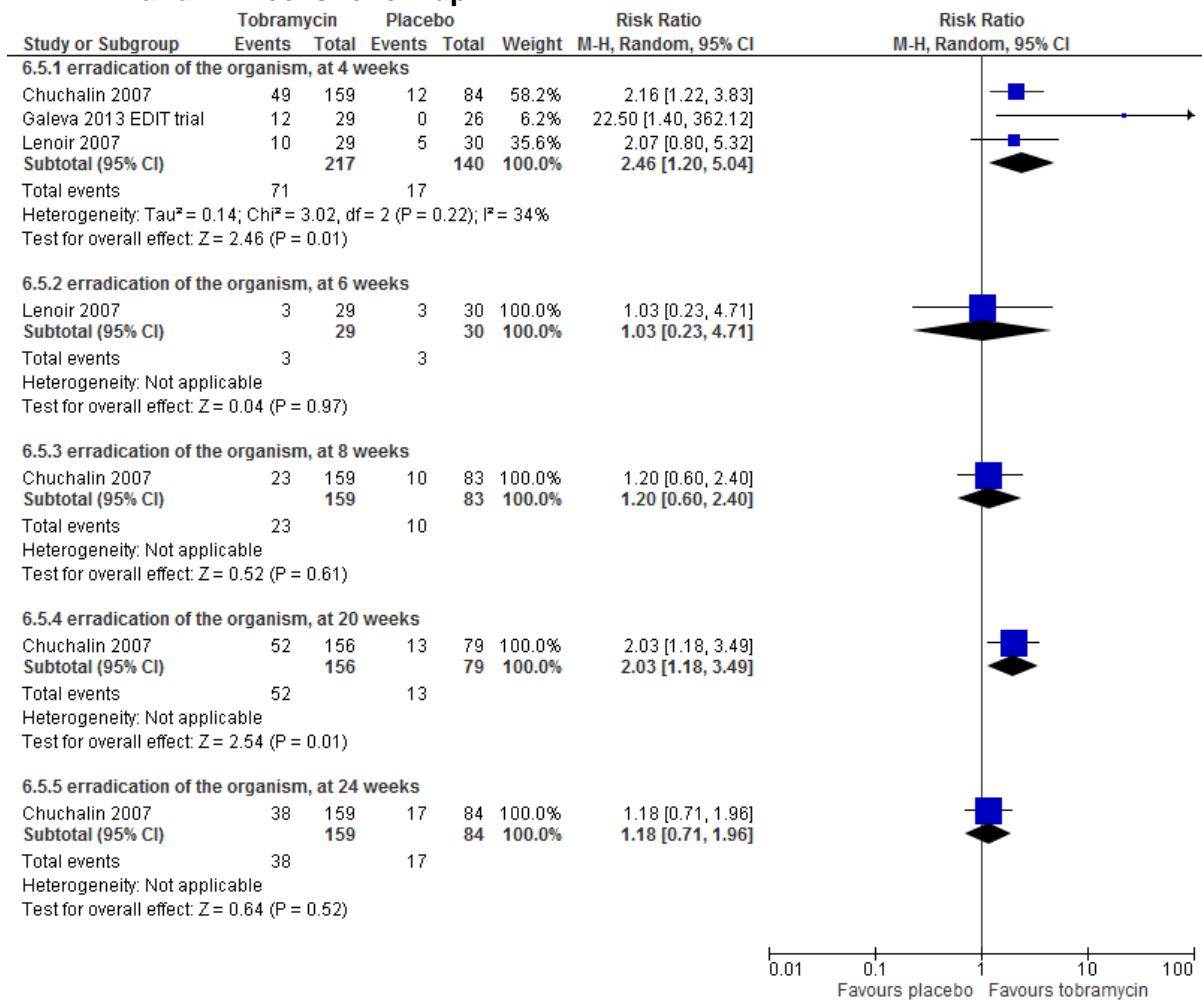

Abbreviations: CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel

Figure 190: Suppression of the organism: change in P. aeruginosa sputum density log10 CFU/G, at 4 weeks follow-up
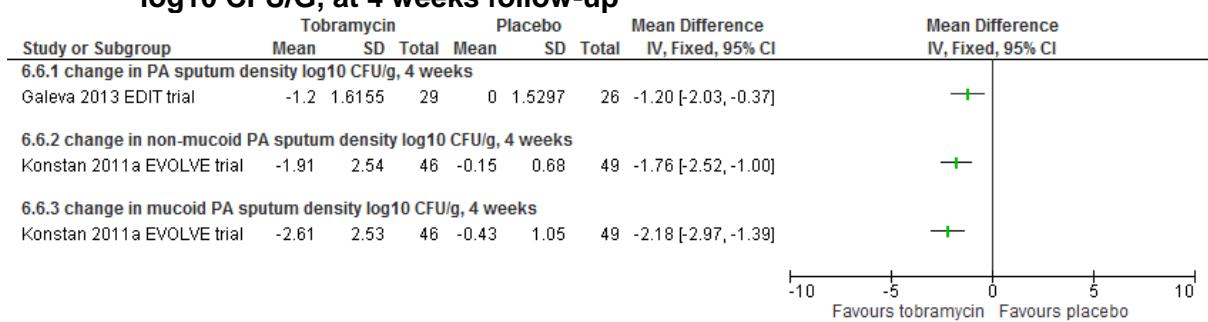

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

### Figure 191: Nutrition: bodyweight change (kg), at 12 and 24 weeks follow-up

	Tobramycin			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
6.6.1 weight change at 12 weeks								
Lenoir 2007	0.39	0.9	29	0.16	0.9	30	0.23 [-0.23, 0.69]	
6.6.2 weight change at 24 weeks								
Chuchalin 2007	1.8	1.93	161	1.05	2.07	84	0.75 [0.22, 1.28]	

Abbreviations: CI: confidence interval; IV: inverse variance; kg: kilograms; SD: standard deviation

### Figure 192: Mild adverse events, at 4, 24 and 42 weeks follow-up

	Tobramycin		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
6.9.1 minor AE (any), at 4 weeks							
Galeva 2013 EDIT trial	8	29	11	26	16.6%	0.65 [0.31, 1.37]	
Konstan 2011a EVOLVE trial	23	46	37	49	83.4%	0.66 [0.48, 0.92]	
Subtotal (95% CI)		75		75	100.0%	0.66 [0.49, 0.89]	
Total events	31		48				
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%							
Test for overall effect: Z = 2.70 (P = 0.007)							
6.9.2 minor AE (any), at 24 weeks							
Chuchalin 2007	25	161	13	85	100.0%	1.02 [0.55, 1.88]	
Subtotal (95% CI)		161		85	100.0%	1.02 [0.55, 1.88]	
Total events	25		13				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.05 (P = 0.96)							
6.9.3 auditory impairment, at 4 weeks							
Galeva 2013 EDIT trial	3	29	2	26	100.0%	1.34 [0.24, 7.43]	
Subtotal (95% CI)		29		26	100.0%	1.34 [0.24, 7.43]	
Total events	3		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.34 (P = 0.73)							
6.9.4 auditory impairment, at 24 weeks							
Ramsey 1999	0	152	0	148		Not estimable	
Subtotal (95% CI)		152		148		Not estimable	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
6.9.5 auditory impairment, at 42 weeks							
Ramsey 1993	0	36	0	35		Not estimable	
Subtotal (95% CI)		36		35		Not estimable	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
6.9.6 cough, at 4 weeks							
Galeva 2013 EDIT trial	5	29	0	26	40.6%	9.90 [0.57, 170.81]	
Konstan 2011a EVOLVE trial	6	46	13	49	59.4%	0.49 [0.20, 1.18]	
Subtotal (95% CI)		75		75	100.0%	1.67 [0.08, 36.11]	
Total events	11		13				
Heterogeneity: Tau² = 3.95; Chi² = 4.41, df = 1 (P = 0.04); I² = 77%							
Test for overall effect: Z = 0.33 (P = 0.75)							
6.9.7 tinnitus, at 24 weeks							
Ramsey 1999	8	258	0	262	100.0%	17.26 [1.00, 297.54]	
Subtotal (95% CI)		258		262	100.0%	17.26 [1.00, 297.54]	
Total events	8		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.96 (P = 0.05)							
6.9.9 headache, at 4 weeks							
Konstan 2011a EVOLVE trial	1	46	3	49	100.0%	0.36 [0.04, 3.29]	
Subtotal (95% CI)		46		49	100.0%	0.36 [0.04, 3.29]	
Total events	1		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.91 (P = 0.36)							

Abbreviations: CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel

Figure 193: Serious adverse events, at 24 weeks follow-up


Abbreviations: CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel

Figure 194: Mortality, at up to 12 months follow-up

*Abbreviations: CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel*

Figure 195: Emergence of resistant organisms, at 24 weeks follow-up
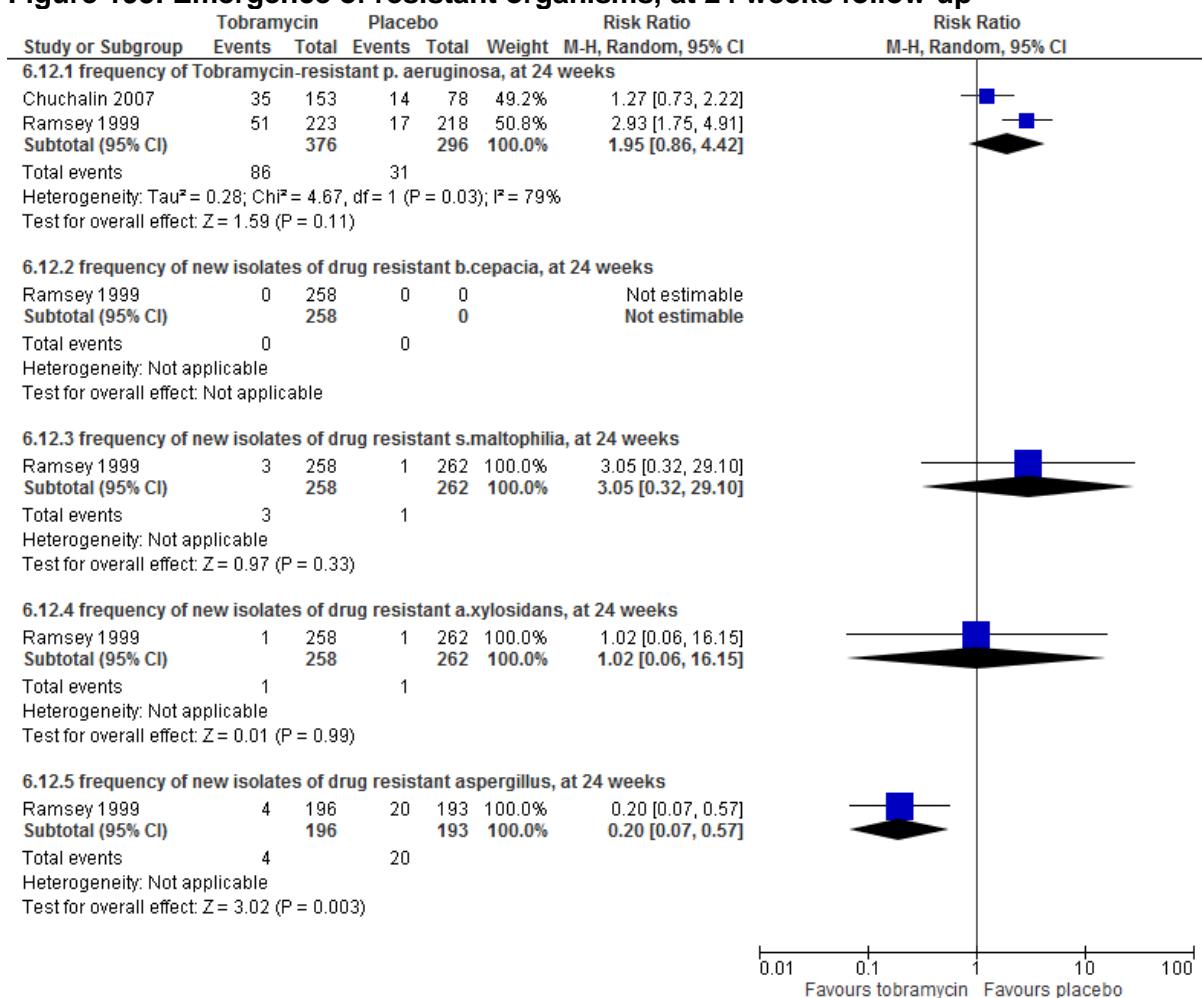
Abbreviations: CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel

Pairwise comparison 4.2. Tobramycin inhalation powder (TOBI DPI) *versus* **tobramycin inhalation solution (TOBI nebulised)**

Figure 196: Lung function: mean change in FEV$_1$% predicted at 4, 20 and 24 weeks follow-up (range of scores: 0-100)
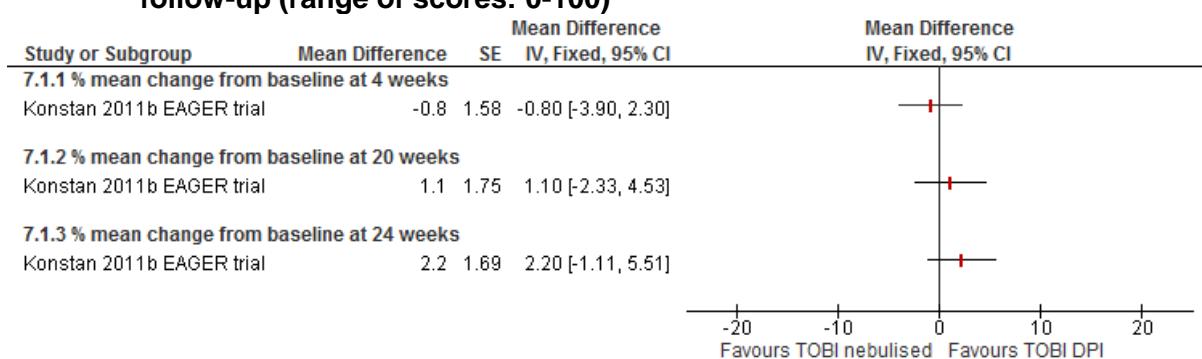
Abbreviations: CI: confidence interval; DPI: dry powder inhalation; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SE: standard error; TOBI: tobramycin

Figure 197: Suppression of the organism: mean change in P. aeruginosa sputum density log10 CFU, at 4 to 20 weeks follow-up
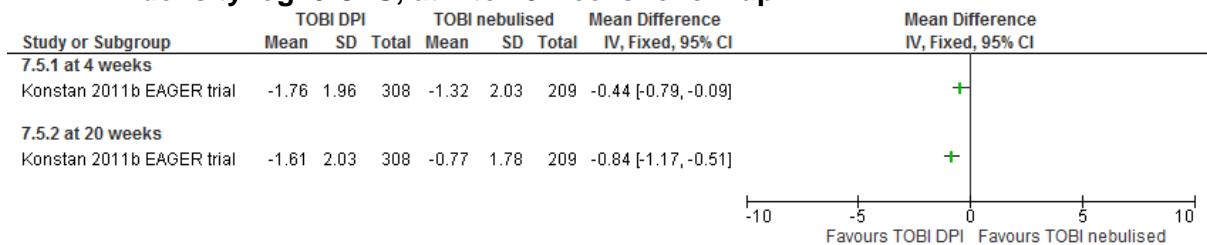
Study or Subgroup	TOBI DPI			TOBI nebulised			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
7.5.1 at 4 weeks								
Konstan 2011b EAGER trial	-1.76	1.96	308	-1.32	2.03	209	-0.44 [-0.79, -0.09]	
7.5.2 at 20 weeks								
Konstan 2011b EAGER trial	-1.61	2.03	308	-0.77	1.78	209	-0.84 [-1.17, -0.51]	

Favours TOBI DPI   Favours TOBI nebulised (scale: -10, -5, 0, 5, 10)

Abbreviations: CI: confidence interval; DPI: dry powder inhalation; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; PA: Pseudomonas aeruginosa; SD: standard deviation; TOBI: tobramycin

Figure 198: Mild adverse events, at 24 weeks follow-up
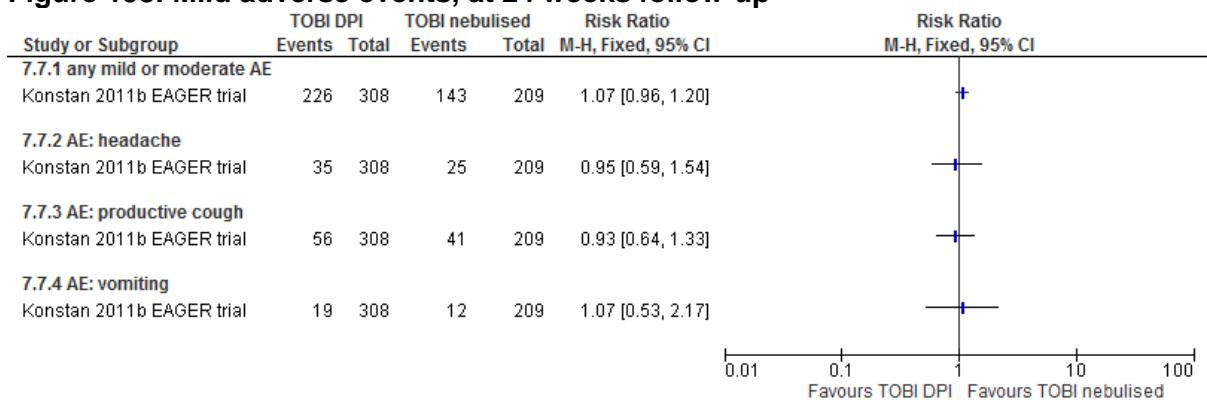
Study or Subgroup	TOBI DPI		TOBI nebulised		Risk Ratio	Risk Ratio
	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
7.7.1 any mild or moderate AE						
Konstan 2011b EAGER trial	226	308	143	209	1.07 [0.96, 1.20]	
7.7.2 AE: headache						
Konstan 2011b EAGER trial	35	308	25	209	0.95 [0.59, 1.54]	
7.7.3 AE: productive cough						
Konstan 2011b EAGER trial	56	308	41	209	0.93 [0.64, 1.33]	
7.7.4 AE: vomiting						
Konstan 2011b EAGER trial	19	308	12	209	1.07 [0.53, 2.17]	

Favours TOBI DPI   Favours TOBI nebulised (scale: 0.01, 0.1, 1, 10, 100)

Abbreviations: CI: confidence interval; DPI: dry powder inhalation; M-H: Mantel-Haenszel; TOBI: tobramycin

Figure 199: Serious adverse events, at 24 weeks follow-up
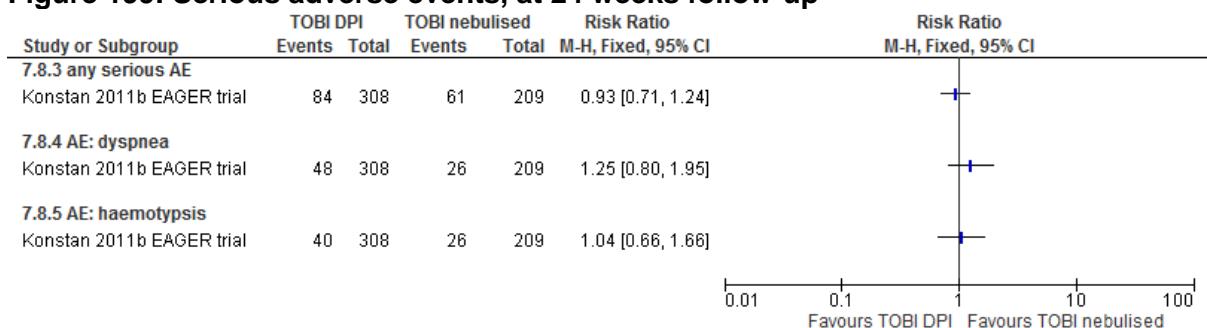
Study or Subgroup	TOBI DPI		TOBI nebulised		Risk Ratio	Risk Ratio
	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
7.8.3 any serious AE						
Konstan 2011b EAGER trial	84	308	61	209	0.93 [0.71, 1.24]	
7.8.4 AE: dyspnea						
Konstan 2011b EAGER trial	48	308	26	209	1.25 [0.80, 1.95]	
7.8.5 AE: haemotypsis						
Konstan 2011b EAGER trial	40	308	26	209	1.04 [0.66, 1.66]	

Favours TOBI DPI   Favours TOBI nebulised (scale: 0.01, 0.1, 1, 10, 100)

Abbreviations: CI: confidence interval; DPI: dry powder inhalation; M-H: Mantel-Haenszel; TOBI: tobramycin

Pairwise comparison 4.3. Tobramycin *versus* Aztreonam lysine

Figure 200: Lung function: % change in FEV₁% predicted at 3 months follow-up (range of scores: 0-100)
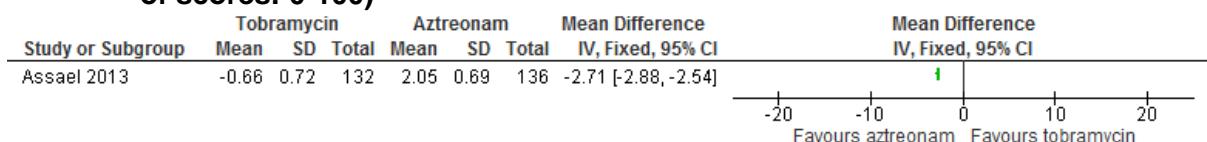
Study or Subgroup	Tobramycin			Aztreonam			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Assael 2013	-0.66	0.72	132	2.05	0.69	136	-2.71 [-2.88, -2.54]	

*Favours aztreonam   Favours tobramycin* (scale: -20, -10, 0, 10, 20)

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation. Calculated across 3x28-day treatment courses

Figure 201: Suppression of the organism: adj mean change sputum density log10 PA CFU/G, at 20 weeks follow-up

	Tobramycin			Aztreonam			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
8.4.1 TOBI neb vs AZLI								
Assael 2013	-0.32	1.8713	97	-0.55	1.8713	97	0.23 [-0.30, 0.76]	

Favours tobramycin   Favours aztreonam
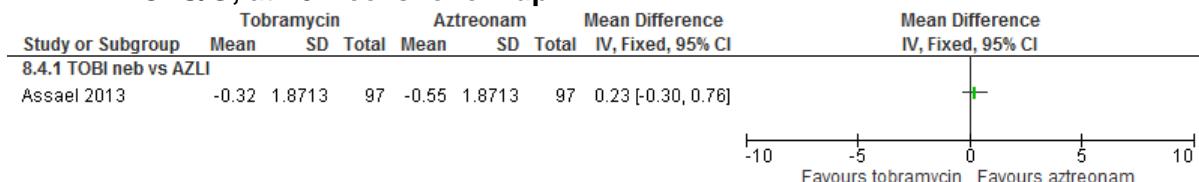
Abbreviations: CI: confidence interval; CFU: colony forming unit; IV: inverse variance; PA: Pseudomonas aeruginosa; SD: standard deviation

Figure 202: Nutritional status: % adj mean weight change (kg), at 24 weeks follow-up
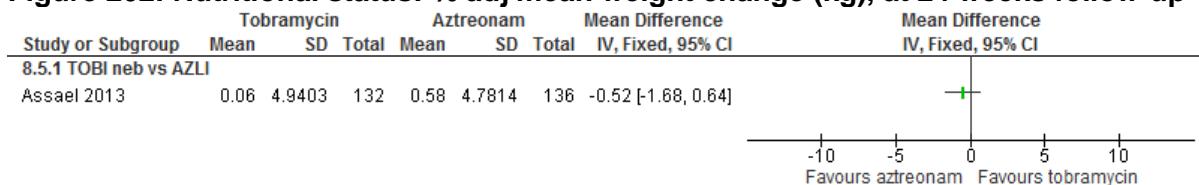
	Tobramycin			Aztreonam			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
8.5.1 TOBI neb vs AZLI								
Assael 2013	0.06	4.9403	132	0.58	4.7814	136	-0.52 [-1.68, 0.64]	

Favours aztreonam   Favours tobramycin

Abbreviations: CI: confidence interval; ; IV: inverse variance; kg: kilograms; SD: standard deviation

Figure 203: Quality of life: CFQ-R respiratory, adj mean change, at 20 weeks follow-up (range of scores: 0-100)
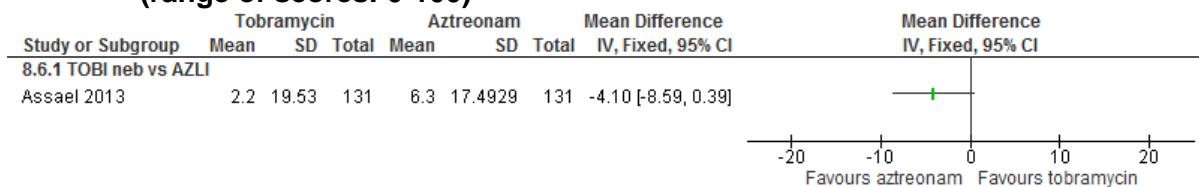
	Tobramycin			Aztreonam			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
8.6.1 TOBI neb vs AZLI								
Assael 2013	2.2	19.53	131	6.3	17.4929	131	-4.10 [-8.59, 0.39]	

Favours aztreonam   Favours tobramycin

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Figure 204: Mild adverse events: chest discomfort, at 3 months follow-up

	Tobramycin		Aztreonam		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
8.7.1 TOBI neb vs AZLI						
Assael 2013	13	132	14	136	0.96 [0.47, 1.96]	

Favours tobramycin   Favours aztreonam
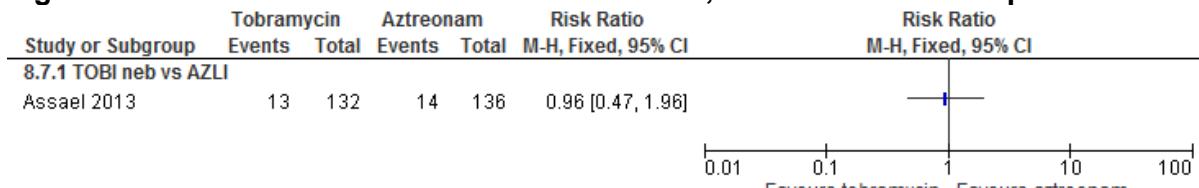
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 205: Mild adverse events: cough, at 3 months follow-up

|	Tobramycin		Aztreonam		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
8.8.1 TOBI neb vs AZLI						
Assael 2013	104	132	96	136	1.12 [0.97, 1.28]	

Favours tobramycin   Favours aztreonam
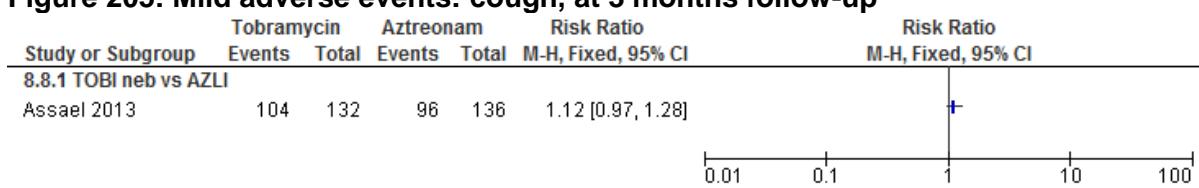
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 206: Mild adverse events: headache, at 3 months follow-up

Study or Subgroup	Tobramycin Events	Total	Aztreonam Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
8.9.1 TOBI neb vs AZLI						
Assael 2013	27	132	29	136	0.96 [0.60, 1.53]	

Favours tobramycin — Favours aztreonam (0.01, 0.1, 1, 10, 100)
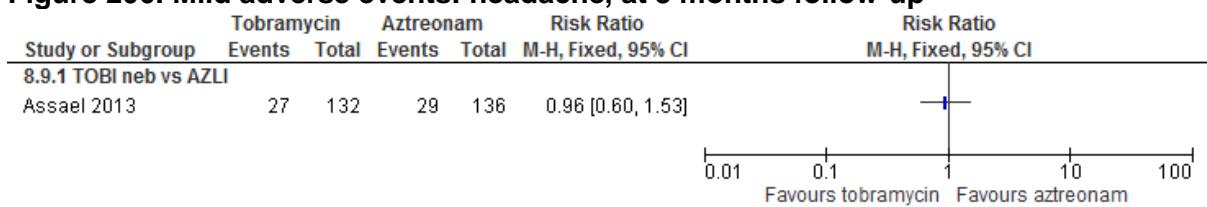
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 207: Mild adverse events: vomiting, at 3 months follow-up

Study or Subgroup	Tobramycin Events	Total	Aztreonam Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
8.10.1 TOBI neb vs AZLI						
Assael 2013	14	132	14	136	1.03 [0.51, 2.08]	

Favours tobramycin — Favours aztreonam (0.01, 0.1, 1, 10, 100)
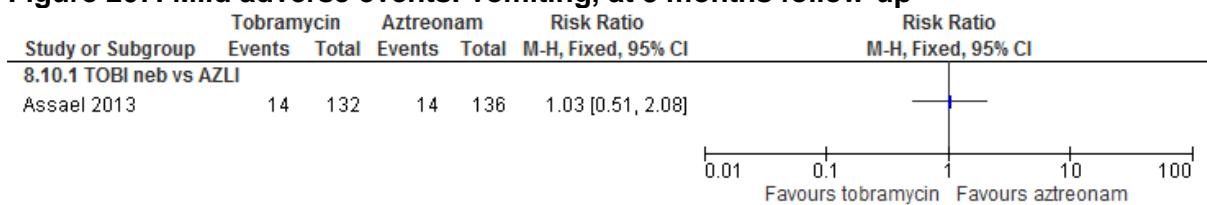
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 208: Serious adverse events: dyspnoea, at 3 months follow-up

Study or Subgroup	Tobramycin Events	Total	Aztreonam Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
8.13.1 TOBI neb vs AZLI						
Assael 2013	21	132	31	136	0.70 [0.42, 1.15]	

Favours tobramycin — Favours aztreonam (0.01, 0.1, 1, 10, 100)
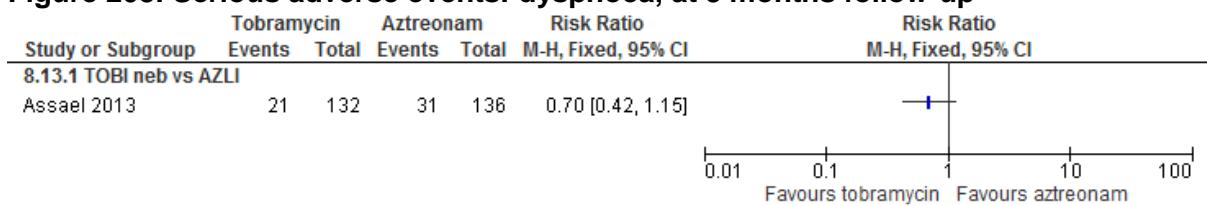
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 209: Serious adverse events: haemoptysis, at 3 months follow-up

Study or Subgroup	Tobramycin Events	Total	Aztreonam Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
8.14.1 TOBI neb vs AZLI						
Assael 2013	21	132	31	136	0.70 [0.42, 1.15]	

Favours tobramycin — Favours aztreonam (0.01, 0.1, 1, 10, 100)
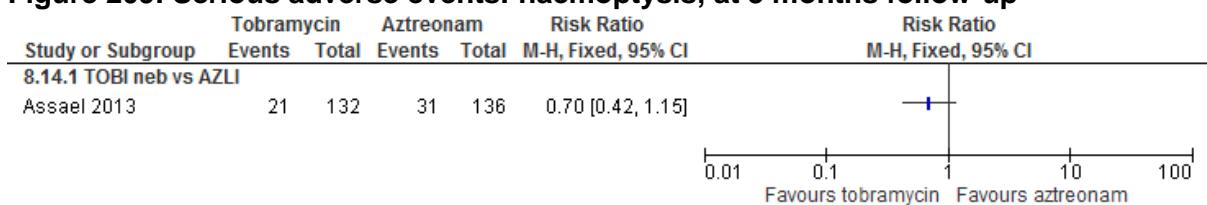
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Pairwise comparison 5. Combination of fosfomycin + tobramycin *versus* placebo

Figure 210: Lung function: relative change in FEV_1% predicted, at 4 weeks follow-up (range of scores: 0-100)

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
9.1.1 FTI 80/20 mg				
Trapnell 2012	7.5	1.99	7.50 [3.60, 11.40]	
9.1.2 FTI 160/40 mg				
Trapnell 2012	6.2	1.93	6.20 [2.42, 9.98]	

Favours placebo — Favours fosfo+TOBI (-20, -10, 0, 10, 20)
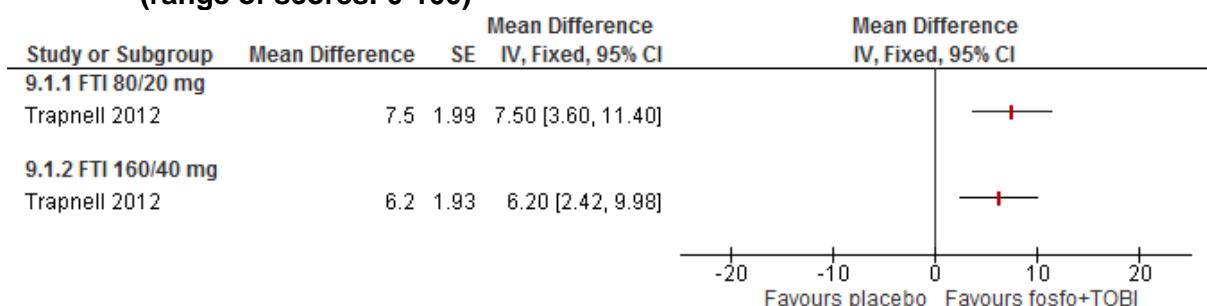
Abbreviations: Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; fosfo+TOBI: fosfomycin + tobramycin; IV: inverse variance; SE: standard error

Figure 211: Suppression of the organism: sputum PA density, log 10 CFU/g at 4 weeks follow-up

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI
9.2.1 FTI 80/20 mg			
Trapnell 2012	-1.04	0.4	-1.04 [-1.82, -0.26]
9.2.3 FTI 160/40 mg			
Trapnell 2012	-0.28	0.4	-0.28 [-1.06, 0.50]

Favours fosfo+TOBI Favours placebo
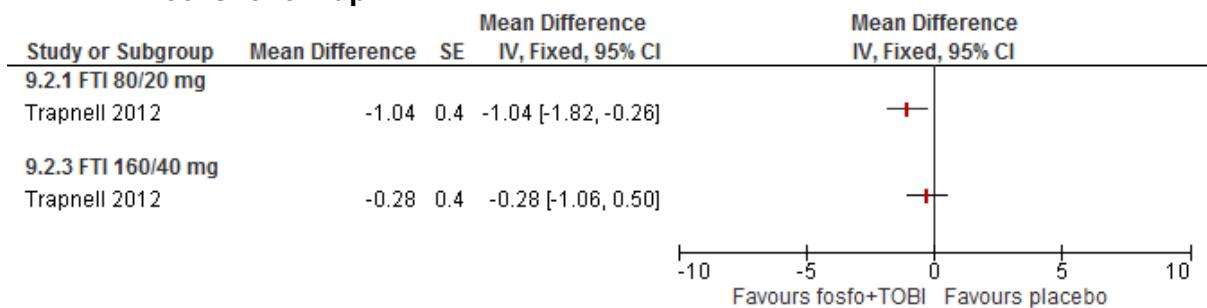
Abbreviations: fosfo+TOBI: fosfomycin + tobramycin; SE: standard error; IV: inverse variance; CI: confidence interval

Pairwise comparison 6. Continuous alternating therapy *versus* intermittent treatment: aztreonam lysine + tobramycin or placebo + tobramycin

Figure 212: Lung function: % change in FEV$_1$% predicted (values at 4 ,12 and 20 weeks were averaged) (range of scores: 0-100)
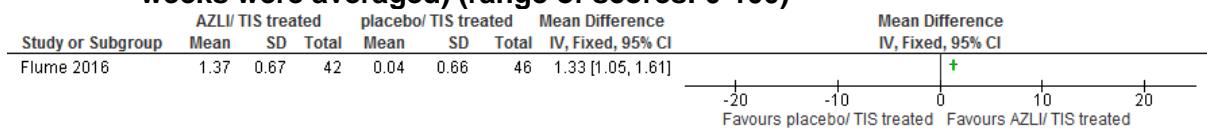
Study or Subgroup	AZLI/ TIS treated Mean	SD	Total	placebo/ TIS treated Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Flume 2016	1.37	0.67	42	0.04	0.66	46	1.33 [1.05, 1.61]

Favours placebo/ TIS treated Favours AZLI/ TIS treated

Abbreviations: AZLI: aztreonam lysine; CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation; TIS: tobramycin inhaled solution

Figure 213: Time to next pulmonary exacerbation
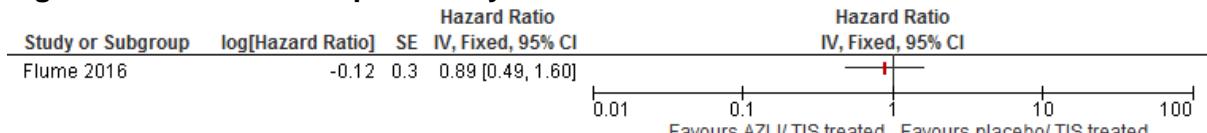
Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
Flume 2016	-0.12	0.3	0.89 [0.49, 1.60]

Favours AZLI/ TIS treated Favours placebo/ TIS treated

Abbreviations: AZLI: aztreonam lysine; CI: confidence interval; IV: inverse variance; SE: standard error; TIS: tobramycin inhaled solution

Figure 214: Quality of life: change in CFQ-R (scores were averaged from weeks 4, 12 and 20) (range of scores: 0-100)
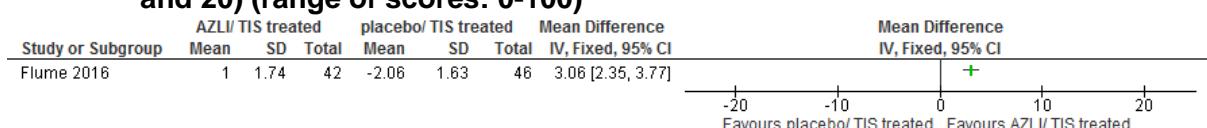
Study or Subgroup	AZLI/ TIS treated Mean	SD	Total	placebo/ TIS treated Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Flume 2016	1	1.74	42	-2.06	1.63	46	3.06 [2.35, 3.77]

Favours placebo/ TIS treated Favours AZLI/ TIS treated

Abbreviations: AZLI: aztreonam lysine; CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation; TIS: tobramycin inhaled solution

Figure 215: Adverse events at 3 months follow-up

Study or Subgroup	AZLI/ TIS treated Events	Total	placebo/ TIS treated Events	Total	Risk Ratio M-H, Fixed, 95% CI
10.6.1 cough					
Flume 2016	32	42	20	46	1.75 [1.21, 2.54]
10.6.2 dyspnea					
Flume 2016	13	42	24	46	0.59 [0.35, 1.01]
10.6.3 serious adverse events (not treatment related)					
Flume 2016	21	42	24	46	0.96 [0.64, 1.44]

Favours AZLI/ TIS treated Favours placebo/ TIS treated
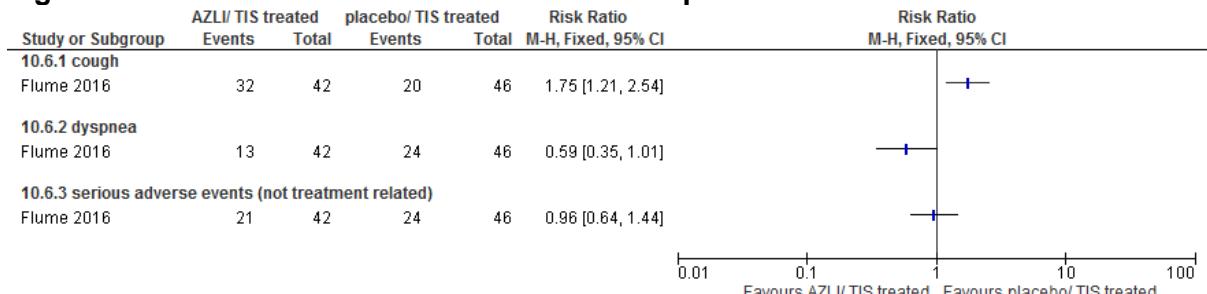
Abbreviations: AZLI: aztreonam lysine; CI: confidence interval; M-H: Mantel-Haenszel; TIS: tobramycin inhaled solution

I.11.2 Staphylococcus Aureus

Not applicable, as no relevant studies were identified.

I.11.3 Burkholderia Cepacia Complex

Not applicable, as no relevant studies were identified.

I.11.4 Aspergillus Fumigatus

Pairwise comparison 7: Itraconazole *versus* placebo

Figure 216: Percentage change in FEV$_1$ from baseline at 24 and 48 weeks follow-up (range of scores: 0-100)
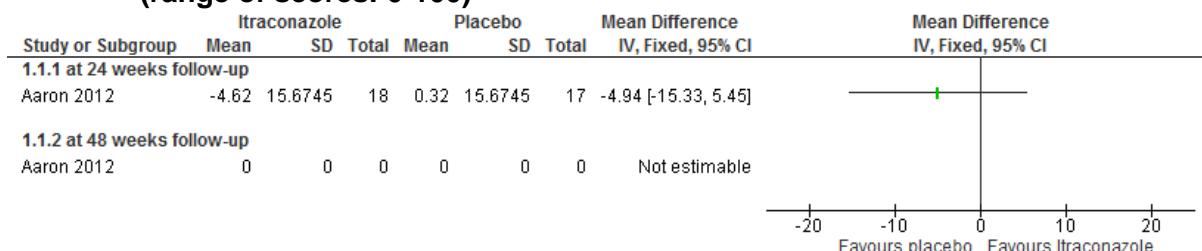

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation. Mean difference (95% CI) at 48-weeks follow-up: -3.71% (-13.26 to 20.28). Not enough data was provided for RevMan.

Figure 217: Time to next pulmonary exacerbation at 24 weeks
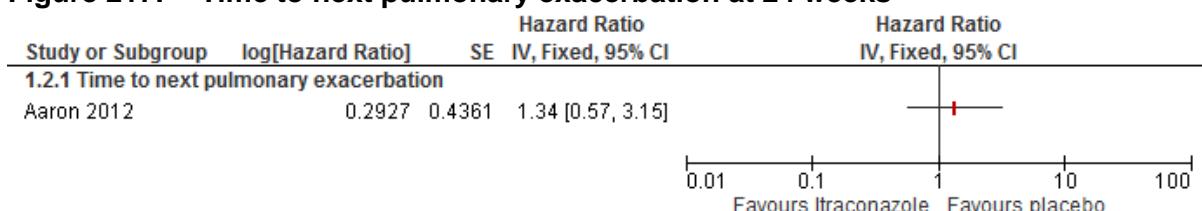
Abbreviations: CI: confidence interval; IV: inverse variance; SE: standard error

Figure 218: Number of pulmonary exacerbations requiring AB or hospitalization, at 24 and 48 weeks follow-up
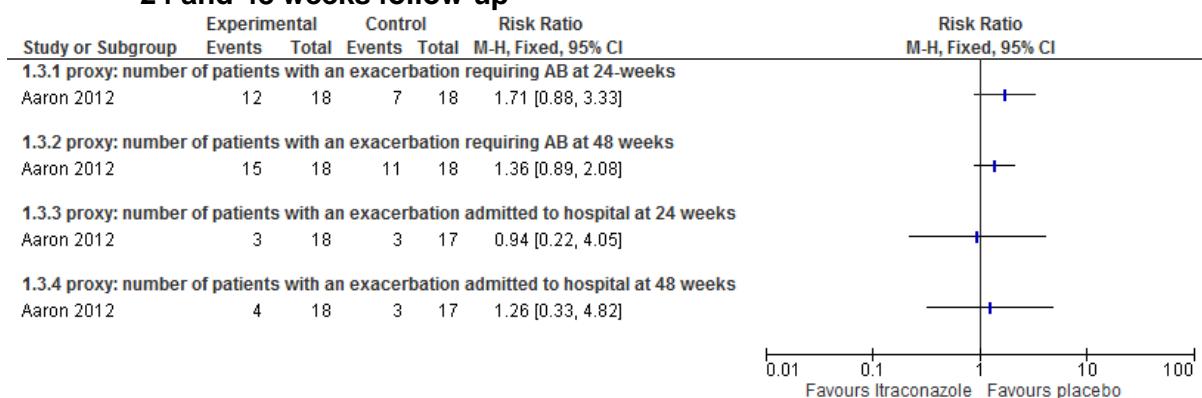
Abbreviations: AB: antibiotics; CI: confidence interval; M-H: Mantel-Haenszel. Proxy outcome.

Figure 219: Quality of life
Data could not be plotted.

Figure 220: **Number of people experiencing minor adverse events at 24 weeks follow-up**

Study or Subgroup	Itraconazole Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
1.7.1 increased dyspnea					
Aaron 2012	2	18	2	16	0.89 [0.14, 5.60]
1.7.2 rash					
Aaron 2012	2	18	1	16	1.78 [0.18, 17.80]
1.7.4 hyperglycaemia					
Aaron 2012	1	18	0	16	2.68 [0.12, 61.58]
1.7.5 flu-like illness					
Aaron 2012	3	18	0	16	6.26 [0.35, 112.70]
1.7.6 diarrhea					
Aaron 2012	0	18	1	16	0.30 [0.01, 6.84]
1.7.7 conjunctivitis					
Aaron 2012	0	18	1	16	0.30 [0.01, 6.84]
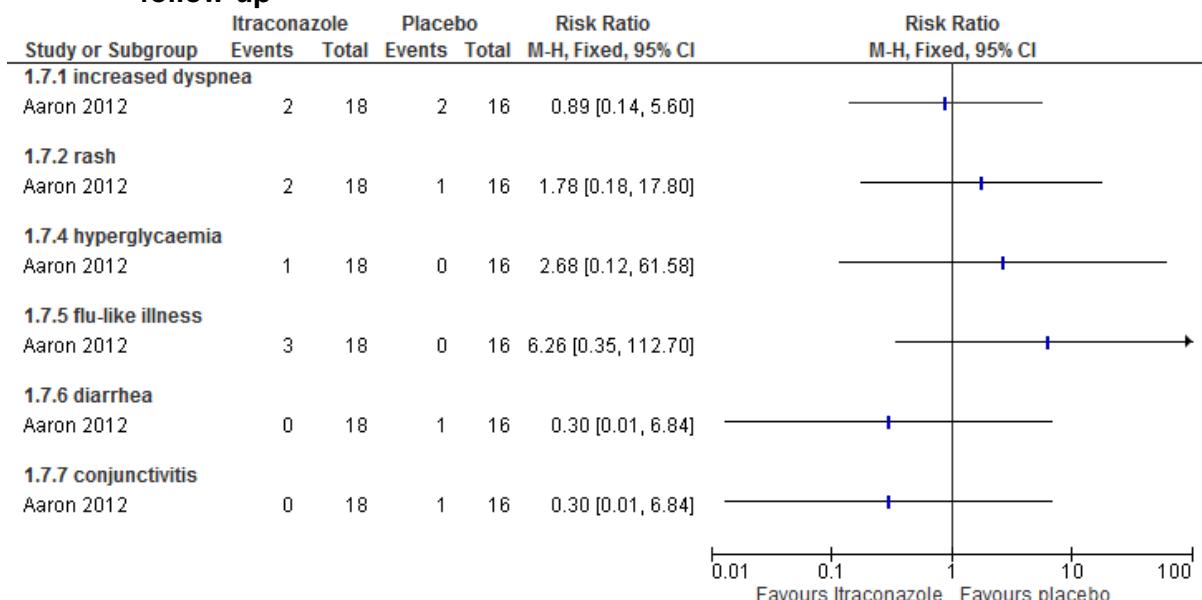
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 221: **Number of people experiencing major adverse events at 24 weeks follow-up**

Study or Subgroup	Experimental Events	Total	Control Events	Total	Risk Ratio M-H, Fixed, 95% CI
1.8.1 spontaneous pneumothorax					
Aaron 2012	1	18	0	17	2.84 [0.12, 65.34]
1.8.3 hemoptysis					
Aaron 2012	2	18	1	16	1.78 [0.18, 17.80]
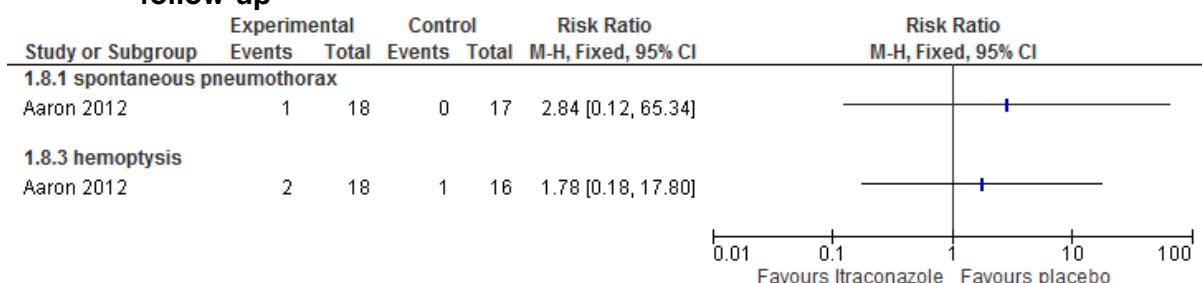
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

I.12 Immunomodulatory agents

I.12.1 NMA outcomes

Pairwise comparison from NMA. Macrolide antibiotics *versus* placebo

Figure 222: **Rate of exacerbations after short-term (1-10 month) treatment**
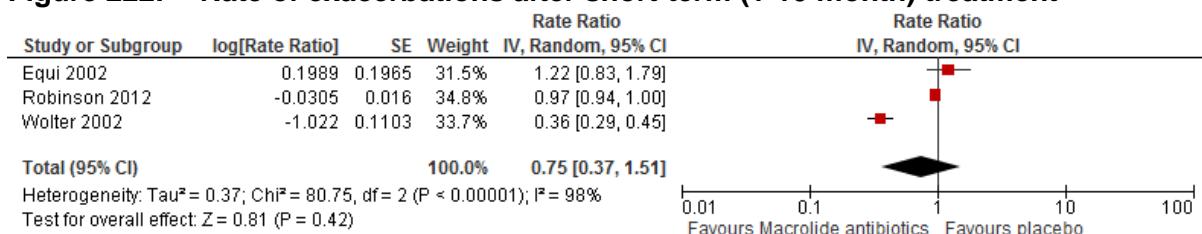
Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
Equi 2002	0.1989	0.1965	31.5%	1.22 [0.83, 1.79]
Robinson 2012	-0.0305	0.016	34.8%	0.97 [0.94, 1.00]
Wolter 2002	-1.022	0.1103	33.7%	0.36 [0.29, 0.45]
Total (95% CI)			**100.0%**	**0.75 [0.37, 1.51]**

Heterogeneity: Tau² = 0.37; Chi² = 80.75, df = 2 (P < 0.00001); I² = 98%
Test for overall effect: Z = 0.81 (P = 0.42)

Abbreviations: CI: confidence interval; df: degrees of freedom; IV: inverse variance; SE: standard error

I.12.2 Non-NMA outcomes (pairwise comparisons)

Pairwise comparison 1. Fluticasone *versus* placebo

**Figure 223:** **Time to next exacerbation at 8 months follow-up**

			Hazard Ratio	Hazard Ratio
			IV, Fixed, 95% CI	IV, Fixed, 95% CI
Study or Subgroup	log[Hazard Ratio]	SE	IV, Fixed, 95% CI	
Balfour-Lynn 2006	0.0677	0.2313	1.07 [0.68, 1.68]	

Favours Fluticasone Favours Placebo
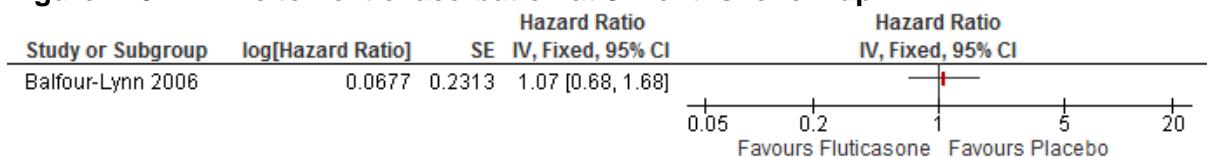
Abbreviations: CI: confidence interval; IV: inverse variance; SE: standard error

Figure 224: **Change in height (height standard deviation score) at 0 to 12 months follow-up**
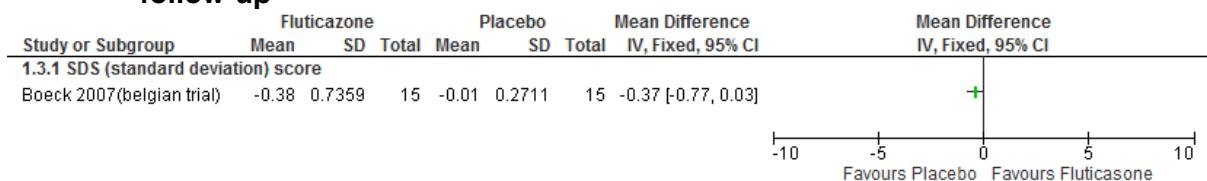
	Fluticazone			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.3.1 SDS (standard deviation) score								
Boeck 2007(belgian trial)	-0.38	0.7359	15	-0.01	0.2711	15	-0.37 [-0.77, 0.03]	

Favours Placebo Favours Fluticasone

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 225: **Change in height (cm) at 8 months follow-up**
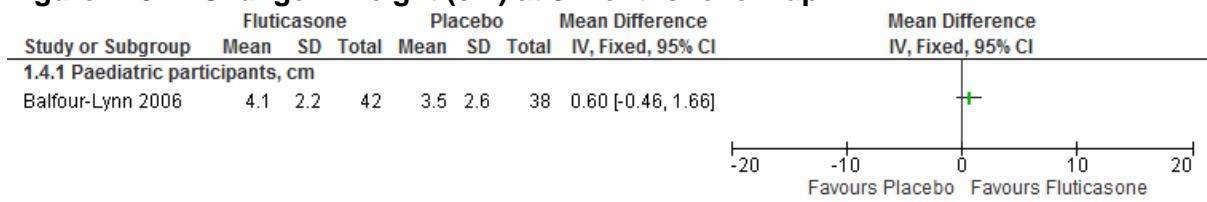
	Fluticasone			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.4.1 Paediatric participants, cm								
Balfour-Lynn 2006	4.1	2.2	42	3.5	2.6	38	0.60 [-0.46, 1.66]	

Favours Placebo Favours Fluticasone

Abbreviations: CI: confidence interval; cm: centimetres; IV: inverse variance; SD: standard deviation

Pairwise comparison 2. Prednisone/ Prednisolone *versus* placebo

Figure 226: **Absolute change in weight (kg) at 12 weeks follow-up**
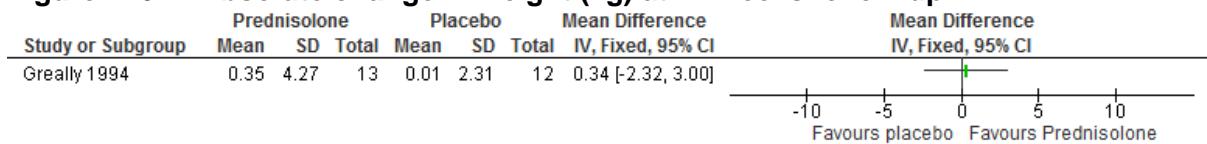
	Prednisolone			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Greally 1994	0.35	4.27	13	0.01	2.31	12	0.34 [-2.32, 3.00]	

Favours placebo Favours Prednisolone

Abbreviations: Ci: confidence interval; IV: inverse variance; kg: kilograms; SD: standard deviation. Intervention: 2mg/kg Prednisolone;

Figure 227: **Weight (kg) at 18 years of age, boys**
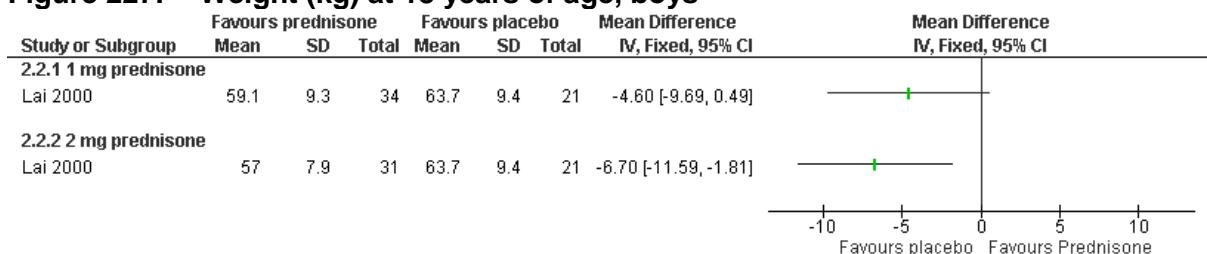
| | Favours prednisone | | | Favours placebo | | | Mean Difference | Mean Difference |
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.2.1 1 mg prednisone								
Lai 2000	59.1	9.3	34	63.7	9.4	21	-4.60 [-9.69, 0.49]	
2.2.2 2 mg prednisone								
Lai 2000	57	7.9	31	63.7	9.4	21	-6.70 [-11.59, -1.81]	

Favours placebo Favours Prednisone

Abbreviations: CI: confidence interval; IV: inverse variance; kg: kilograms; SD: standard deviation

Figure 228: Weight (kg) at 18 years of age, girls
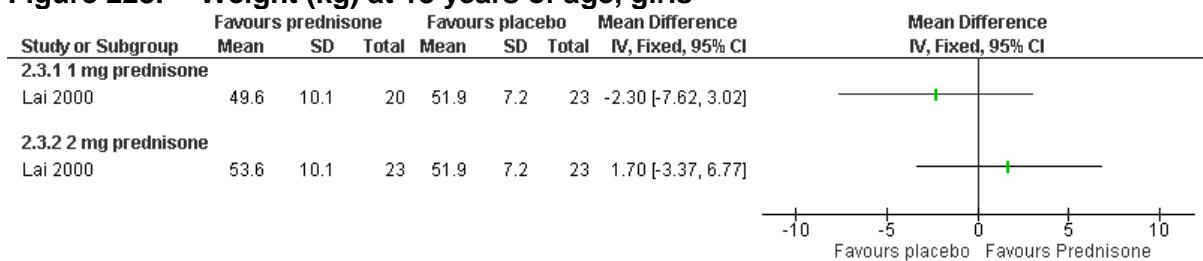
Study or Subgroup	Favours prednisone Mean	SD	Total	Favours placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
2.3.1 1 mg prednisone								
Lai 2000	49.6	10.1	20	51.9	7.2	23	-2.30 [-7.62, 3.02]	
2.3.2 2 mg prednisone								
Lai 2000	53.6	10.1	23	51.9	7.2	23	1.70 [-3.37, 6.77]	

Abbreviations: CI: confidence interval; IV: inverse variance; kg: kilograms; SD: standard deviation

Figure 229: Height (cm) at 18 years of age, boys
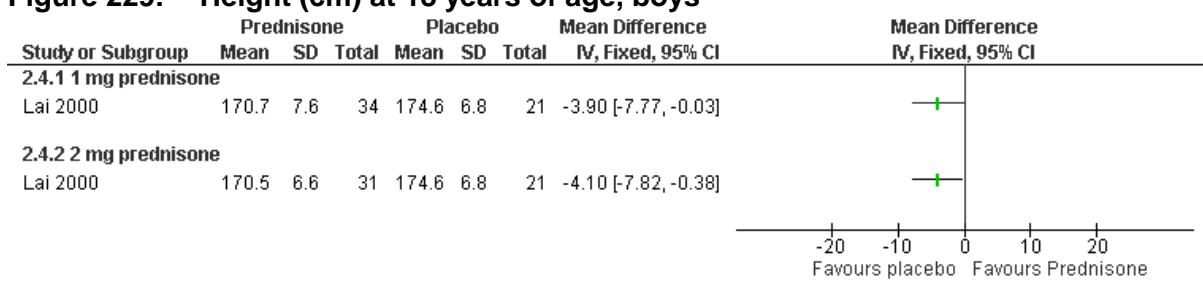
Study or Subgroup	Prednisone Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
2.4.1 1 mg prednisone								
Lai 2000	170.7	7.6	34	174.6	6.8	21	-3.90 [-7.77, -0.03]	
2.4.2 2 mg prednisone								
Lai 2000	170.5	6.6	31	174.6	6.8	21	-4.10 [-7.82, -0.38]	

Abbreviations: CI: confidence interval; cm: centimetres; IV: inverse variance; SD: standard deviation

Figure 230: Height (cm) at 18 years of age, girls
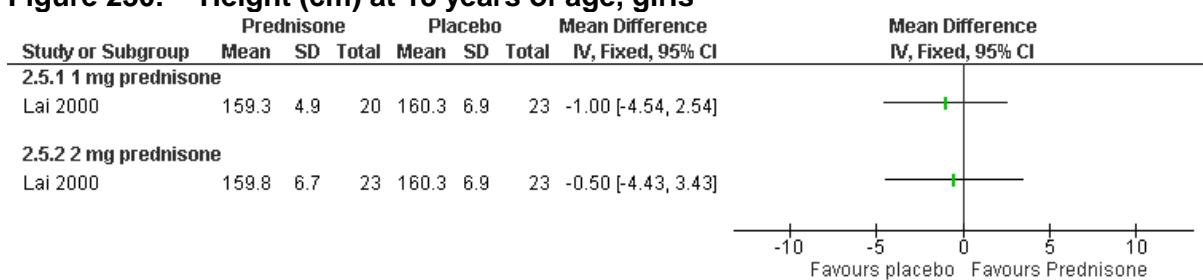
Study or Subgroup	Prednisone Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
2.5.1 1 mg prednisone								
Lai 2000	159.3	4.9	20	160.3	6.9	23	-1.00 [-4.54, 2.54]	
2.5.2 2 mg prednisone								
Lai 2000	159.8	6.7	23	160.3	6.9	23	-0.50 [-4.43, 3.43]	

Abbreviations: CI: confidence interval; cm: centimetres; IV: inverse variance; SD: standard deviation

Figure 231:   Adverse effects, at 3 and 4 years follow-up

Study or Subgroup	Prednisone Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.6.1 Cataracts (1 mg prednisone) up to 4 yrs						
Eigen 1995	3	95	7	95	0.43 [0.11, 1.61]	
2.6.2 Cataracts (2mg prednisone) up to 3 years						
Eigen 1995	11	95	7	95	1.57 [0.64, 3.88]	
2.6.3 Diabetes mellitus (1 mg prednisone) up to 4 yrs						
Eigen 1995	3	95	1	95	3.00 [0.32, 28.33]	
2.6.4 Diabetes mellitus (2 mg prednisone) up to 3 yrs						
Eigen 1995	6	95	1	95	6.00 [0.74, 48.89]	
2.6.5 Glycosuria (1 mg prednisone) up to 4 yrs						
Eigen 1995	6	95	4	95	1.50 [0.44, 5.15]	
2.6.6 Glycosuria (2 mg prednisone) up to 3 yrs						
Eigen 1995	10	95	4	95	2.50 [0.81, 7.69]	
2.6.7 Hyperglycaemia (1 mg prednisone) up to 4 yrs						
Eigen 1995	3	95	2	95	1.50 [0.26, 8.78]	
2.6.8 Hyperglycaemia (2 mg prednisone) up to 3 yrs						
Eigen 1995	10	95	2	95	5.00 [1.13, 22.21]	

0.01   0.1   1   10   100
Favours prednisone   Favours placebo

Abbreviations: CI: confidence interval; : M-H: Mantel-Haenszel

Figure 232:   Mortality with 2mg/kg prednisone, at 4 year follow-up

Study or Subgroup	Prednisone Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Auberch 1985	0	21	1	24	0.38 [0.02, 8.83]	

0.01   0.1   1   10   100
Favours Prednisone   Favours placebo
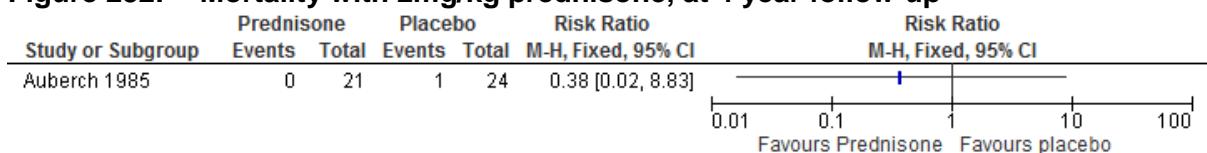
Abbreviations: CI: confidence interval; kg: kilograms; M-H: Mantel-Haenszel; mg: milligrams

Pairwise comparison 3. Azithromycin *versus* placebo

Figure 233:   Time to next exacerbation at 6 months follow-up
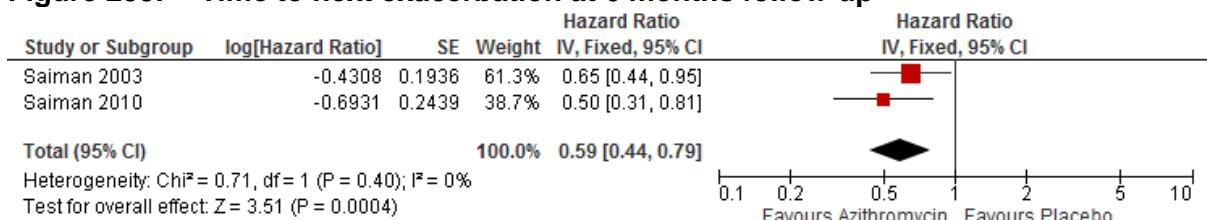
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
Saiman 2003	-0.4308	0.1936	61.3%	0.65 [0.44, 0.95]	
Saiman 2010	-0.6931	0.2439	38.7%	0.50 [0.31, 0.81]	
Total (95% CI)			100.0%	0.59 [0.44, 0.79]	

Heterogeneity: Chi² = 0.71, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 3.51 (P = 0.0004)

0.1   0.2   0.5   1   2   5   10
Favours Azithromycin   Favours Placebo

Abbreviations: CI: confidence interval; df: degrees of freedom; IV: inverse variance; SE: standard error

Figure 234:   Time to next exacerbation at 12 months follow-up

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
Clement 2006	-0.9943	0.2715	0.37 [0.22, 0.63]	

0.1   0.2   0.5   1   2   5   10
Favours Azithromycin   Favours Placebo

Abbreviations: CI: confidence interval; IV: inverse variance; SE: standard error

Figure 235:   Change in BMI z score at 12 months follow-up
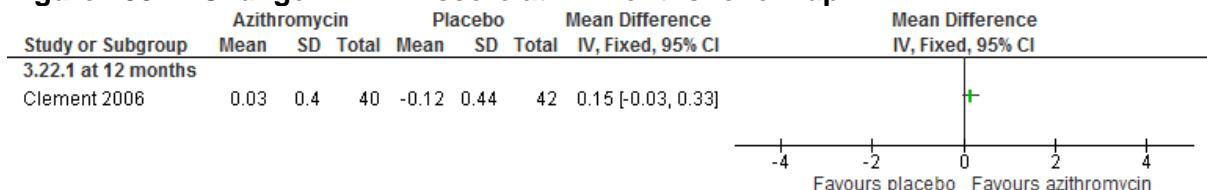
| Study or Subgroup | Azithromycin | | | Placebo | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
3.22.1 at 12 months								
Clement 2006	0.03	0.4	40	-0.12	0.44	42	0.15 [-0.03, 0.33]	

*Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation*

Figure 236:   Change in weight (kg) at 6 months follow-up

| Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Saiman 2003	0.7	0.33	0.70 [0.05, 1.35]	
Saiman 2010	0.58	0.22	0.58 [0.15, 1.01]	
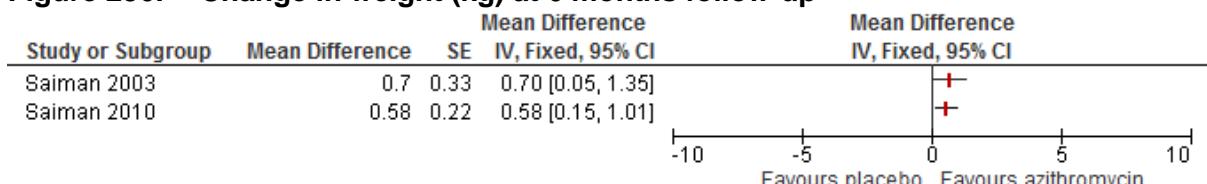
Abbreviations: CI: confidence interval; IV: inverse variance; kg: kilograms; SE: standard error

Figure 237:   Change in quality of life (CFQ-R) at 6 months follow-up (range of scores: 0-100)
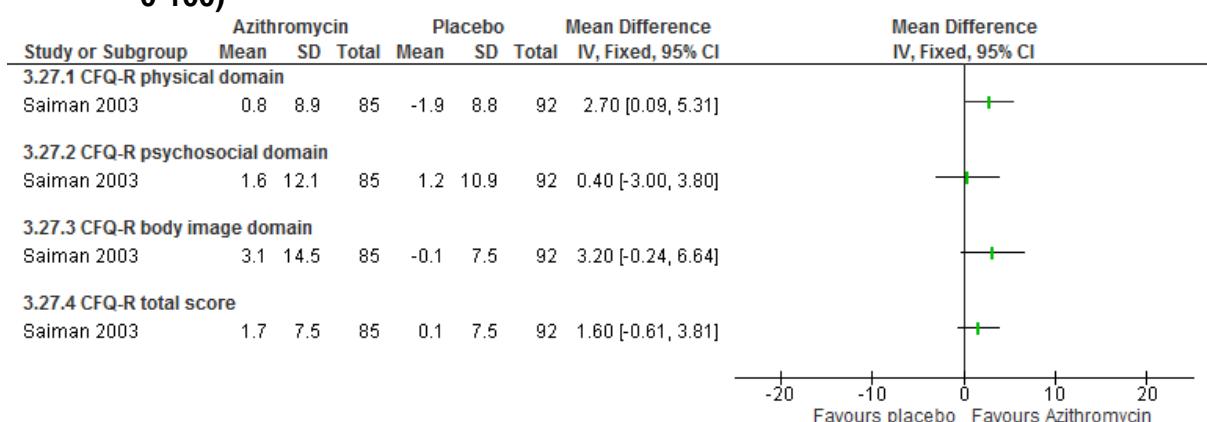
| Study or Subgroup | Azithromycin | | | Placebo | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
3.27.1 CFQ-R physical domain								
Saiman 2003	0.8	8.9	85	-1.9	8.8	92	2.70 [0.09, 5.31]	
3.27.2 CFQ-R psychosocial domain								
Saiman 2003	1.6	12.1	85	1.2	10.9	92	0.40 [-3.00, 3.80]	
3.27.3 CFQ-R body image domain								
Saiman 2003	3.1	14.5	85	-0.1	7.5	92	3.20 [-0.24, 6.64]	
3.27.4 CFQ-R total score								
Saiman 2003	1.7	7.5	85	0.1	7.5	92	1.60 [-0.61, 3.81]	

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Figure 238:   Adverse side effects at 6 months follow-up

| Study or Subgroup | Azithromycin | | Placebo | | Risk Ratio | Risk Ratio |
	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
3.5.20 Hearing impairment						
Saiman 2003	1	87	1	98	1.13 [0.07, 17.74]	
3.5.21 Tinnitus						
Saiman 2003	1	87	1	98	1.13 [0.07, 17.74]	
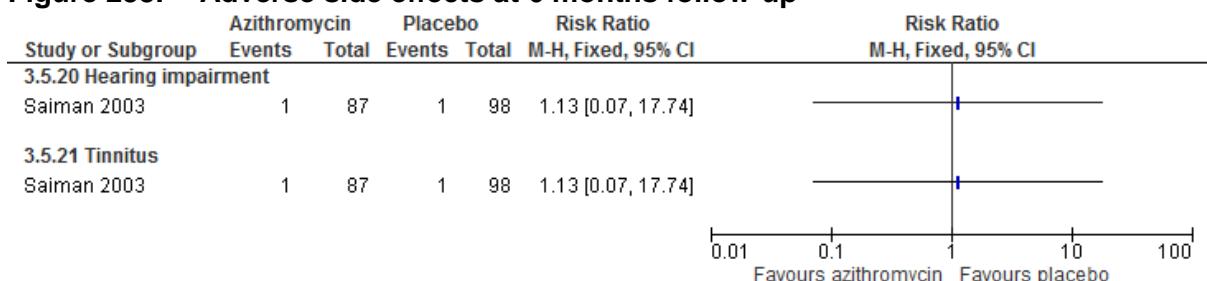
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Pairwise comparison 4. Ibuprofen *versus* placebo

Figure 239:   Annual rate of change in % ideal body weight at 4 years follow-up
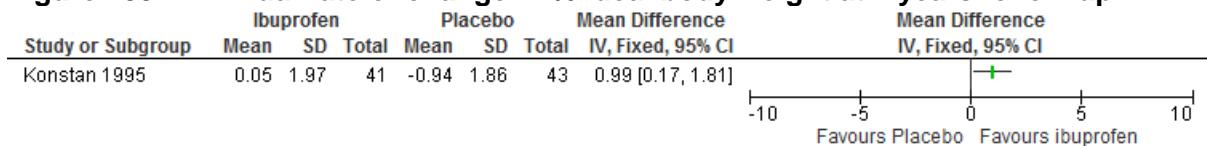
Study or Subgroup	Ibuprofen Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Konstan 1995	0.05	1.97	41	-0.94	1.86	43	0.99 [0.17, 1.81]	

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 240:   Annual rate of change in % ideal body weight by age at 4 years follow-up
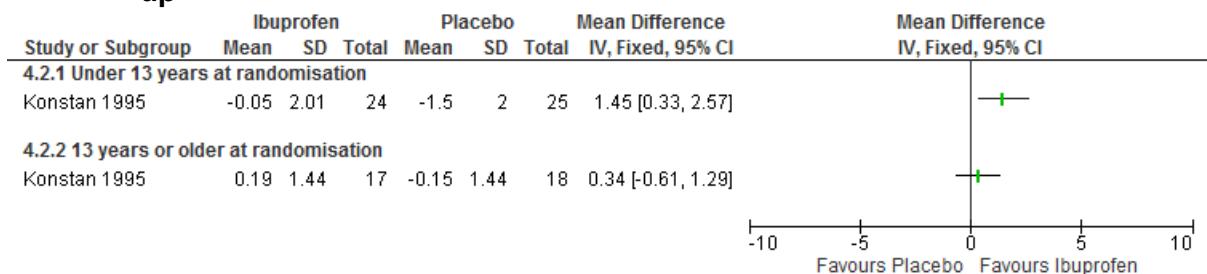
Study or Subgroup	Ibuprofen Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.2.1 Under 13 years at randomisation								
Konstan 1995	-0.05	2.01	24	-1.5	2	25	1.45 [0.33, 2.57]	
4.2.2 13 years or older at randomisation								
Konstan 1995	0.19	1.44	17	-0.15	1.44	18	0.34 [-0.61, 1.29]	

Abbreviations: CI: Confidence interval; IV: inverse variance; SD: standard deviation

Figure 241:   Adverse effects: abdominal pain at 2 and 4 years follow-up

Study or Subgroup	Ibuprofen Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
4.3.1 up to 2 years follow-up						
Lands 2007	1	70	4	72	0.26 [0.03, 2.24]	
4.3.2 up to 4 years follow-up						
Konstan 1995	5	41	7	43	0.75 [0.26, 2.17]	
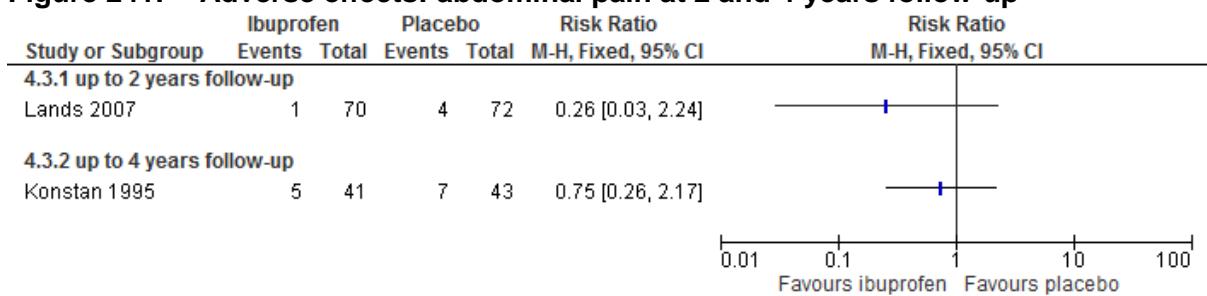
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 242:   Adverse effects: gastrointestinal bleeding) at 2 years follow-up

Study or Subgroup	Ibuprofen Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Lands 2007	1	70	0	72	3.08 [0.13, 74.46]	

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

I.13 Nutritional interventions

Comparison 1. Oral supplements *versus* usual care

Figure 243: Change in weight (kg) at 3, 6, 12 months follow-up

Study or Subgroup	Oral supplementation			Usual care				Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.1.1 At 3 months									
Poustie 2006	1.11	1.25	48	0.77	0.73	51	100.0%	0.34 [-0.07, 0.75]	
Subtotal (95% CI)			48			51	100.0%	0.34 [-0.07, 0.75]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.64 (P = 0.10)									
1.1.2 At 6 months									
Hanning 1993	2.52	1.33	9	1.33	1.35	7	16.8%	1.19 [-0.13, 2.51]	
Poustie 2006	2.05	1.8	50	1.72	1.18	51	83.2%	0.33 [-0.26, 0.92]	
Subtotal (95% CI)			59			58	100.0%	0.47 [-0.07, 1.02]	
Heterogeneity: Chi² = 1.35, df = 1 (P = 0.25); I² = 26%									
Test for overall effect: Z = 1.71 (P = 0.09)									
1.1.3 At 1 year									
Poustie 2006	3.13	2.35	50	2.97	1.97	52	100.0%	0.16 [-0.68, 1.00]	
Subtotal (95% CI)			50			52	100.0%	0.16 [-0.68, 1.00]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.37 (P = 0.71)									

-20 -10 0 10 20
Favours Usual care Favours Oral supplementation

Abbreviations: kg: kilograms; SD: standard deviation; IV: inverse variance; CI: confidence interval

### Figure 244: Change in height (cm) at 3, 6, and 12 months follow-up

Study or Subgroup	Oral supplementation			Usual care			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.2.1 At 3 months								
Poustie 2006	1.65	0.86	48	1.68	0.8	51	-0.03 [-0.36, 0.30]	
1.2.2 At 6 months								
Poustie 2006	3.09	1.03	50	3.56	2.92	51	-0.47 [-1.32, 0.38]	
1.2.3 At 1 year								
Poustie 2006	5.91	0.85	50	5.85	1.85	52	0.06 [-0.50, 0.62]	

-20 -10 0 10 20
Favours Usual care Favours Oral supplementation

Abbreviations: CI: confidence interval; cm: centimetres; IV: inverse variance; SD: standard deviation;

Figure 245: Change in weight as % expected for age and height at 6 months follow-up

Study or Subgroup	Oral supplementation			Usual care			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hanning 1993	0.6	9.77	9	-2.7	9.62	7	3.30 [-6.27, 12.87]	

-20 -10 0 10 20
Favours Usual care Favours Oral supplementation

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation;
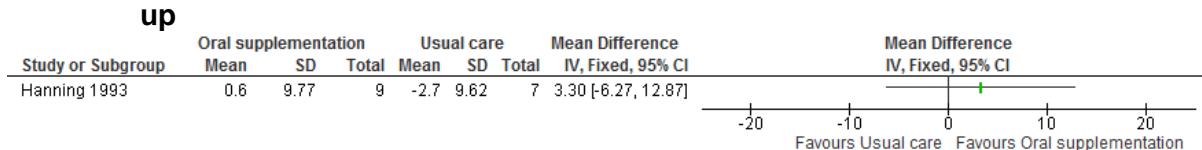
### Figure 246: Change in BMI (kg/m2) at 3, 6 and 12 months follow-up

Study or Subgroup	Oral supplementation			Usual care			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.4.1 At 3 months								
Poustie 2006	0.19	0.65	48	0.05	0.41	51	0.14 [-0.08, 0.36]	
1.4.2 At 6 months								
Poustie 2006	0.39	0.87	50	0.15	0.67	51	0.24 [-0.06, 0.54]	
1.4.3 At 1 year								
Poustie 2006	0.32	1.03	50	0.24	0.78	52	0.08 [-0.28, 0.44]	

-20 -10 0 10 20
Favours Usual care Favours Oral supplementation

Abbreviations: BMI: body mass index; CI: confidence interval; kg: kilograms; IV: inverse variance; m²: square metres; SD: standard deviation

Figure 247:   Change in BMI (centile) at 3, 6 and 12 months follow-up

Study or Subgroup	Oral supplementation Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.5.1 At 3 months							
Poustie 2006	2.72	11.42	48	-0.56	8.47	51	3.28 [-0.70, 7.26]
1.5.2 At 6 months							
Poustie 2006	4.46	15.5	50	-1.29	12.66	51	5.75 [0.22, 11.28]
1.5.3 At 1 year							
Poustie 2006	0.67	18.2	50	-2.32	9.63	52	2.99 [-2.69, 8.67]

Mean Difference IV, Fixed, 95% CI
-20 -10 0 10 20
Favours Usual care   Favours Oral supplementation

Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 248:   Change in weight (centile) at 3, 6, and 12 months follow-up

Study or Subgroup	Oral supplementation Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.6.1 At 3 months							
Poustie 2006	2.12	6.58	48	0.4	4.98	51	1.72 [-0.59, 4.03]
1.6.2 At 6 months							
Poustie 2006	2.75	9.56	50	0.63	5.6	51	2.12 [-0.94, 5.18]
1.6.3 At 1 year							
Poustie 2006	0.83	10.96	50	-1	7.14	52	1.83 [-1.77, 5.43]

Mean Difference IV, Fixed, 95% CI
-20 -10 0 10 20
Favours Usual care   Favours Oral supplementation

Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

**Figure 249:   Change in height (centile) at 3, 6 and 12 months follow-up**
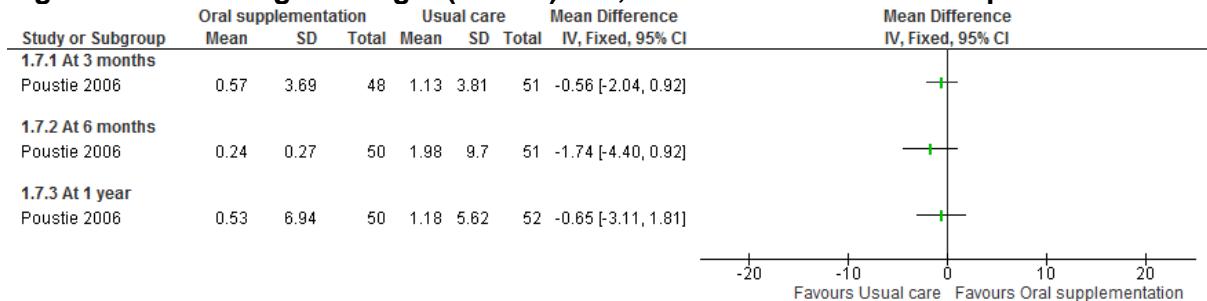
Study or Subgroup	Oral supplementation Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.7.1 At 3 months							
Poustie 2006	0.57	3.69	48	1.13	3.81	51	-0.56 [-2.04, 0.92]
1.7.2 At 6 months							
Poustie 2006	0.24	0.27	50	1.98	9.7	51	-1.74 [-4.40, 0.92]
1.7.3 At 1 year							
Poustie 2006	0.53	6.94	50	1.18	5.62	52	-0.65 [-3.11, 1.81]

Mean Difference IV, Fixed, 95% CI
-20 -10 0 10 20
Favours Usual care   Favours Oral supplementation

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 250:   Change in height as % expected for age at 6-months follow-up
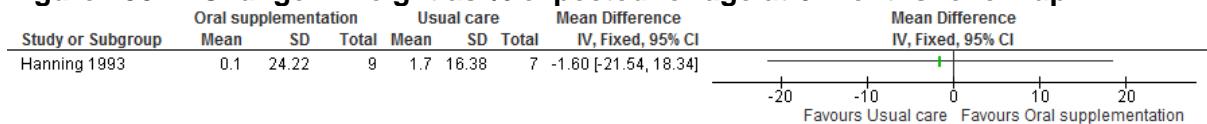
Study or Subgroup	Oral supplementation Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Hanning 1993	0.1	24.22	9	1.7	16.38	7	-1.60 [-21.54, 18.34]

Mean Difference IV, Fixed, 95% CI
-20 -10 0 10 20
Favours Usual care   Favours Oral supplementation

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 251:   Change in FEV₁ % predicted at 3, 6 and 12 months follow-up (range of scores: 0-100)
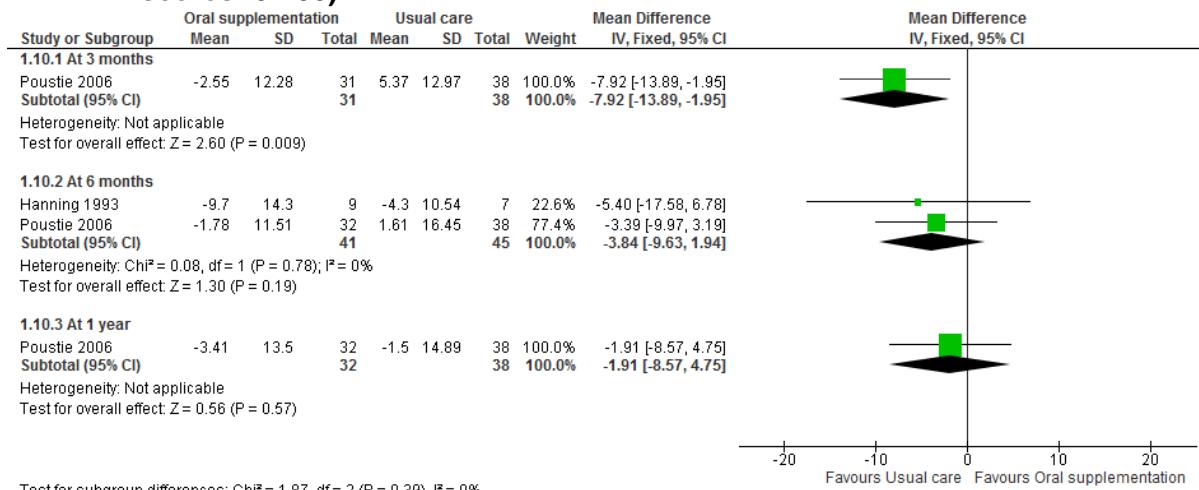
Abbreviations: CI: confidence interval; df: degrees of freedom; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Comparison 1.2 Oral calorie supplementation *versus* nutritional advice

Figure 252:   Change in weight (kg) at 3 months follow-up
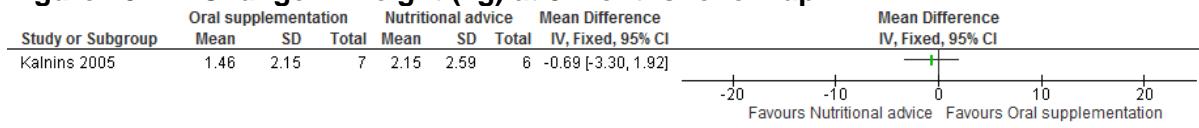
Abbreviations: kg: kilograms; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 253:   Change in weight for height (%) at 3 months follow-up
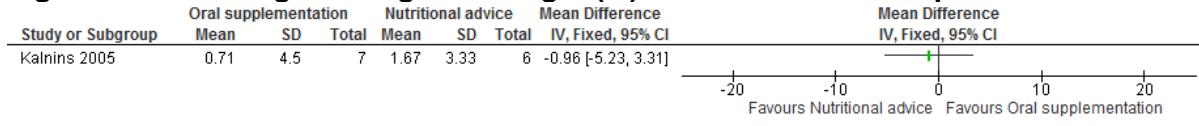
Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 254:   Change in weight z score at 3 and 6 months follow-up
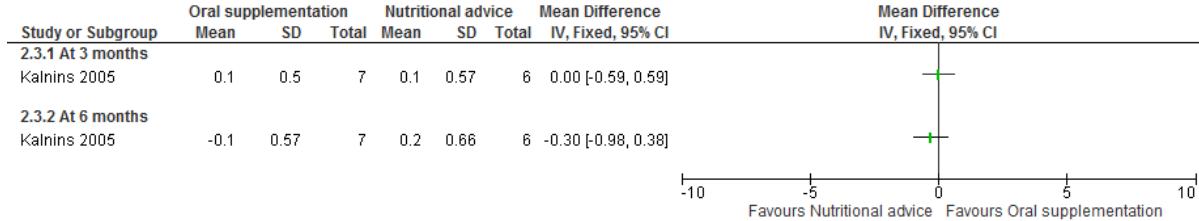
Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

**Figure 255:   Change in % ideal body weight at 3 and 6 months follow-up**
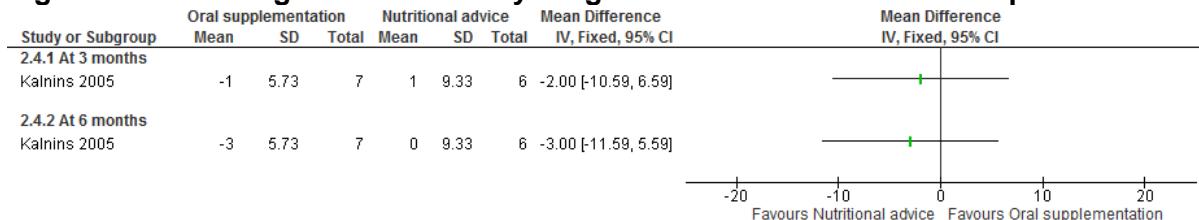
Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 256:   Change in height (cm) at 3 months follow-up
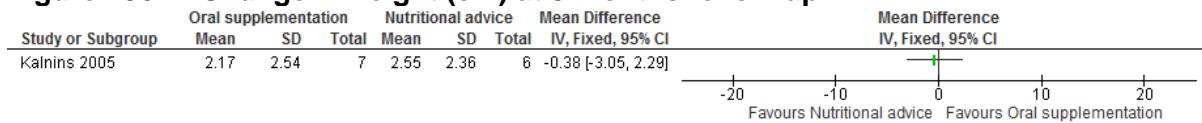
Study or Subgroup	Oral supplementation Mean	SD	Total	Nutritional advice Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Kalnins 2005	2.17	2.54	7	2.55	2.36	6	-0.38 [-3.05, 2.29]

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 257:   Change in height z score at 3 and 6 months follow-up
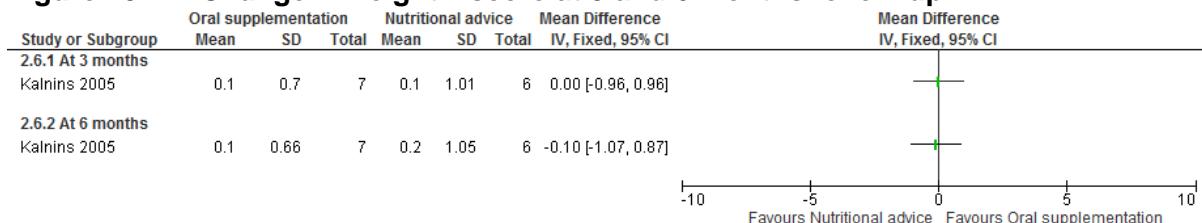
Study or Subgroup	Oral supplementation Mean	SD	Total	Nutritional advice Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
2.6.1 At 3 months							
Kalnins 2005	0.1	0.7	7	0.1	1.01	6	0.00 [-0.96, 0.96]
2.6.2 At 6 months							
Kalnins 2005	0.1	0.66	7	0.2	1.05	6	-0.10 [-1.07, 0.87]

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

**Figure 258:   Change in FEV$_1$ % predicted at 3 and 6 months follow-up (range of scores: 0-100)**
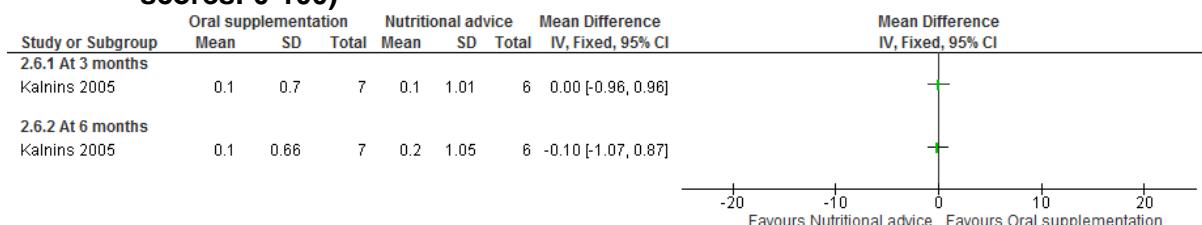
Study or Subgroup	Oral supplementation Mean	SD	Total	Nutritional advice Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
2.6.1 At 3 months							
Kalnins 2005	0.1	0.7	7	0.1	1.01	6	0.00 [-0.96, 0.96]
2.6.2 At 6 months							
Kalnins 2005	0.1	0.66	7	0.2	1.05	6	-0.10 [-1.07, 0.87]

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Comparison 2. Enteral tube feeding *versus* nutritional advice

Figure 259:   Change in weight (kg) at 1, 2, and 3 years follow-up
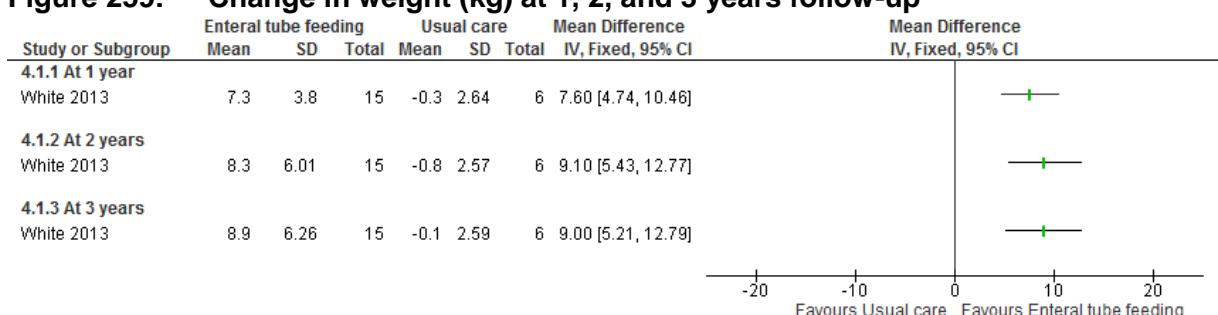
Study or Subgroup	Enteral tube feeding Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
4.1.1 At 1 year							
White 2013	7.3	3.8	15	-0.3	2.64	6	7.60 [4.74, 10.46]
4.1.2 At 2 years							
White 2013	8.3	6.01	15	-0.8	2.57	6	9.10 [5.43, 12.77]
4.1.3 At 3 years							
White 2013	8.9	6.26	15	-0.1	2.59	6	9.00 [5.21, 12.79]

Abbreviations: kg: kilograms; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 260:   Change in weight z score at 6 and 12 months follow-up
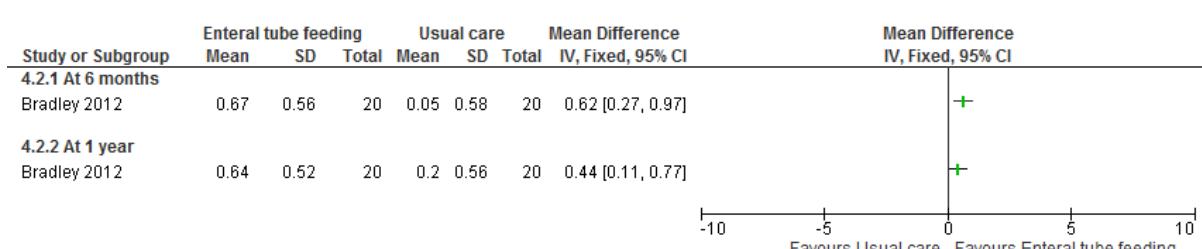
Study or Subgroup	Enteral tube feeding Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
4.2.1 At 6 months							
Bradley 2012	0.67	0.56	20	0.05	0.58	20	0.62 [0.27, 0.97]
4.2.2 At 1 year							
Bradley 2012	0.64	0.52	20	0.2	0.56	20	0.44 [0.11, 0.77]

Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 261:   Change in height z score at 6 and 12 months follow-up
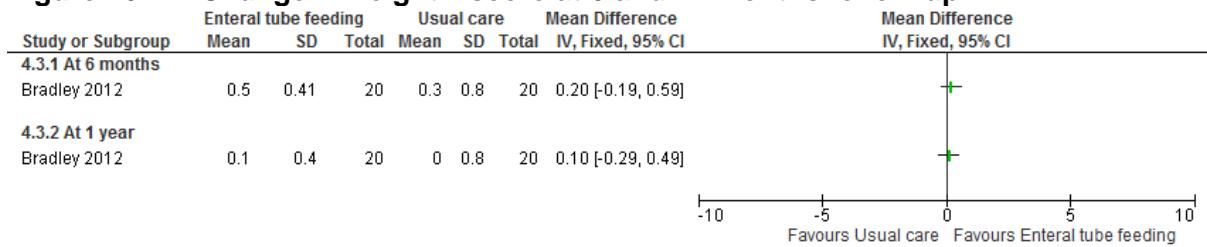
Study or Subgroup	Enteral tube feeding			Usual care			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
4.3.1 At 6 months								
Bradley 2012	0.5	0.41	20	0.3	0.8	20	0.20 [-0.19, 0.59]	
4.3.2 At 1 year								
Bradley 2012	0.1	0.4	20	0	0.8	20	0.10 [-0.29, 0.49]	

Favours Usual care Favours Enteral tube feeding

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 262:   Change in BMI z score at 6 and 12 months follow-up
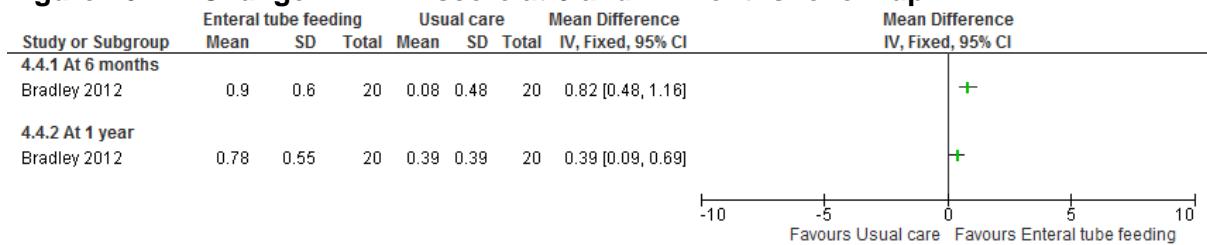
Study or Subgroup	Enteral tube feeding			Usual care			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
4.4.1 At 6 months								
Bradley 2012	0.9	0.6	20	0.08	0.48	20	0.82 [0.48, 1.16]	
4.4.2 At 1 year								
Bradley 2012	0.78	0.55	20	0.39	0.39	20	0.39 [0.09, 0.69]	

Favours Usual care Favours Enteral tube feeding

Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 263:   Change in BMI (kg/m^2) at 1, 2 and 3 years follow-up
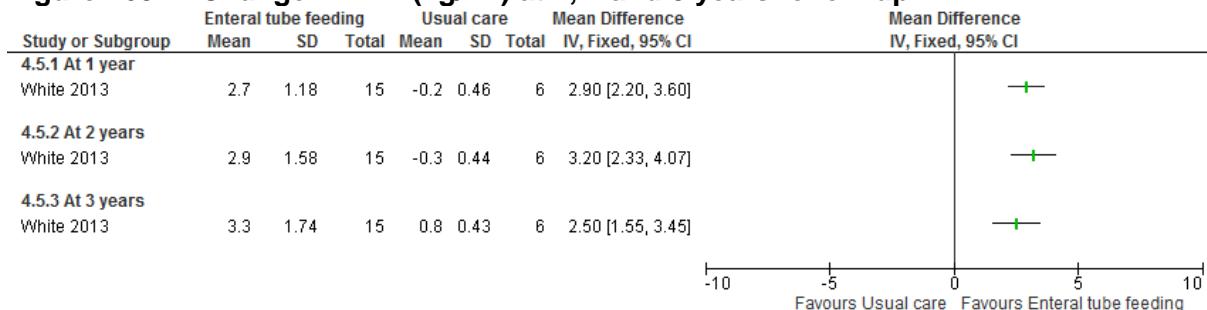
Study or Subgroup	Enteral tube feeding			Usual care			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
4.5.1 At 1 year								
White 2013	2.7	1.18	15	-0.2	0.46	6	2.90 [2.20, 3.60]	
4.5.2 At 2 years								
White 2013	2.9	1.58	15	-0.3	0.44	6	3.20 [2.33, 4.07]	
4.5.3 At 3 years								
White 2013	3.3	1.74	15	0.8	0.43	6	2.50 [1.55, 3.45]	

Favours Usual care Favours Enteral tube feeding

Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; kg: kilograms; m^2: square metres; SD: standard deviation

Figure 264:   Change in FEV$_1$ % predicted at 6 months and at 1, 2, 3 years follow-up (range of scores: 0-100)

Study or Subgroup	Enteral tube feeding			Usual care			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
4.6.1 At 6 months, age 2-20								
Bradley 2012	-1.3	16.24	14	3.2	14.72	13	-4.50 [-16.18, 7.18]	
4.6.2 At 1 year, age 2-20								
Bradley 2012	-1.6	15.94	14	6.6	16.62	13	-8.20 [-20.50, 4.10]	
4.6.3 At 1 year - adults								
White 2013	5.3	14.41	15	-5.3	24.53	6	10.60 [-10.34, 31.54]	
4.6.4 At 2 years - adults								
White 2013	4.2	14.65	15	-8	15.96	6	12.20 [-2.57, 26.97]	
4.6.5 At 3 years - adults								
White 2013	1.2	13.95	15	-11	15.16	6	12.20 [-1.84, 26.24]	

Favours Usual care Favours Enteral tube feeding

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

**Figure 265:   Change in IV treatment days at 1, 2, 3 years follow-up**
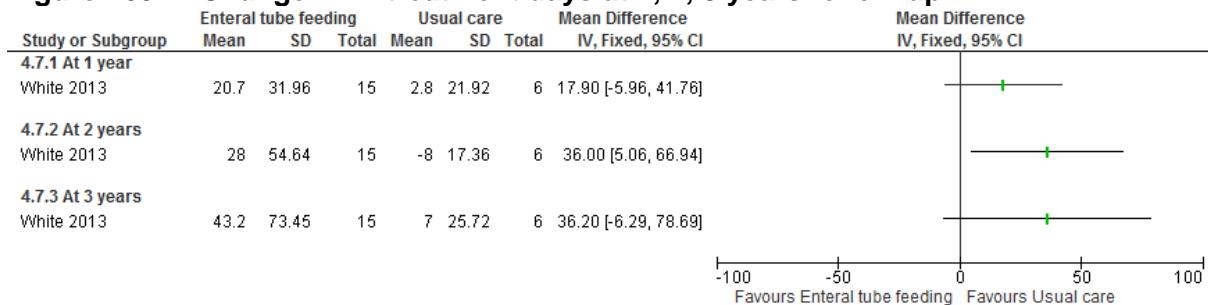
| Study or Subgroup | Enteral tube feeding | | | Usual care | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
4.7.1 At 1 year								
White 2013	20.7	31.96	15	2.8	21.92	6	17.90 [-5.96, 41.76]	
4.7.2 At 2 years								
White 2013	28	54.64	15	-8	17.36	6	36.00 [5.06, 66.94]	
4.7.3 At 3 years								
White 2013	43.2	73.45	15	7	25.72	6	36.20 [-6.29, 78.69]	

Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Comparison 3. Appetite stimulants *versus* placebo

Figure 266:   Change in weight (kg) at 3 and 6 months follow-up

| Study or Subgroup | Appetite stimulants | | | Placebo | | | Weight | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI	IV, Fixed, 95% CI
5.1.1 At 3 months									
Eubanks 2002	4.3	2.9	10	1.3	1.4	7	95.1%	3.00 [0.92, 5.08]	
Homnick 2004	3.45	9.01	8	1.1	9.68	8	4.9%	2.35 [-6.81, 11.51]	
Subtotal (95% CI)			18			15	100.0%	2.97 [0.94, 4.99]	
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%									
Test for overall effect: Z = 2.87 (P = 0.004)									
5.1.2 At 6 months									
Eubanks 2002	5.3	3.6	10	1.5	1.6	7	100.0%	3.80 [1.27, 6.33]	
Subtotal (95% CI)			10			7	100.0%	3.80 [1.27, 6.33]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.95 (P = 0.003)									

Abbreviations: kg: kilograms; SD: standard deviation; IV: inverse variance; CI: confidence interval; df: degrees of freedom

Figure 267:   Change in weight z score at 3 and 6 months follow-up

| Study or Subgroup | Appetite stimulants | | | Placebo | | | Weight | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI	IV, Fixed, 95% CI
5.2.1 At 3 months									
Eubanks 2002	0.72	0.77	10	0.07	0.22	7	40.0%	0.65 [0.15, 1.15]	
Homnick 2004	0.572	0.457	5	0.04	0.305	7	48.2%	0.53 [0.07, 0.99]	
Marchand 2000	0.742	0.783	5	-0.05	0.783	6	11.8%	0.79 [-0.14, 1.72]	
Subtotal (95% CI)			20			20	100.0%	0.61 [0.29, 0.93]	
Heterogeneity: Chi² = 0.28, df = 2 (P = 0.87); I² = 0%									
Test for overall effect: Z = 3.75 (P = 0.0002)									
5.2.2 At 6 months									
Eubanks 2002	0.76	0.73	10	0.02	0.2	7	100.0%	0.74 [0.26, 1.22]	
Subtotal (95% CI)			10			7	100.0%	0.74 [0.26, 1.22]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 3.05 (P = 0.002)									

Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval; df: degrees of freedom

Figure 268:   Change in height (cm) at 3 months follow-up
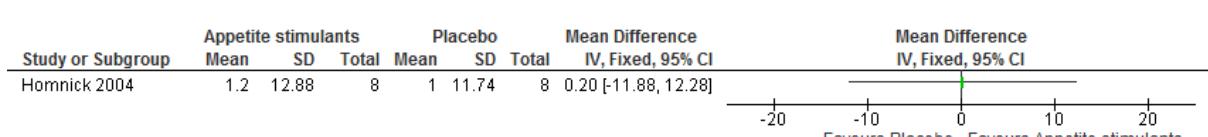
| Study or Subgroup | Appetite stimulants | | | Placebo | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Homnick 2004	1.2	12.88	8	1	11.74	8	0.20 [-11.88, 12.28]	

Abbreviations: CI: confidence interval; cm: centimetres; IV: inverse variance; SD: standard deviation

Figure 269:   Change in FEV$_1$ % predicted at 3 and 6 months follow-up (range of scores: 0-100)
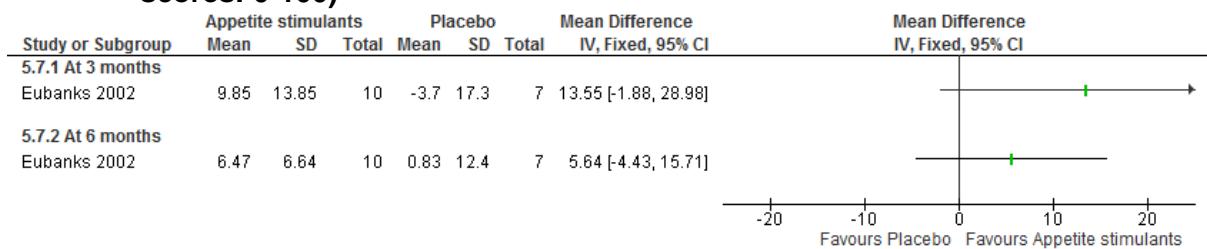
	Appetite stimulants			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
5.7.1 At 3 months								
Eubanks 2002	9.85	13.85	10	-3.7	17.3	7	13.55 [-1.88, 28.98]	
5.7.2 At 6 months								
Eubanks 2002	6.47	6.64	10	0.83	12.4	7	5.64 [-4.43, 15.71]	

Favours Placebo Favours Appetite stimulants

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 270:   Change in BMI (kg/m^2) at 3 months follow-up
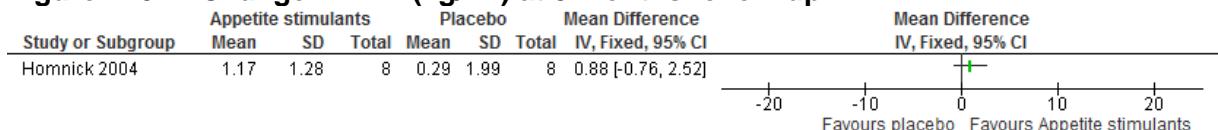
	Appetite stimulants			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Homnick 2004	1.17	1.28	8	0.29	1.99	8	0.88 [-0.76, 2.52]	

Favours placebo Favours Appetite stimulants

Abbreviations: BMI: body mass index; CI: confidence interval; kg: kilograms; IV: inverse variance; m^2: square metres; SD: standard deviation

Figure 271:   Change in BMI percentile at 3 months follow-up
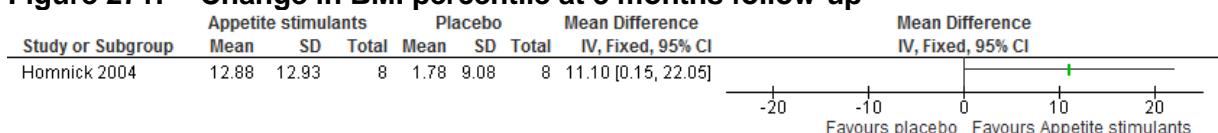
	Appetite stimulants			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Homnick 2004	12.88	12.93	8	1.78	9.08	8	11.10 [0.15, 22.05]	

Favours placebo Favours Appetite stimulants

Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 272:   Change in % ideal body weight at 3 months follow-up
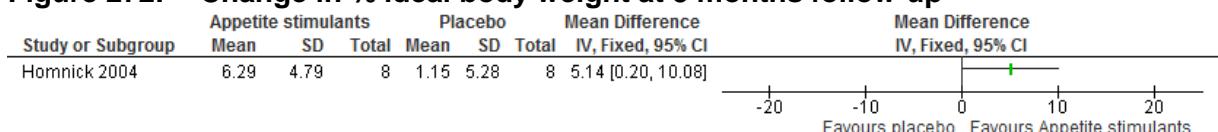
	Appetite stimulants			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Homnick 2004	6.29	4.79	8	1.15	5.28	8	5.14 [0.20, 10.08]	

Favours placebo Favours Appetite stimulants

Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 273:   Number of pulmonary exacerbations at 3 months follow-up

	Appetite stimulants		Placebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Marchand 2000	5	6	3	6	1.67 [0.69, 4.00]	

Favours Appetite stimulants Favours Placebo
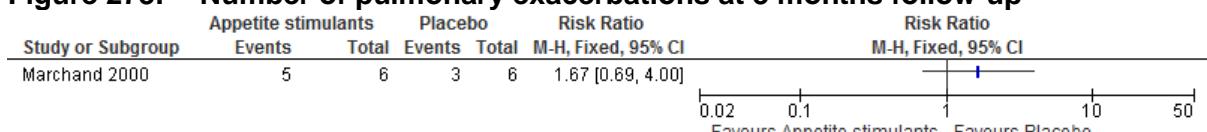
Abbreviations: M-H: Mantel-Haenszel; CI: confidence interval

Figure 274:   Adverse effects: constipation at 6 months follow-up

	Appetite stimulants		Placebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Eubanks 2002	1	10	0	7	2.18 [0.10, 46.92]	

Favours Appetite stimulants Favours Placebo
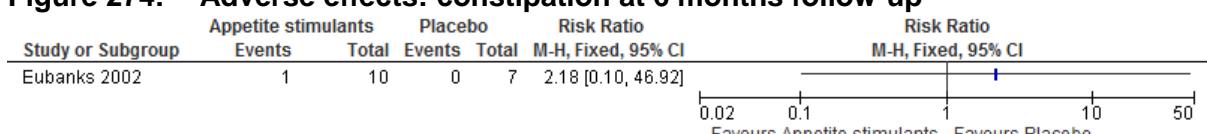
Abbreviations: M-H: Mantel-Haenszel; CI: confidence interval

Figure 275:   Adverse effects: decreased morning cortisol levels <30 nmol/L at 6 months follow-up

Study or Subgroup	Appetite stimulants Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Eubanks 2002	7	10	0	7	10.91 [0.72, 164.61]	

0.02   0.1   1   10   50
Favours Appetite stimulants   Favours Placebo

Abbreviations: M-H: Mantel-Haenszel; CI: confidence interval

Comparison 4. Nutrition education *versus* usual care

Figure 276:   Change in weight (kg) at 6 and 12 months follow-up
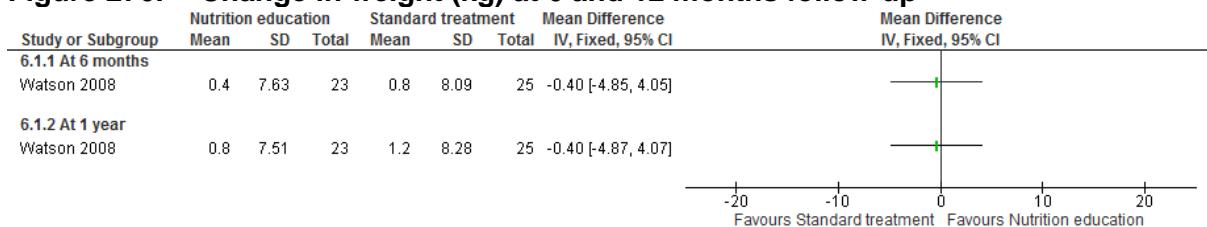
Study or Subgroup	Nutrition education Mean	SD	Total	Standard treatment Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
6.1.1 At 6 months								
Watson 2008	0.4	7.63	23	0.8	8.09	25	-0.40 [-4.85, 4.05]	
6.1.2 At 1 year								
Watson 2008	0.8	7.51	23	1.2	8.28	25	-0.40 [-4.87, 4.07]	

-20   -10   0   10   20
Favours Standard treatment   Favours Nutrition education

Abbreviations: kg: kilograms; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 277:   Change in FEV_1 % predicted at 6 and 12 months follow-up (range of scores: 0-100)
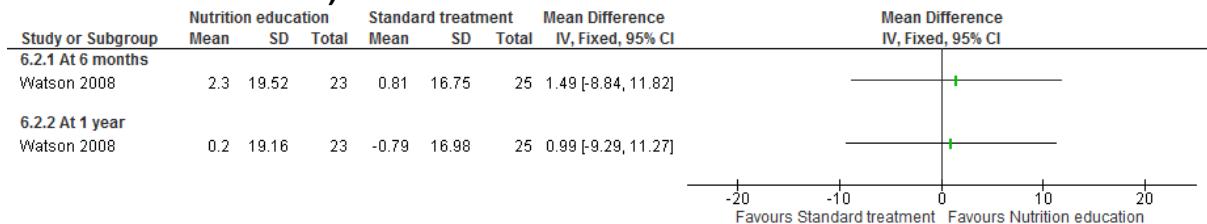
Study or Subgroup	Nutrition education Mean	SD	Total	Standard treatment Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
6.2.1 At 6 months								
Watson 2008	2.3	19.52	23	0.81	16.75	25	1.49 [-8.84, 11.82]	
6.2.2 At 1 year								
Watson 2008	0.2	19.16	23	-0.79	16.98	25	0.99 [-9.29, 11.27]	

-20   -10   0   10   20
Favours Standard treatment   Favours Nutrition education

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Comparison 5.1 Behavioural intervention *versus* usual care

Figure 278:   Change in weight (kg) at 6 weeks follow-up
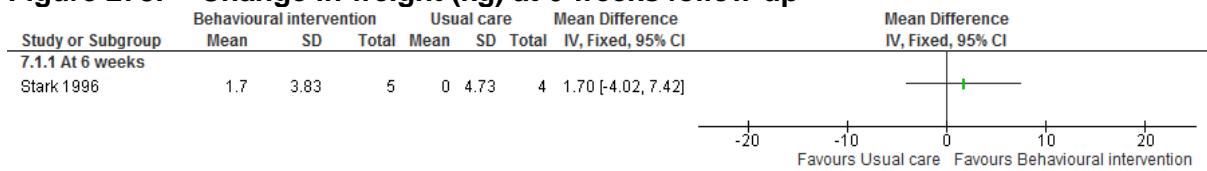
Study or Subgroup	Behavioural intervention Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
7.1.1 At 6 weeks								
Stark 1996	1.7	3.83	5	0	4.73	4	1.70 [-4.02, 7.42]	

-20   -10   0   10   20
Favours Usual care   Favours Behavioural intervention

Abbreviations: kg: kilograms; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 279:   Change in height (cm) at 6 weeks follow-up
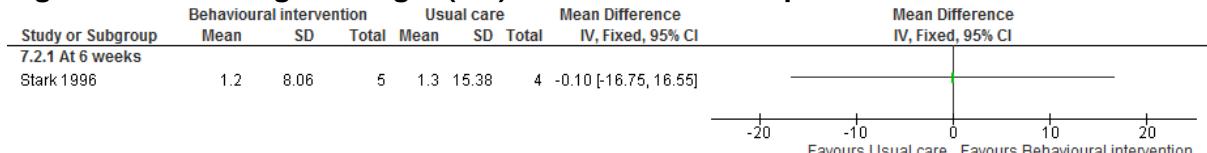
Study or Subgroup	Behavioural intervention Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
7.2.1 At 6 weeks								
Stark 1996	1.2	8.06	5	1.3	15.38	4	-0.10 [-16.75, 16.55]	

-20   -10   0   10   20
Favours Usual care   Favours Behavioural intervention

Abbreviations: CI: confidence interval; cm: centimetres; IV: inverse variance; SD: standard deviation

Figure 280:   Change in weight z score at 6 weeks follow-up
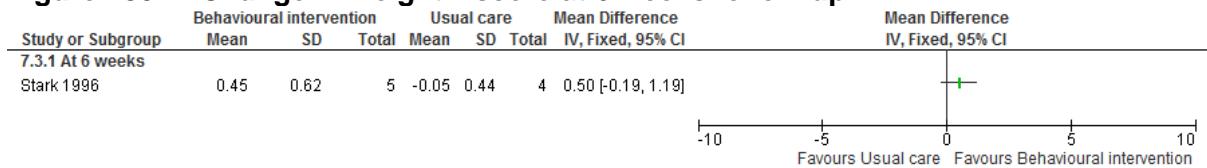
Study or Subgroup	Behavioural intervention Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
7.3.1 At 6 weeks							
Stark 1996	0.45	0.62	5	-0.05	0.44	4	0.50 [-0.19, 1.19]

Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 281:   Change in FEV₁ % predicted at 6 weeks follow-up (range of scores: 0-100)
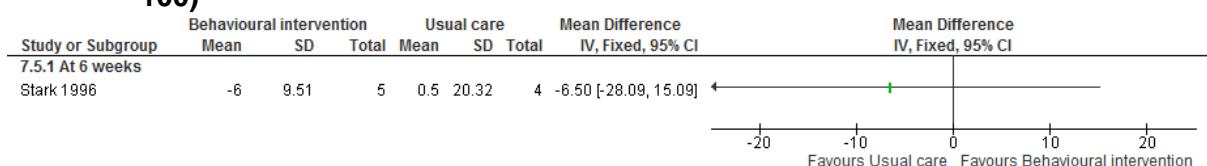
Study or Subgroup	Behavioural intervention Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
7.5.1 At 6 weeks							
Stark 1996	-6	9.51	5	0.5	20.32	4	-6.50 [-28.09, 15.09]

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

**Comparison 5.2 Behavioural intervention *versus* education and attention control treatment**

Figure 282:   Change in weight z score at 6 and 18 months follow-up
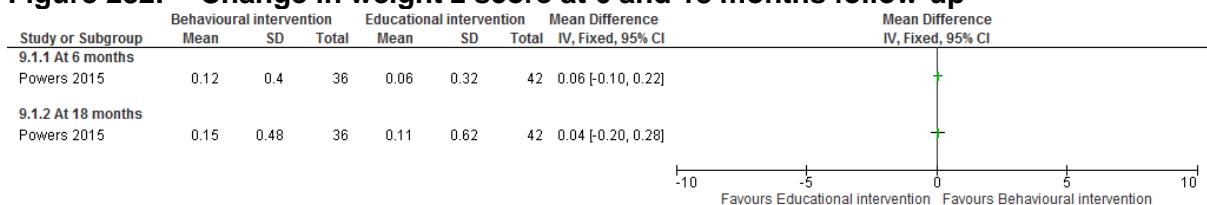
Study or Subgroup	Behavioural intervention Mean	SD	Total	Educational intervention Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
9.1.1 At 6 months							
Powers 2015	0.12	0.4	36	0.06	0.32	42	0.06 [-0.10, 0.22]
9.1.2 At 18 months							
Powers 2015	0.15	0.48	36	0.11	0.62	42	0.04 [-0.20, 0.28]

Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 283:   Change in height z score at 18 months follow-up
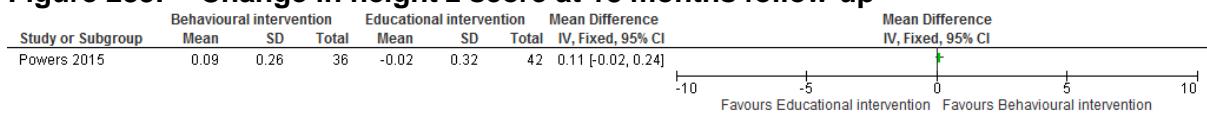
Study or Subgroup	Behavioural intervention Mean	SD	Total	Educational intervention Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Powers 2015	0.09	0.26	36	-0.02	0.32	42	0.11 [-0.02, 0.24]

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 284:   Adverse effects (digestive system) at 6 months follow-up

Study or Subgroup	Behavioural intervention Events	Total	Educational intervention Events	Total	Risk Ratio M-H, Fixed, 95% CI
Powers 2015	29	36	21	42	1.61 [1.14, 2.27]

Comparison 5.3. Behavioural management training plus educational intervention *versus* educational intervention alone

Figure 285: Change in weight (kg) at 2,12 and 24 months follow-up

Study or Subgroup	BEH plus EDU Mean	SD	Total	EDU Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
10.1.1 At 2 months							
Stark 2009	1.47	1.27	33	0.92	1.03	34	0.55 [-0.00, 1.10]
10.1.2 At 1 year							
Powers 2003	1.32	0.64	4	1.75	0.57	4	-0.43 [-1.27, 0.41]
10.1.3 At 2 years							
Stark 2009	6.97	3.6	28	6.45	3.67	31	0.52 [-1.34, 2.38]
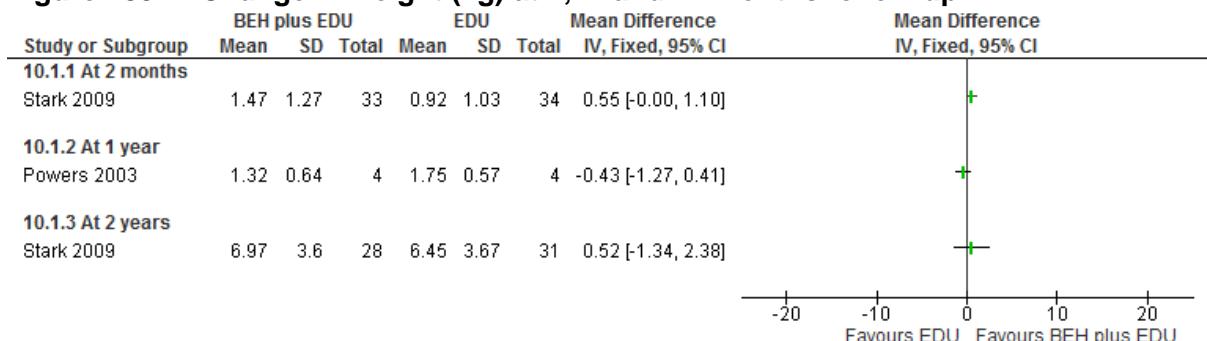
Abbreviations: kg: kilograms; BEH plus EDU: Behavioural management training plus educational intervention; EDU: educational intervention alone; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 286: Change in BMI z score at 2 and 24 months follow-up

Study or Subgroup	BEH plus EDU Mean	SD	Total	EDU Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
10.2.1 At 2 months							
Stark 2009	0.38	0.46	33	0.18	0.47	34	0.20 [-0.02, 0.42]
10.2.2 At 2 years							
Stark 2009	0.13	0.81	28	-0.22	0.5	31	0.35 [0.00, 0.70]
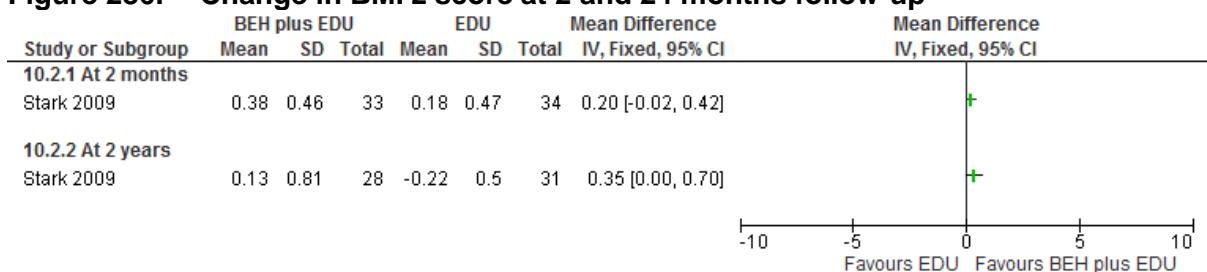
Abbreviations: BMI: body mass index; BEH plus EDU: Behavioural management training plus educational intervention; CI: confidence interval; EDU: educational intervention alone; IV: inverse variance; SD: standard deviation

Figure 287: Change in % ideal body weight at 12 months follow-up
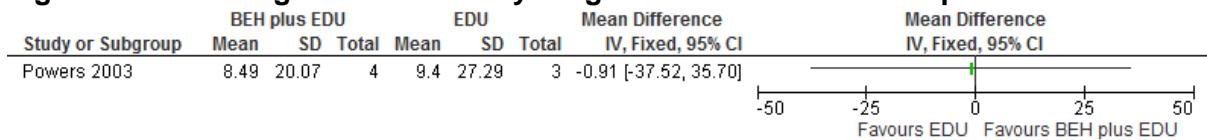
Study or Subgroup	BEH plus EDU Mean	SD	Total	EDU Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Powers 2003	8.49	20.07	4	9.4	27.29	3	-0.91 [-37.52, 35.70]

Abbreviations: BEH plus EDU: Behavioural management training plus educational intervention; EDU: educational intervention alone; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 288: Change in weight % for age at 12 months follow-up
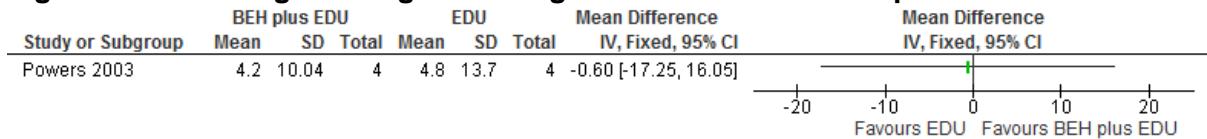
Study or Subgroup	BEH plus EDU Mean	SD	Total	EDU Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Powers 2003	4.2	10.04	4	4.8	13.7	4	-0.60 [-17.25, 16.05]

Abbreviations: BEH plus EDU: Behavioural management training plus educational intervention; EDU: educational intervention alone; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 289: Change in height (cm) at 12 and 24 months follow-up
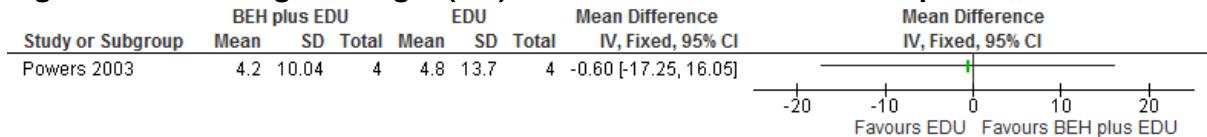
Study or Subgroup	BEH plus EDU Mean	SD	Total	EDU Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Powers 2003	4.2	10.04	4	4.8	13.7	4	-0.60 [-17.25, 16.05]

Abbreviations: BEH plus EDU: Behavioural management training plus educational intervention; CI: confidence interval; cm: centimetres; EDU: educational intervention alone; IV: inverse variance; SD: standard deviation

Figure 290:   Change in height z score at 24 months follow-up
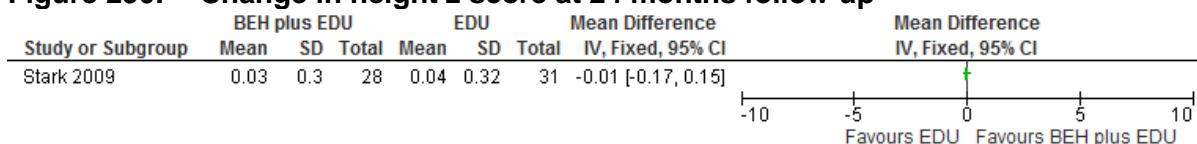
| Study or Subgroup | BEH plus EDU | | | EDU | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Stark 2009	0.03	0.3	28	0.04	0.32	31	-0.01 [-0.17, 0.15]	

-10 -5 0 5 10
Favours EDU Favours BEH plus EDU

Abbreviations: BEH plus EDU: Behavioural management training plus educational intervention; CI: confidence interval; cm: centimetres; EDU: educational intervention alone; IV: inverse variance; SD: standard deviation

Figure 291:   Change in FEV₁ % predicted at 2 years follow-up
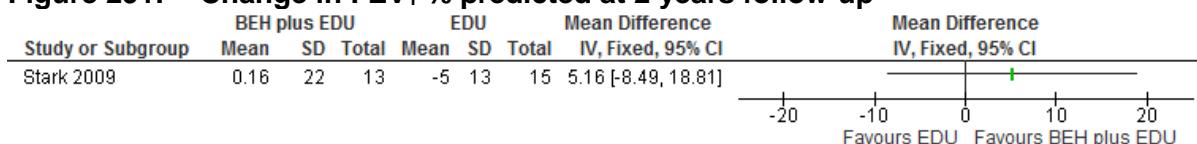
| Study or Subgroup | BEH plus EDU | | | EDU | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Stark 2009	0.16	22	13	-5	13	15	5.16 [-8.49, 18.81]	

-20 -10 0 10 20
Favours EDU Favours BEH plus EDU

Abbreviations: BEH plus EDU: Behavioural management training plus educational intervention; CI: confidence interval; EDU: educational intervention alone; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation.
Note: The study does not specify the unit of measurement for FEV₁.

I.14 Exocrine Pancreatic insufficiency

Comparison 1. Acid suppressing agents as adjuvant therapy to PERT

No forest plots available.

Comparison 2. High dose *versus* low dose PERT

Comparison 2.1. High-dose PERT *versus* low dose PERT in children

Figure 292:   Faecal fat excretion (g/ kg per day) at 14 days follow-up
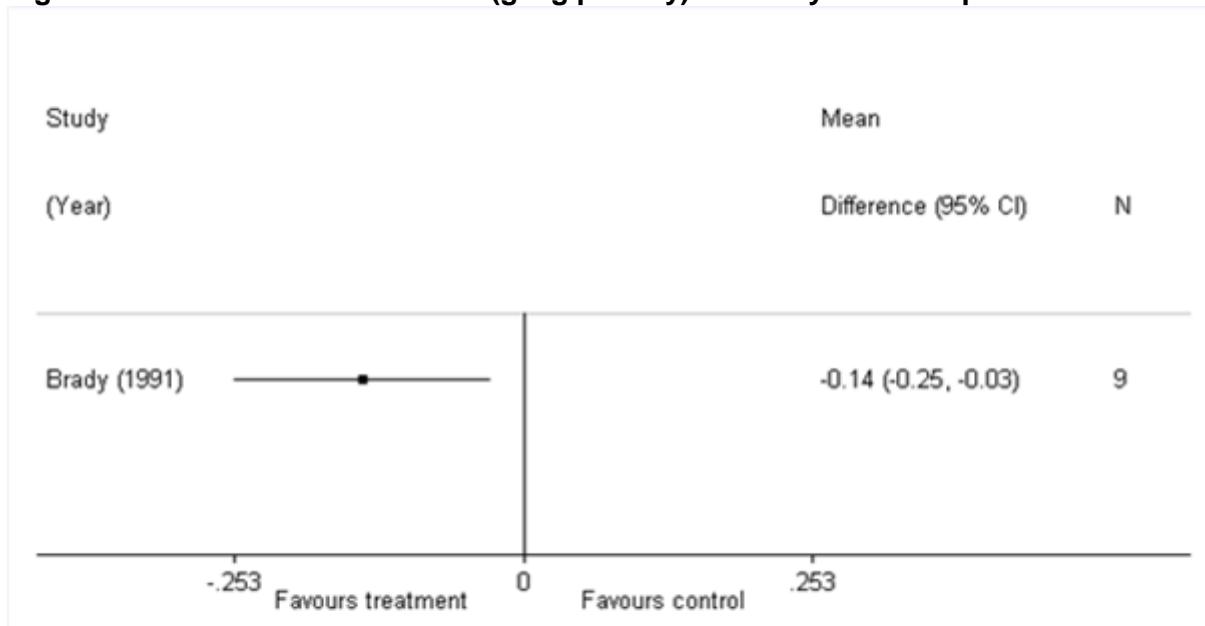
Abbreviations: g: grams; kg: kilograms; CI: confidence interval

Figure 293*:* **Faecal fat excretion (g/ day) at 9 days follow-up**
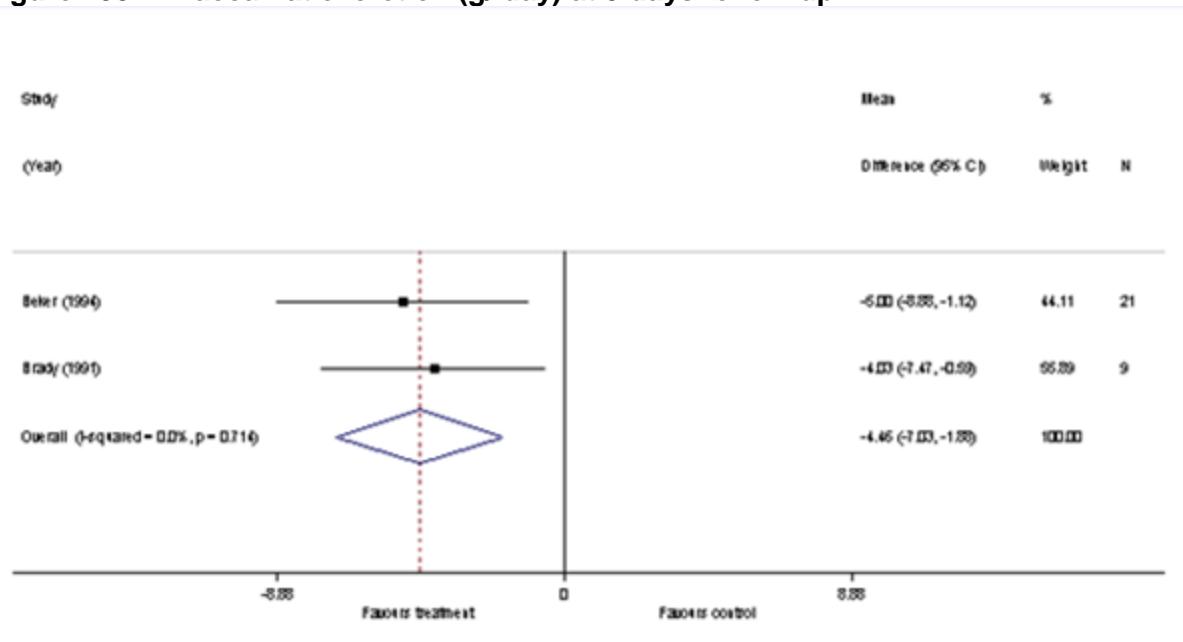
Abbreviations: g: grams; CI: confidence interval

Figure 294: **Stool frequency (bowel movement per day) at 4 weeks follow-up**
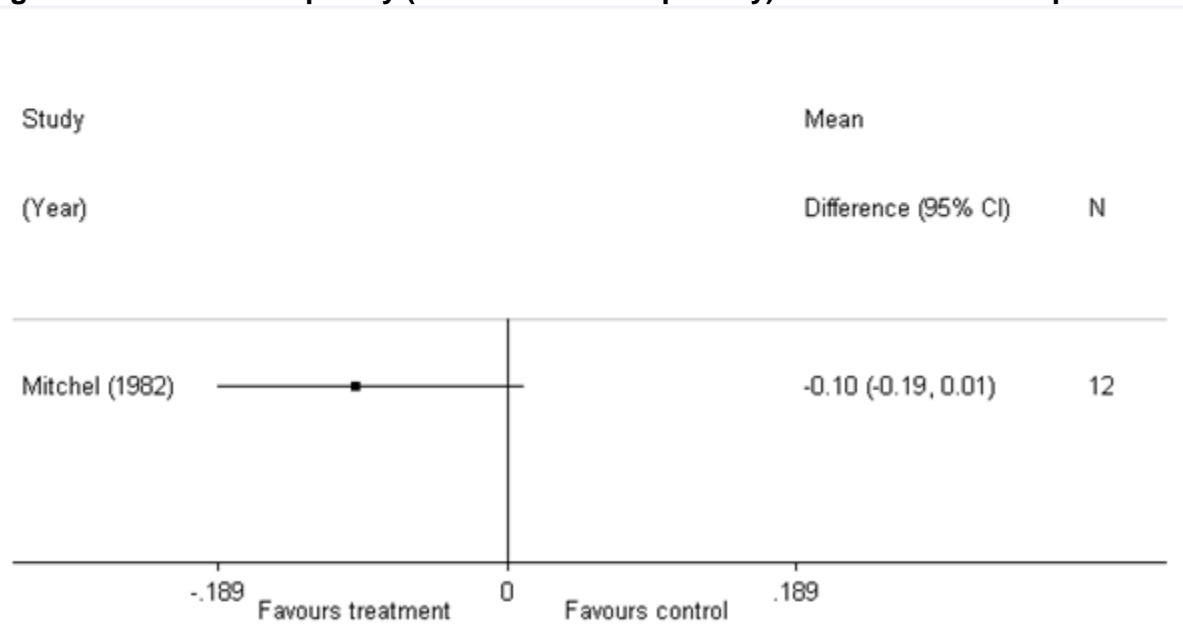
Abbreviations: CI: confidence interval

Comparison 2.1. High-dose PERT *versus* low dose PERT in children

No forest plots available.

I.15 Distal ileal obstruction syndrome

Not applicable, as no studies were included in this review.

I.16 Monitoring liver disease

Not applicable to this review.

I.17 Ursodeoxycholic acid

Comparison 1. UDCA *versus* placebo or control

Figure 295: **Lack of normalisation of hepatobiliary enzymes at 6 months follow-up**

Abbreviations: UDCA: ursodeoxycholic acid; M-H: Mantel-Haenszel; CI: confidence interval; df: degrees of freedom
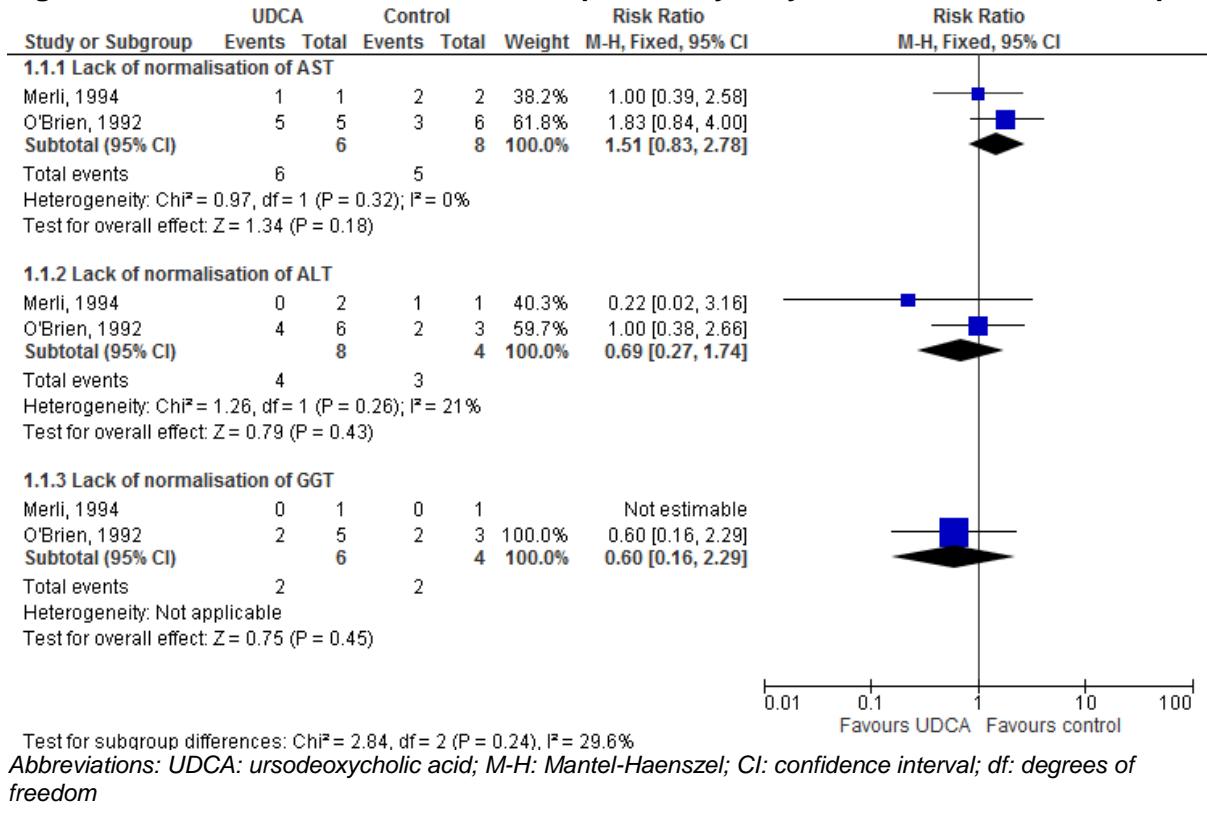
Figure 296: **Final value of bilirubin value (umol/L) at 6 months follow-up**

Abbreviations: UDCA: ursodeoxycholic acid; SD: standard deviation; IV: inverse variance; CI: confidence interval
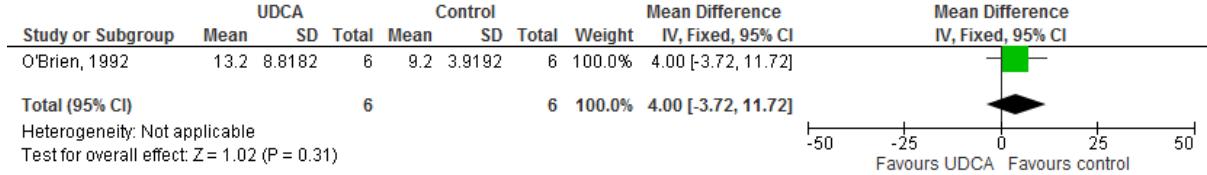
Figure 297: **Percentage change in hepatobiliary enzymes at 12 months follow-up**
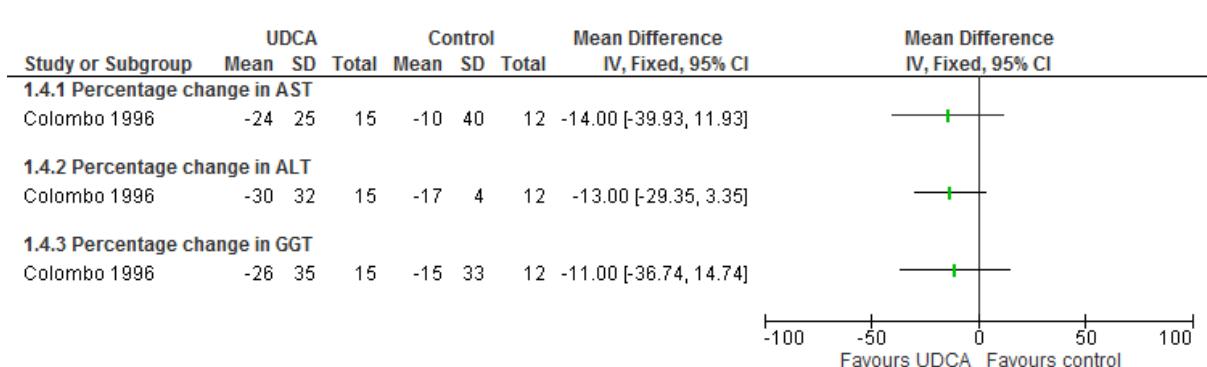
Abbreviations: UDCA: ursodeoxycholic acid; SD: standard deviation; IV: inverse variance; CI: confidence interval. Colombo: Data reported as multiples of the upper limit of normal reference values.

Figure 298: **No development of liver disease at 6 months follow-up**

Data cannot be plotted. None of the participants developed liver disease in either treatment arm.

Figure 299: **Liver failure at 12 months follow-up**

Abbreviations: UDCA: ursodeoxycholic acid; M-H: Mantel-Haenszel; CI: confidence interval

Figure 300: **Liver transplantation at 12 months follow-up**

Abbreviations: UDCA: ursodeoxycholic acid; M-H: Mantel-Haenszel; CI: confidence interval

I.18 Monitoring for CF related diabetes

Not applicable, as no studies were identified for this review.

I.19 Bone mineral density

Not applicable to this review.

I.20 Exercise

Comparison 1. Aerobic exercise training programme *versus* no exercise programme

Figure 301: **Change in FEV$_1$ % predicted at hospital discharge (mean ≈ 19 days) (range of scores: 0-100)**
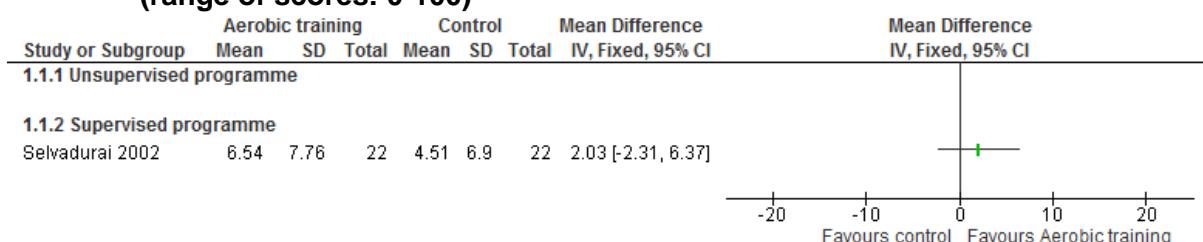
Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 302: Change in FEV$_1$ % predicted at 3 months follow-up (range of scores: 0-100)
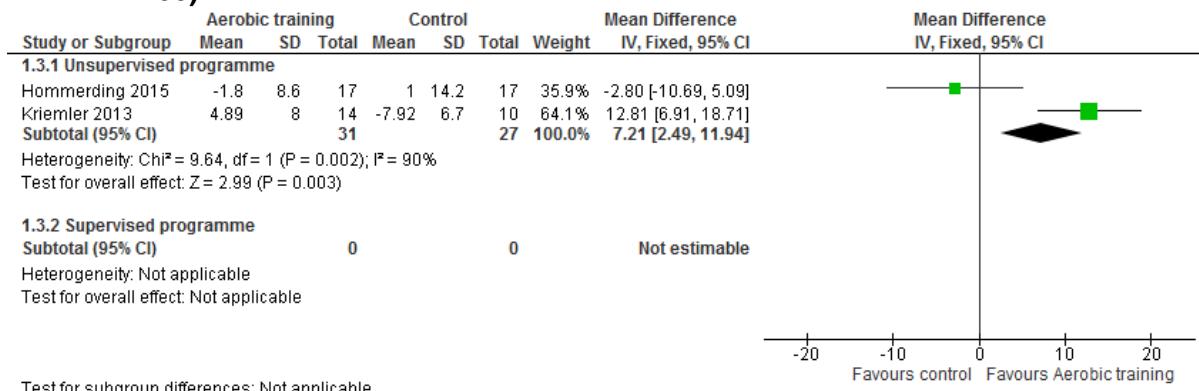
Abbreviations: CI: confidence interval; df: degrees of freedom; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 303: Change in FEV$_1$ % predicted at 6 months follow-up (range of scores: 0-100)
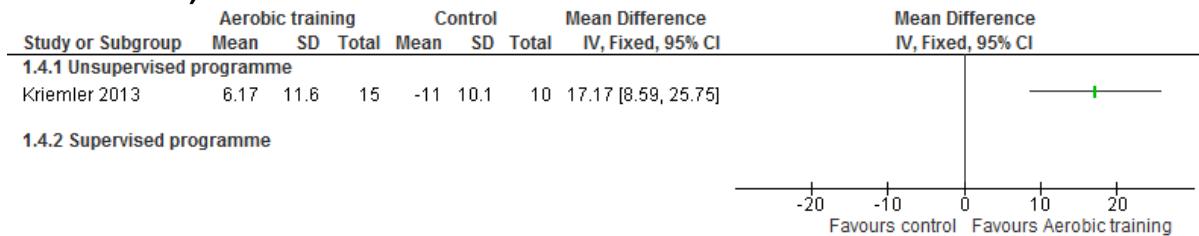
Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 304: Change in FEV$_1$ % predicted at 3 years follow-up (range of scores: 0-100)
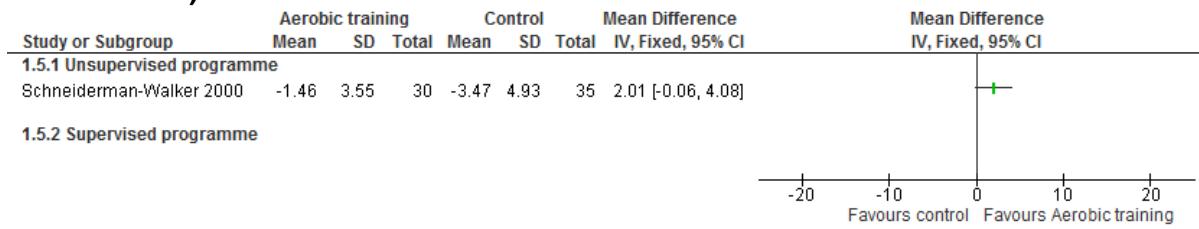
Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 305: Change in FVC % predicted at hospital discharge (mean ≈ 19 days) (range of scores: 0-100)
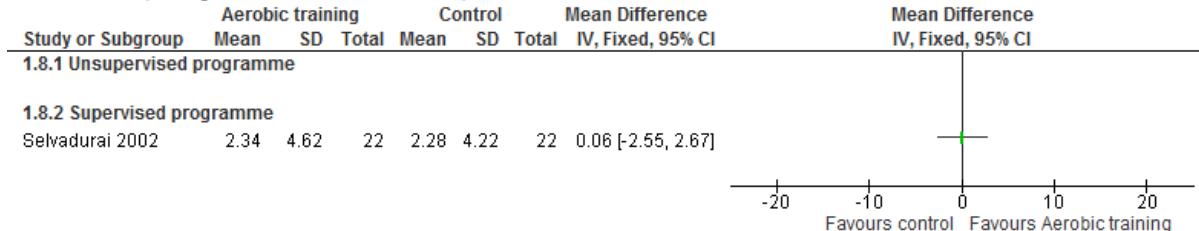
Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 306: Change in FVC % predicted at 3 months follow-up (range of scores: 0-100)

	Aerobic training			Control				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 Unsupervised programme									
Hommerding 2015	0.4	6.7	17	2	12.2	17	40.2%	-1.60 [-8.22, 5.02]	
Kriemler 2013	3.67	7.3	14	-5.57	6.2	10	59.8%	9.24 [3.82, 14.66]	
Subtotal (95% CI)			31			27	100.0%	4.89 [0.69, 9.08]	
Heterogeneity: Chi² = 6.17, df = 1 (P = 0.01); I² = 84%									
Test for overall effect: Z = 2.28 (P = 0.02)									
1.10.2 Supervised programme									
Subtotal (95% CI)			0			0		Not estimable	
Heterogeneity: Not applicable									
Test for overall effect: Not applicable									

Test for subgroup differences: Not applicable

Abbreviations: CI: confidence interval; df: degrees of freedom; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation;

Figure 307: Change in FVC % predicted at 6 months follow-up (range of scores: 0-100)
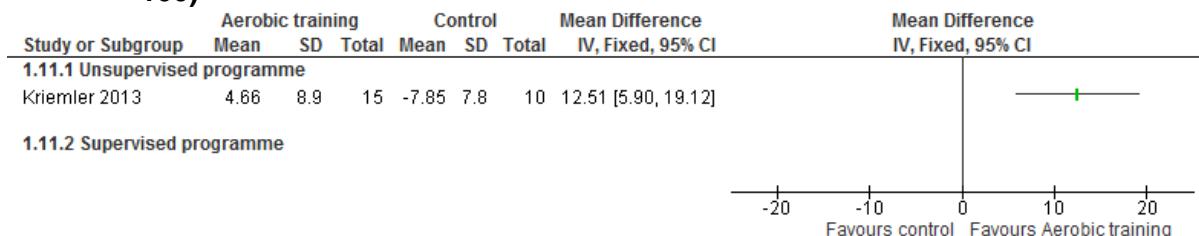
	Aerobic training			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.11.1 Unsupervised programme								
Kriemler 2013	4.66	8.9	15	-7.85	7.8	10	12.51 [5.90, 19.12]	
1.11.2 Supervised programme								

Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 308: Change in FVC % predicted at 3 years follow-up (range of scores: 0-100)
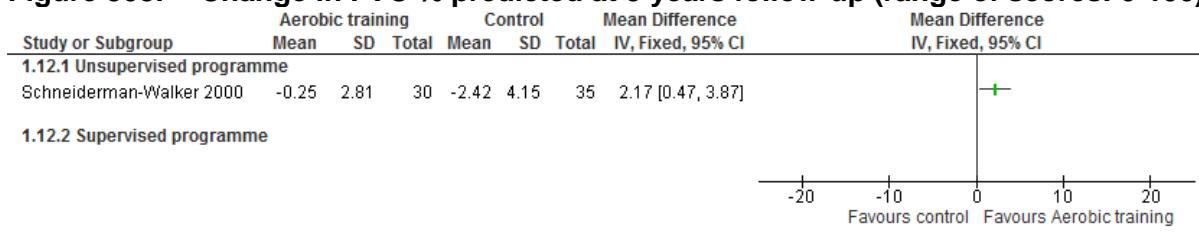
	Aerobic training			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.12.1 Unsupervised programme								
Schneiderman-Walker 2000	-0.25	2.81	30	-2.42	4.15	35	2.17 [0.47, 3.87]	
1.12.2 Supervised programme								

Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 309: Change in VO$_2$ max. at hospital discharge (mean ≈ 19 days)
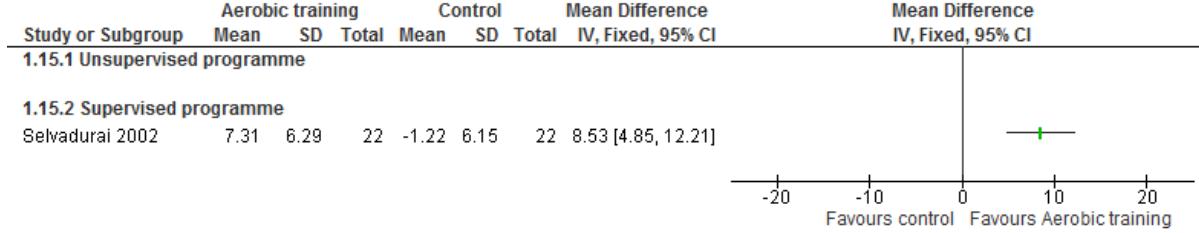
	Aerobic training			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.15.1 Unsupervised programme								
1.15.2 Supervised programme								
Selvadurai 2002	7.31	6.29	22	-1.22	6.15	22	8.53 [4.85, 12.21]	

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation; VO$_2$ max: maximal oxygen consumption

Figure 310: Change in VO₂ max. at 3 months follow-up

Abbreviations: CI: confidence interval; df: degrees of freedom; IV: inverse variance; SD: standard deviation; VO₂ max: maximal oxygen consumption

Figure 311: Change in VO₂ max. at 6 months follow-up
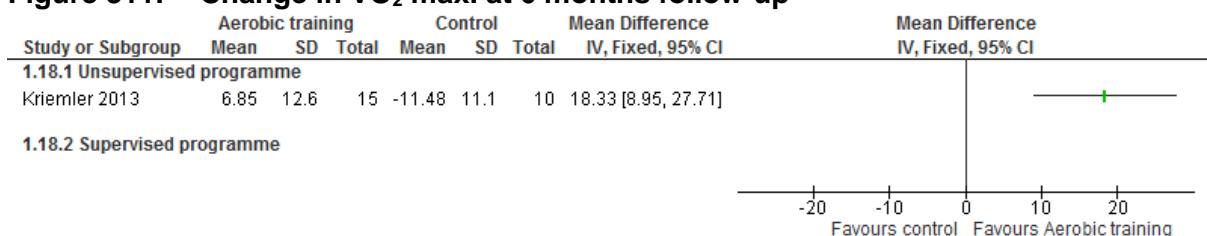
Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation; VO₂ max: maximal oxygen consumption

**Figure 312: Change in BMI at 3 months follow-up**
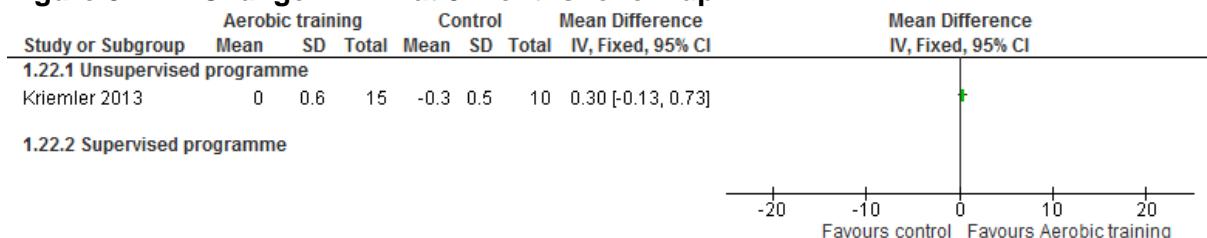
Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 313: Change in BMI at 6 months follow-up
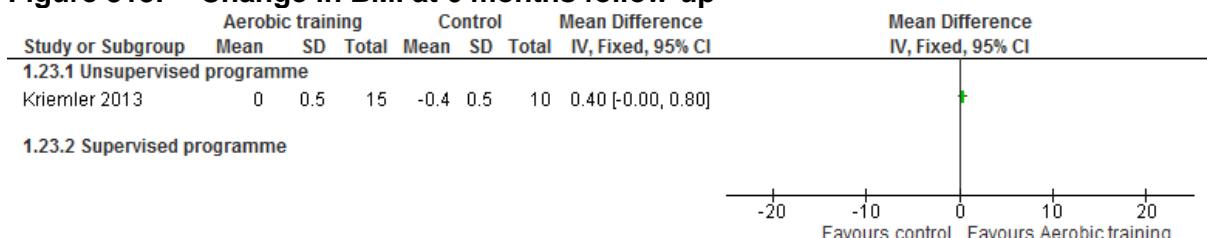
Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Comparison 2.1. Strength resistance/ anaerobic training programme *versus* no exercise programme

Figure 314: Change in FEV$_1$ % predicted at hospital discharge (mean ≈ 19 days) (range of scores: 0-100)
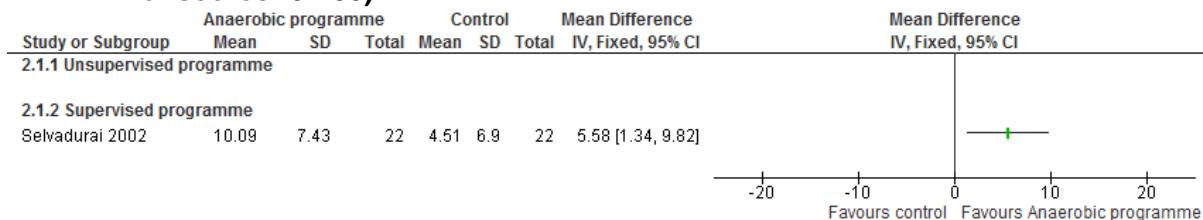
| Study or Subgroup	Anaerobic programme			Control			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.1.1 Unsupervised programme								
2.1.2 Supervised programme								
Selvadurai 2002	10.09	7.43	22	4.51	6.9	22	5.58 [1.34, 9.82]	

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 315: Change in FEV$_1$ % predicted at 3 months follow-up (range of scores: 0-100)
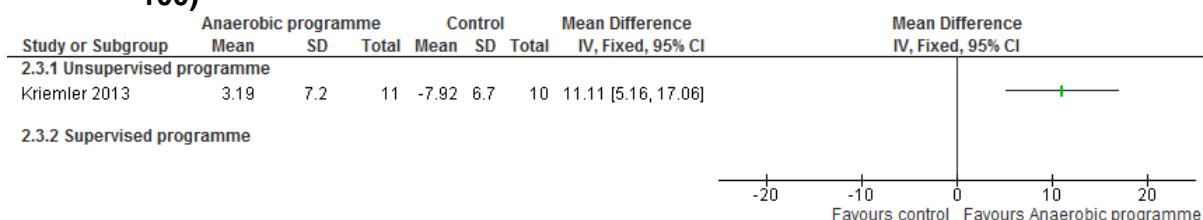
Study or Subgroup	Anaerobic programme			Control			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.3.1 Unsupervised programme								
Kriemler 2013	3.19	7.2	11	-7.92	6.7	10	11.11 [5.16, 17.06]	
2.3.2 Supervised programme								

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 316: Change in FEV$_1$ % predicted at 6 months follow-up (range of scores: 0-100)
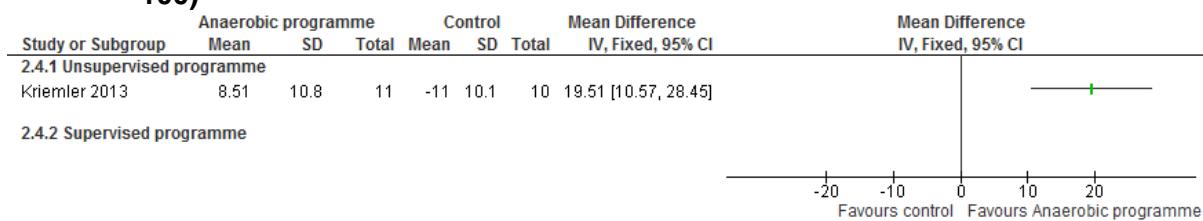
Study or Subgroup	Anaerobic programme			Control			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.4.1 Unsupervised programme								
Kriemler 2013	8.51	10.8	11	-11	10.1	10	19.51 [10.57, 28.45]	
2.4.2 Supervised programme								

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 317: Change in FVC % predicted at hospital discharge (mean ≈ 19 days) (range of scores: 0-100)
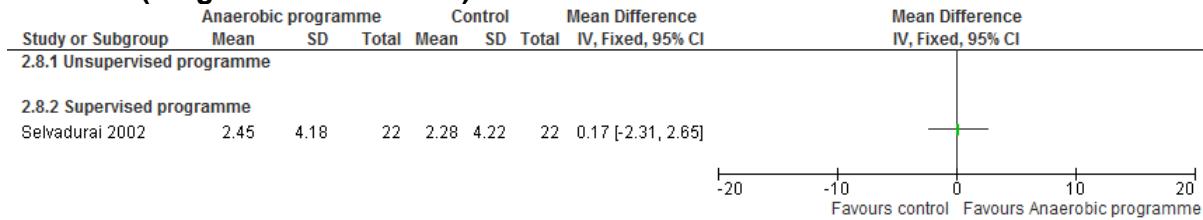
| Study or Subgroup	Anaerobic programme			Control			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.8.1 Unsupervised programme								
2.8.2 Supervised programme								
Selvadurai 2002	2.45	4.18	22	2.28	4.22	22	0.17 [-2.31, 2.65]	

Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

**Figure 318:   Change in FVC % predicted at 3 months follow-up (range of scores: 0-100)**
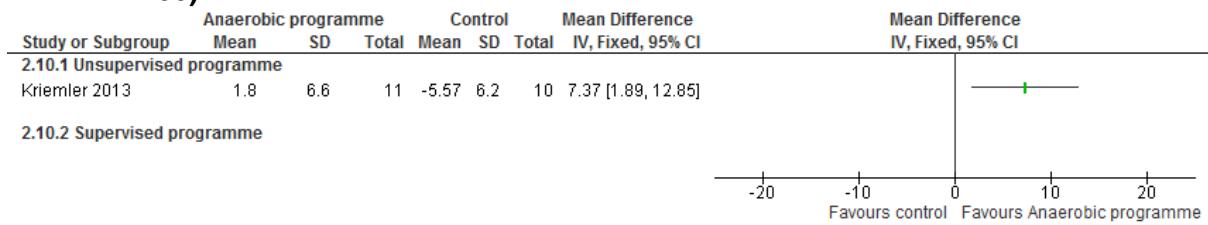
Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 319:   Change in FVC % predicted at 6 months follow-up (range of scores: 0-100)
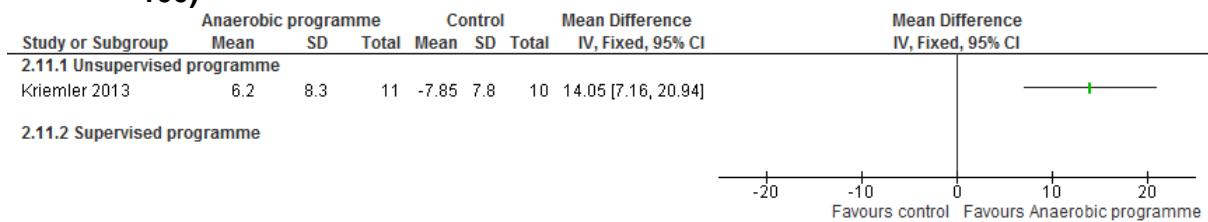
Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 320:   Change in VO$_2$ max at hospital discharge (mean ≈ 19 days)
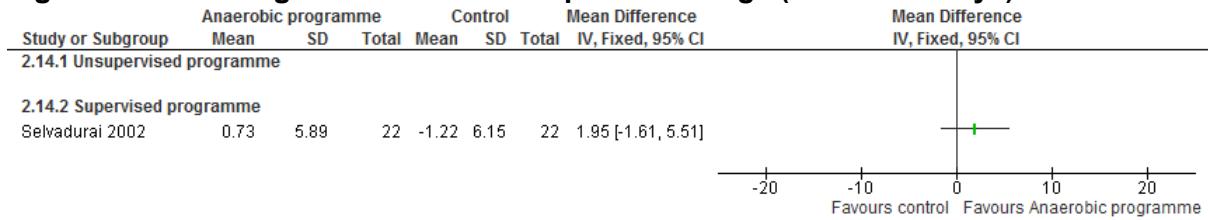

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation; VO$_2$ max: maximal oxygen consumption

Figure 321:   Change in VO$_2$ max at 3 months follow-up
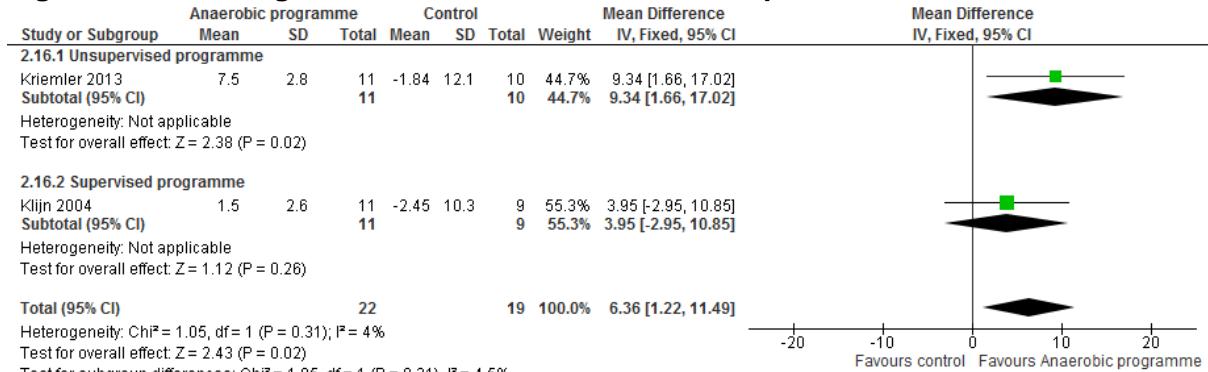
Abbreviations: CI: confidence interval; df: degrees of freedom; IV: inverse variance; SD: standard deviation; VO$_2$ max: maximal oxygen consumption

**Figure 322:   Change in VO$_2$ max at 6 months follow-up**
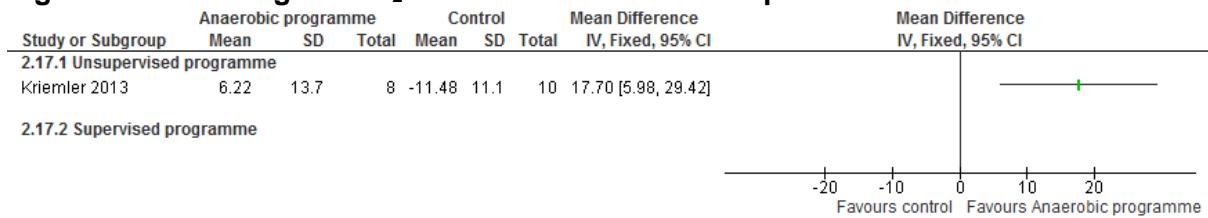
Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation; VO$_2$ max: maximal oxygen

consumption

Figure 323:   Change in BMI at 3 months follow-up
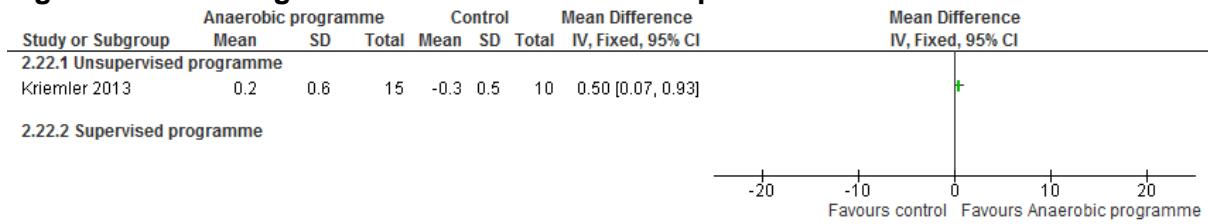
Study or Subgroup	Anaerobic programme			Control			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.22.1 Unsupervised programme								
Kriemler 2013	0.2	0.6	15	-0.3	0.5	10	0.50 [0.07, 0.93]	
2.22.2 Supervised programme								

Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 324:   Change in BMI at 6 months follow-up
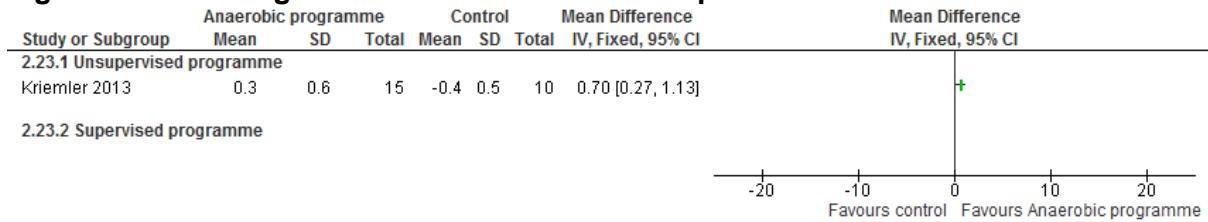
Study or Subgroup	Anaerobic programme			Control			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.23.1 Unsupervised programme								
Kriemler 2013	0.3	0.6	15	-0.4	0.5	10	0.70 [0.27, 1.13]	
2.23.2 Supervised programme								

Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 325:   Change in quality of life (CFQ-R physical domain) at 3 months follow-up (range of scores: 0-100)
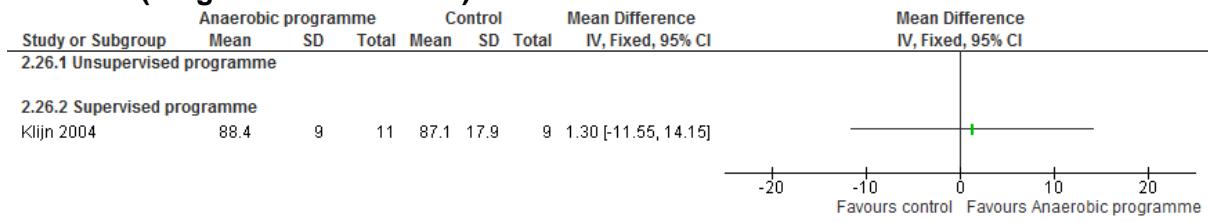
Study or Subgroup	Anaerobic programme			Control			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.26.1 Unsupervised programme								
2.26.2 Supervised programme								
Klijn 2004	88.4	9	11	87.1	17.9	9	1.30 [-11.55, 14.15]	

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Comparison 2.2. Strength/ anaerobic training programme *versus* aerobic training programme

Figure 326:   Change in FEV$_1$ % predicted at hospital discharge (mean ≈ 19 days) (range of scores: 0-100)
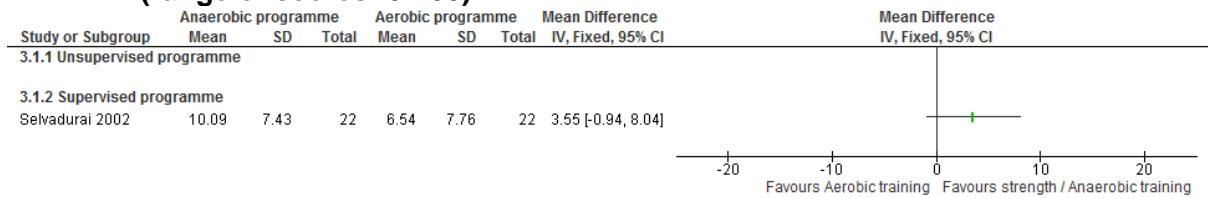
| Study or Subgroup	Anaerobic programme			Aerobic programme			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
3.1.1 Unsupervised programme								
3.1.2 Supervised programme								
Selvadurai 2002	10.09	7.43	22	6.54	7.76	22	3.55 [-0.94, 8.04]	

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

**Figure 327:   Change in FEV$_1$ % predicted at 3 months follow-up (range of scores: 0-100)**
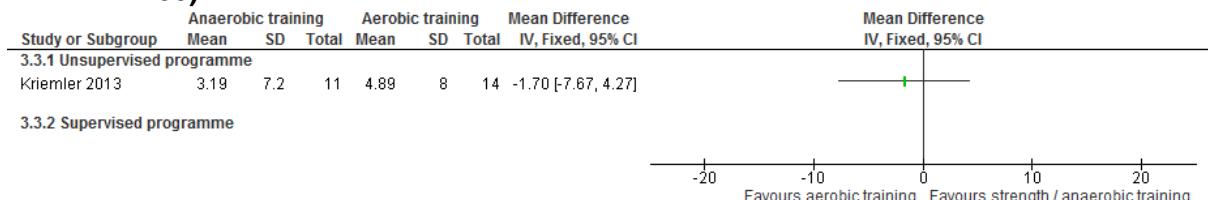
Study or Subgroup	Anaerobic training			Aerobic training			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
3.3.1 Unsupervised programme								
Kriemler 2013	3.19	7.2	11	4.89	8	14	-1.70 [-7.67, 4.27]	
3.3.2 Supervised programme								

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD:

standard deviation

Figure 328: Change in FEV₁ % predicted at 6 months follow-up (range of scores: 0-100)
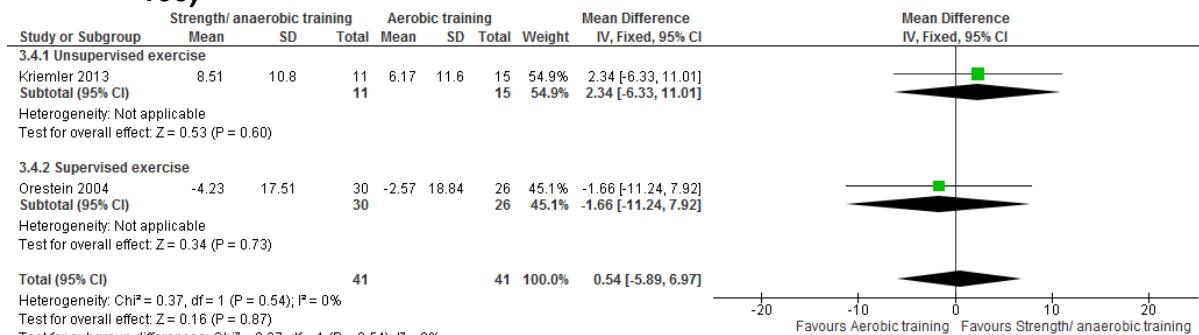
Abbreviations: CI: confidence interval; df: degrees of freedom; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 329: Change in FEV₁ % predicted at 12 months follow-up (range of scores: 0-100)
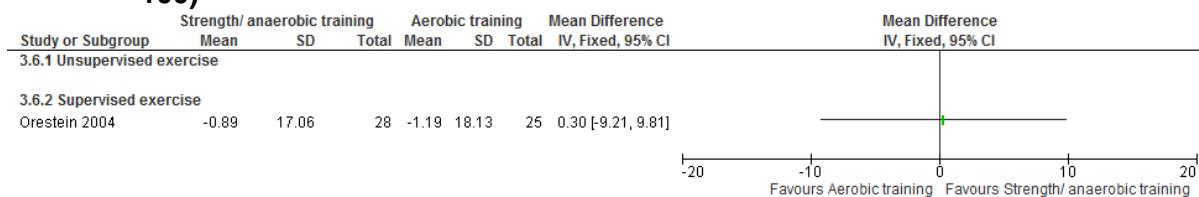
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 330: Change in FVC% predicted at hospital discharge (mean aprox. 19 days) (range of scores: 0-100)
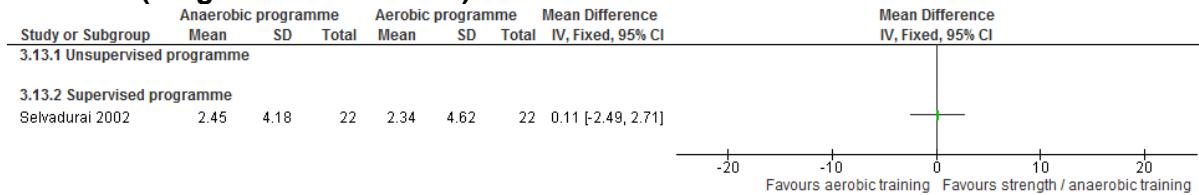
Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 331: Change in FVC% predicted at 3 months follow-up (range of scores: 0-100)
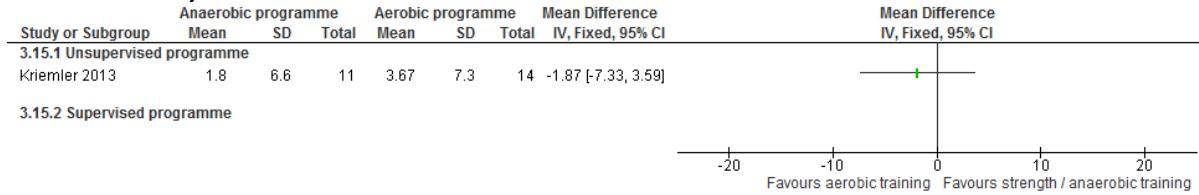
Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 332: Change in FVC % predicted at 6 months follow-up (range of scores: 0-100)
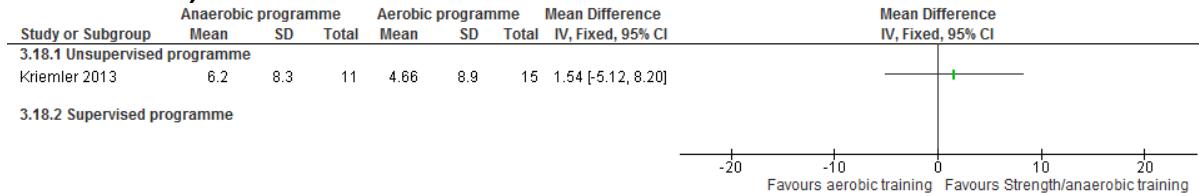
Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 333: Change in VO$_2$ max at hospital discharge (mean ≈ 19 days)
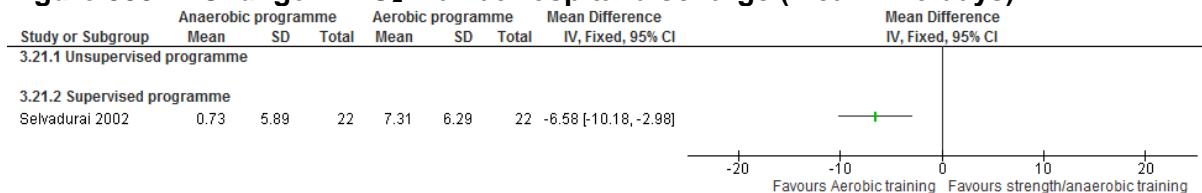
Study or Subgroup	Anaerobic programme Mean	SD	Total	Aerobic programme Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
3.21.1 Unsupervised programme								
3.21.2 Supervised programme								
Selvadurai 2002	0.73	5.89	22	7.31	6.29	22	-6.58 [-10.18, -2.98]	

Favours Aerobic training Favours strength/anaerobic training

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation; VO$_2$ max: maximal oxygen consumption

Figure 334: Change in VO$_2$ max at 3 months follow-up
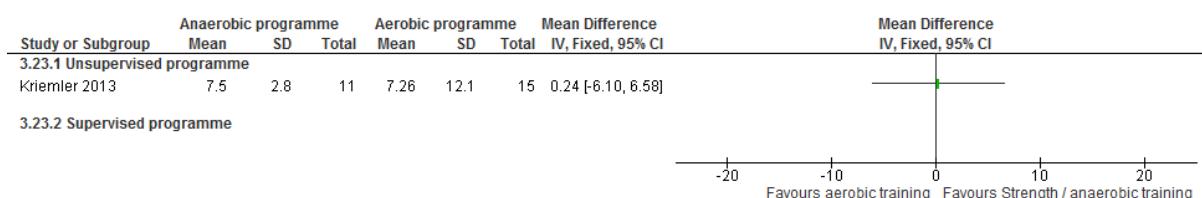
Study or Subgroup	Anaerobic programme Mean	SD	Total	Aerobic programme Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
3.23.1 Unsupervised programme								
Kriemler 2013	7.5	2.8	11	7.26	12.1	15	0.24 [-6.10, 6.58]	
3.23.2 Supervised programme								

Favours aerobic training Favours Strength / anaerobic training

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation; VO$_2$ max: maximal oxygen consumption

Figure 335: Change in VO$_2$ max at 6 months follow-up

Study or Subgroup	Strength/ anaerobic training Mean	SD	Total	Aerobic training Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
3.25.1 Unsupervised exercise									
Kriemler 2013	6.22	13.7	11	6.85	12.6	15	8.3%	-0.63 [-10.94, 9.68]	
Subtotal (95% CI)			11			15	8.3%	-0.63 [-10.94, 9.68]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.12 (P = 0.90)									
3.25.2 Supervised exercise									
Orestein 2004	-2.16	6.05	30	-1.91	5.78	26	91.7%	-0.25 [-3.35, 2.85]	
Subtotal (95% CI)			30			26	91.7%	-0.25 [-3.35, 2.85]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.16 (P = 0.87)									
Total (95% CI)			41			41	100.0%	-0.28 [-3.25, 2.69]	

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.19 (P = 0.85)
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.94), I² = 0%

Favours Aerobic training Favours Strength/ anaerobic training

Abbreviations: CI: confidence interval; df: degrees of freedom; IV: inverse variance; SD: standard deviation; VO$_2$ max: maximal oxygen consumption

Figure 336: Change in BMI at 3 months follow-up
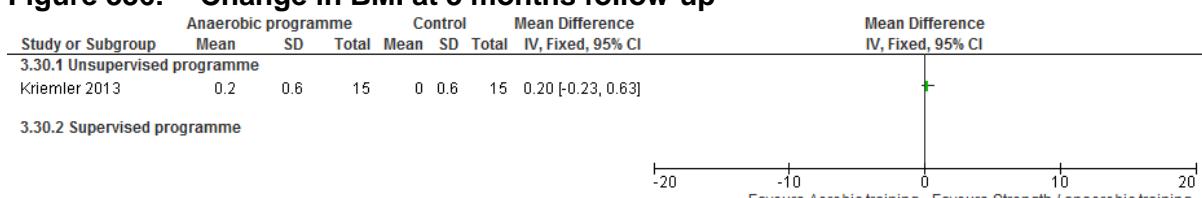
Study or Subgroup	Anaerobic programme Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
3.30.1 Unsupervised programme								
Kriemler 2013	0.2	0.6	15	0	0.6	15	0.20 [-0.23, 0.63]	
3.30.2 Supervised programme								

Favours Aerobic training Favours Strength / anaerobic training

Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 337: Change in BMI at 6 months follow-up
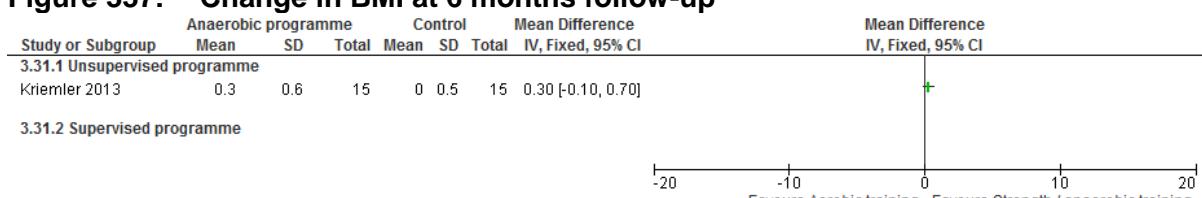
Study or Subgroup	Anaerobic programme Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
3.31.1 Unsupervised programme								
Kriemler 2013	0.3	0.6	15	0	0.5	15	0.30 [-0.10, 0.70]	
3.31.2 Supervised programme								

Favours Aerobic training Favours Strength / anaerobic training

Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Comparison 3. High-intensity interval training *versus* standard aerobic and anaerobic exercise programme

Figure 338:   Change in FEV₁ % predicted at 6 weeks follow-up (range of scores: 0-100)
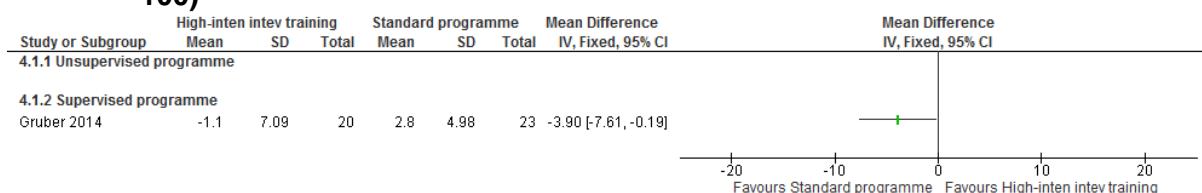
Study or Subgroup	High-inten intev training Mean	SD	Total	Standard programme Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.1.1 Unsupervised programme								
4.1.2 Supervised programme								
Gruber 2014	-1.1	7.09	20	2.8	4.98	23	-3.90 [-7.61, -0.19]	

Favours Standard programme Favours High-inten intev training

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 339:   Change in VC % (range of scores: 0-100) predicted at 6 weeks follow-up

Study or Subgroup	High-inten intev training Mean	SD	Total	Standard programme Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.2.1 Unsupervised programme								
4.2.2 Supervised programme								
Gruber 2014	-1.2	10.57	20	3.9	9.12	23	-5.10 [-11.05, 0.85]	

Favours Standard programme Favours High-inten intev training
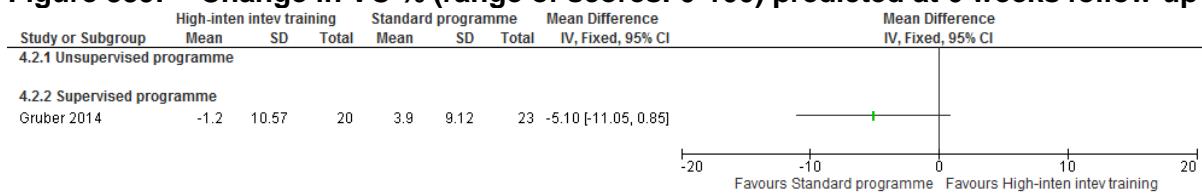
Abbreviations: VC: vital capacity; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 340:   Change in VO₂ max at 6 weeks follow-up
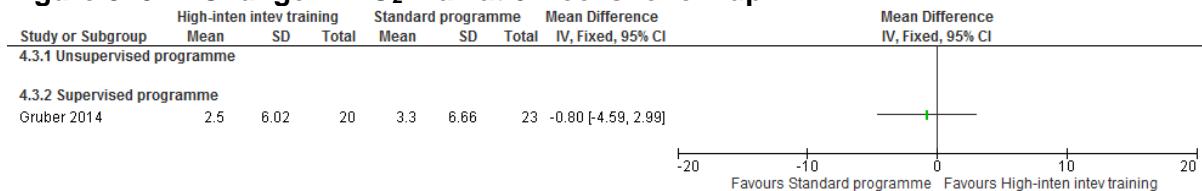
Study or Subgroup	High-inten intev training Mean	SD	Total	Standard programme Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.3.1 Unsupervised programme								
4.3.2 Supervised programme								
Gruber 2014	2.5	6.02	20	3.3	6.66	23	-0.80 [-4.59, 2.99]	

Favours Standard programme Favours High-inten intev training

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation; VO₂ max: maximal oxygen consumption

Figure 341:   Change in BMI at 6 weeks follow-up
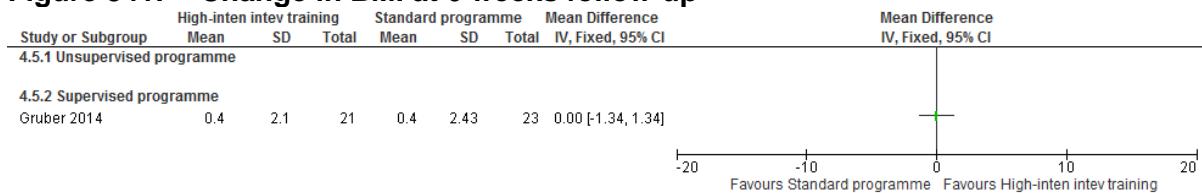
Study or Subgroup	High-inten intev training Mean	SD	Total	Standard programme Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.5.1 Unsupervised programme								
4.5.2 Supervised programme								
Gruber 2014	0.4	2.1	21	0.4	2.43	23	0.00 [-1.34, 1.34]	

Favours Standard programme Favours High-inten intev training

Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Comparison 4. Inspiratory muscle training (IMT) at 80% of maximal effort *versus* usual care

Figure 342:   Change in FEV₁ litres at 2 to 6 months follow-up

Study or Subgroup	IMT 80% Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Enright 2004	2	1	9	2	1	10	0.00 [-0.90, 0.90]	

Favours usual care Favours IMT 80%
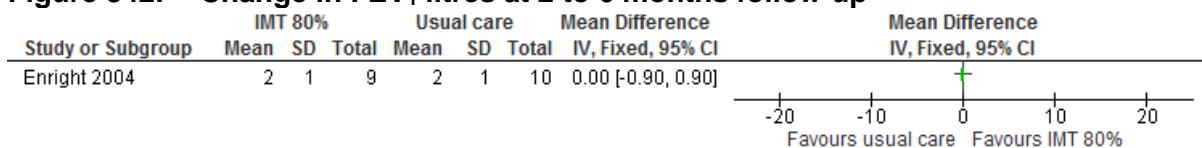
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IMT 80%: inspiratory muscle training at 80% of maximal effort; IV: inverse variance; SD: standard deviation

Figure 343: Change in FVC litres at 2 to 6 months follow-up
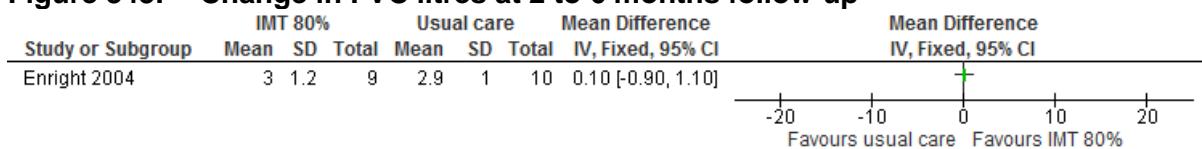
Abbreviations: CI: confidence interval; FVC: forced vital capacity; IMT 80%: inspiratory muscle training at 80% of maximal effort; IV: inverse variance; SD: standard deviation

Comparison 5. Combined aerobic and anaerobic training programme *versus* no exercise programme

Figure 344: Change in FEV$_1$ % predicted at 3 months follow-up (range of scores: 0-100)
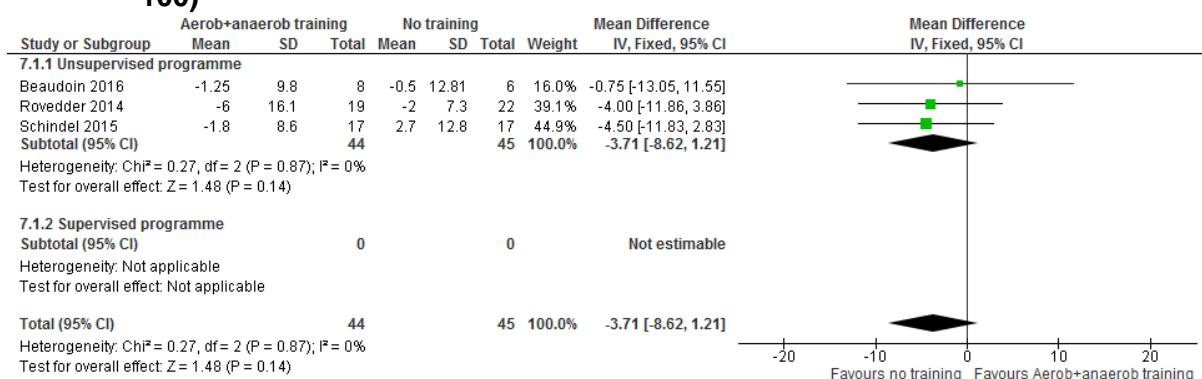
Abbreviations: CI: confidence interval; df: degrees of freedom; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 345: Change in FEV$_1$ % predicted at 3 to 6 months follow-up (range of scores: 0-100)
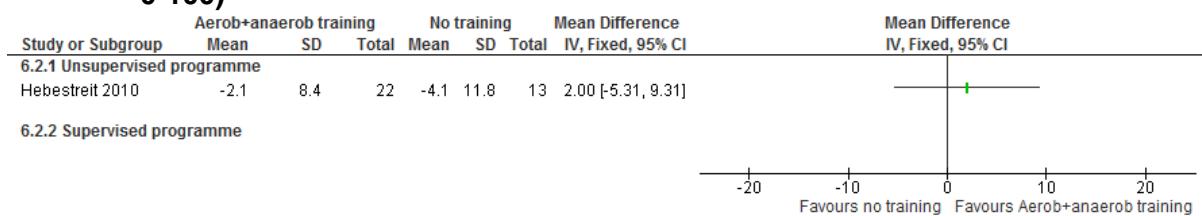
Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 346: Change in FVC% predicted at 3 months follow-up (range of scores: 0-100)
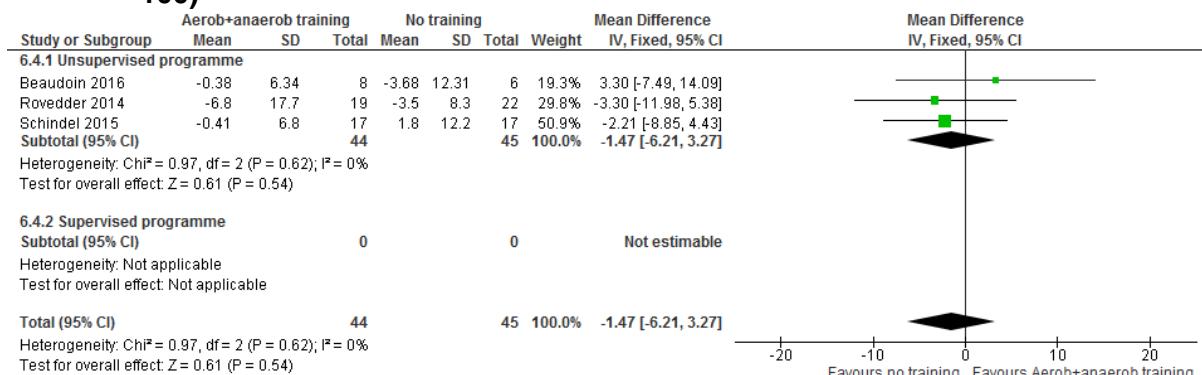
Abbreviations: CI: confidence interval; df: degrees of freedom; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 347:   Change in FVC % predicted at 3 to 6 months follow-up (range of scores: 0-100)
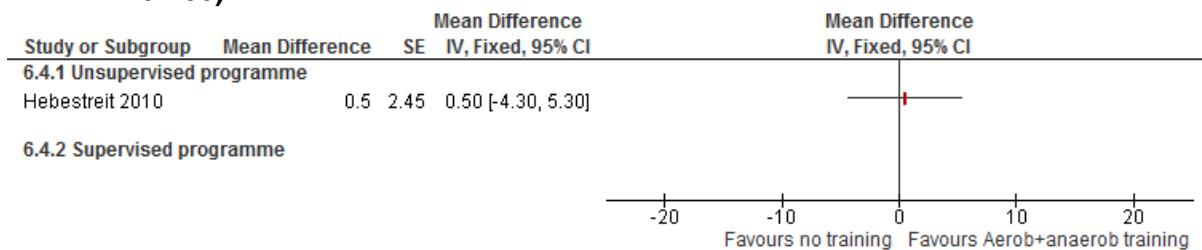
Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 348:   Change in VO$_2$ peak at 3 months follow-up
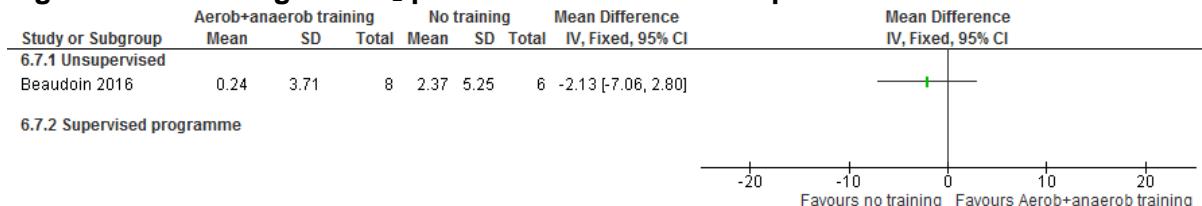
Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation; VO$_2$ max: maximal oxygen consumption

Figure 349:   Change in VO$_2$ peak at 3 to 6 months follow-up
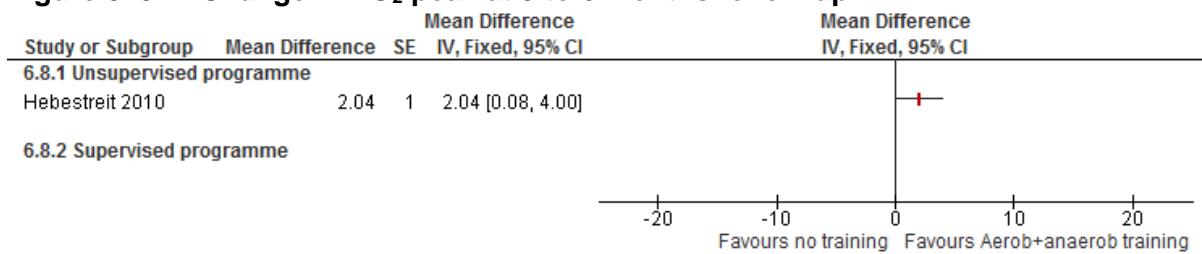
Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation; VO$_2$ max: maximal oxygen consumption

Figure 350:   Change in weight (kg) at 3 months follow-up
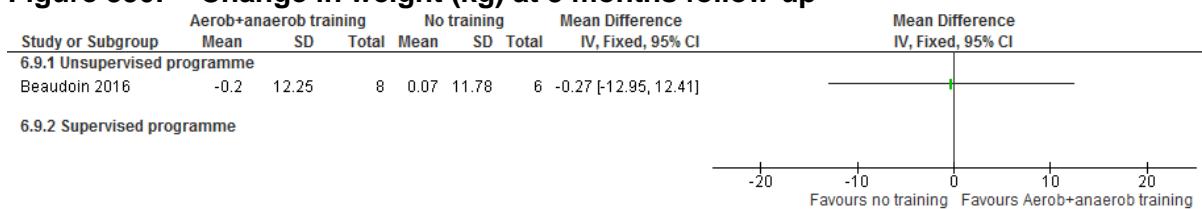
Abbreviations: kg: kilograms; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 351:   Change in BMI at 3 months follow-up
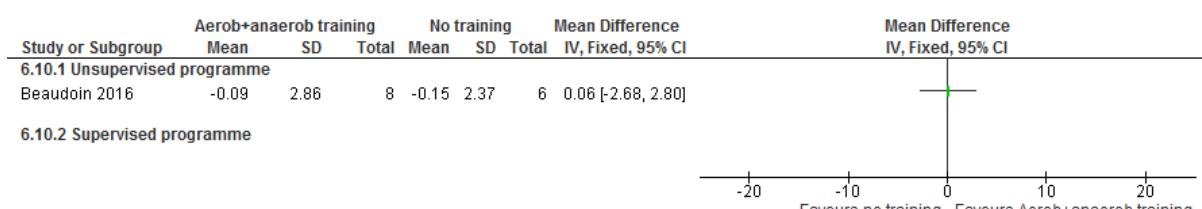
Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 352:   Change in BMI at 3 to 6 months follow-up
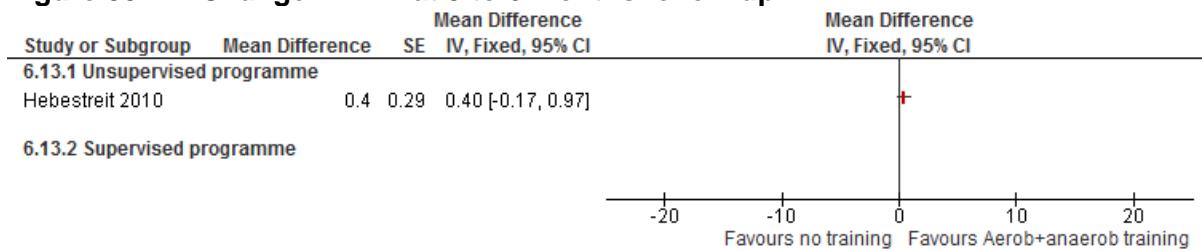
Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 353:   Change in BMI at 12 months follow-up
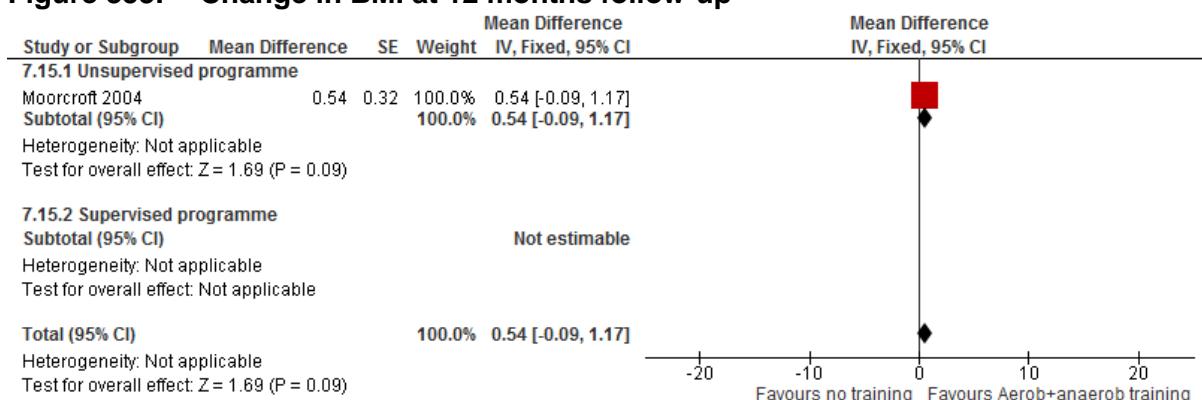
Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 354:   Change in quality of life – CFQ-R physical functioning at 3 months follow-up (range of scores: 0-100)
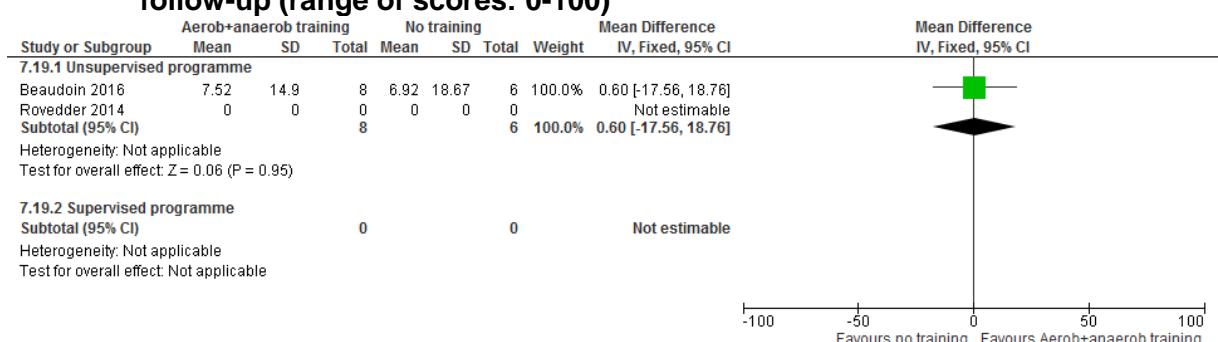
Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 355:   Change in quality of life – CFQ-R vitality at 3 months follow-up (range of scores: 0-100)
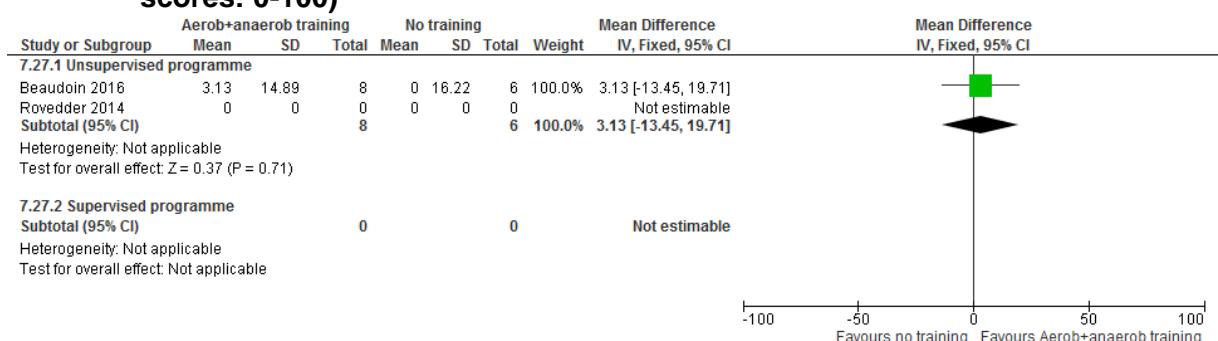
Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Figure 356:   Change in quality of life – CFQ-R emotional state at 3 months follow-up (range of scores: 0-100)
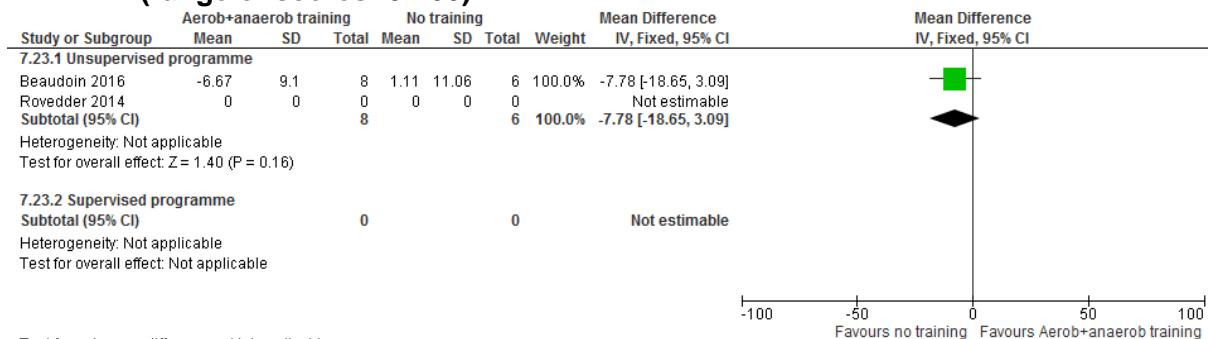
Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Figure 357:   Change in quality of life – CFQ-R treatment burden at 3 months follow-up (range of scores: 0-100)
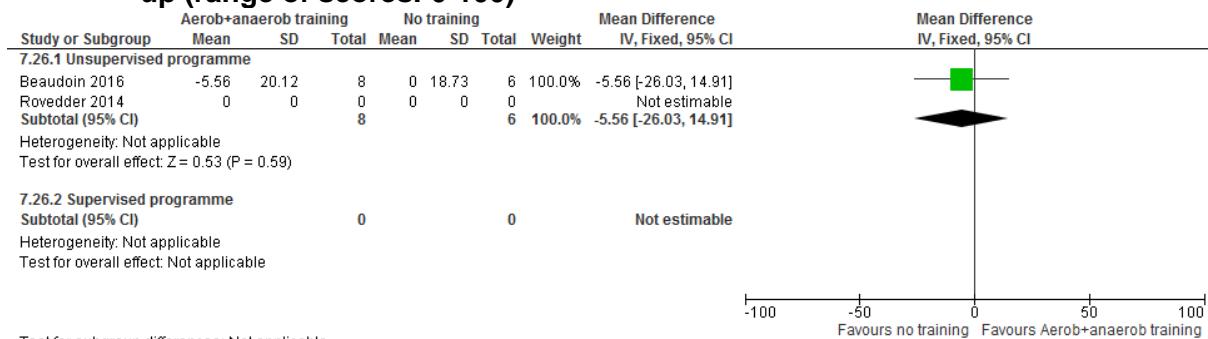
Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Figure 358:   Change in quality of life – CFQ-R health perception at 3 months follow-up (range of scores: 0-100)
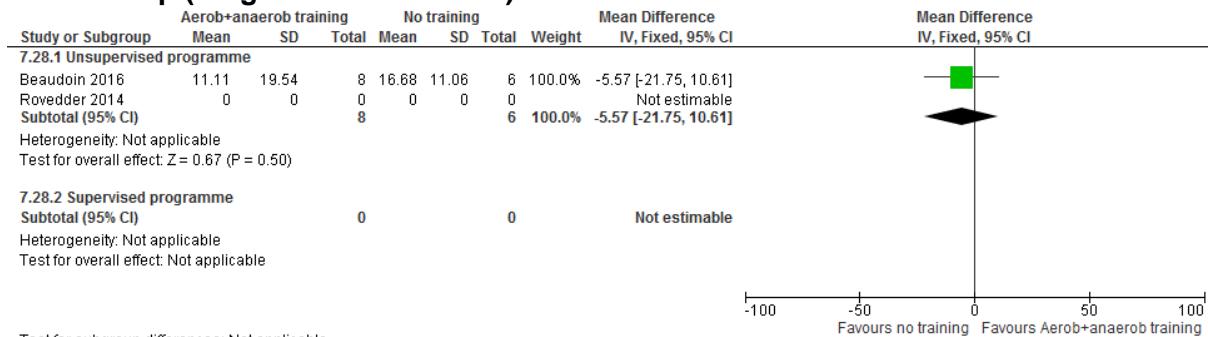
Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Figure 359: Change in quality of life – CFQ-R social limitations at 3 months follow-up (range of scores: 0-100)
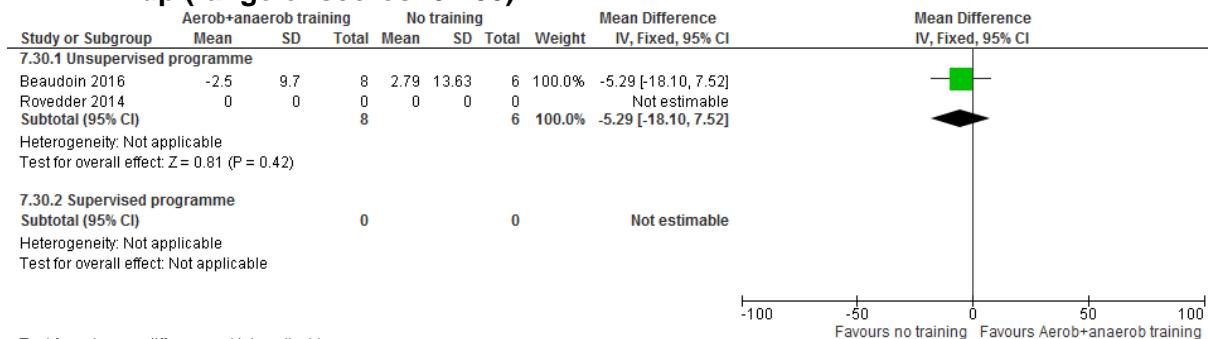
Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Figure 360: Change in quality of life – CFQ-R body image at 3 months follow-up (range of scores: 0-100)
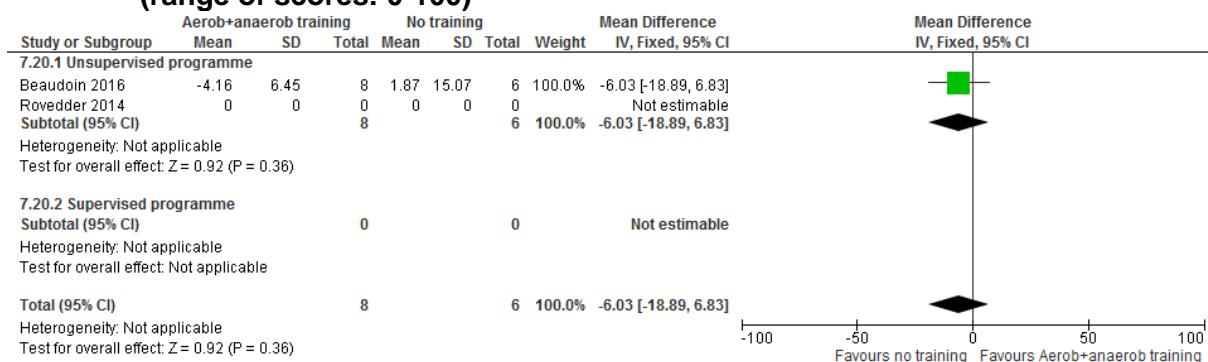
Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

**Figure 361: Change in quality of life – CFQ-R role limitations at 3 months follow-up (range of scores: 0-100)**
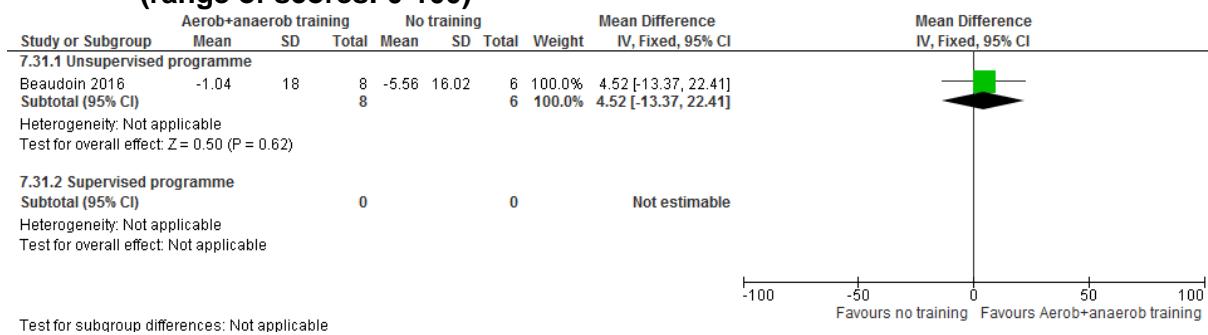
Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 362: Change in quality of life – CFQ-R weight problems at 3 months follow-up
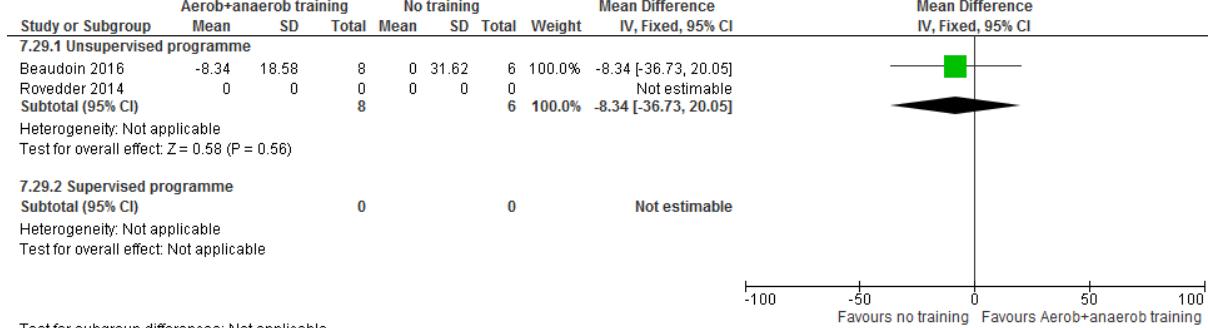
Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Figure 363: Change in quality of life – CFQ-R respiratory symptoms at 3 months follow-up
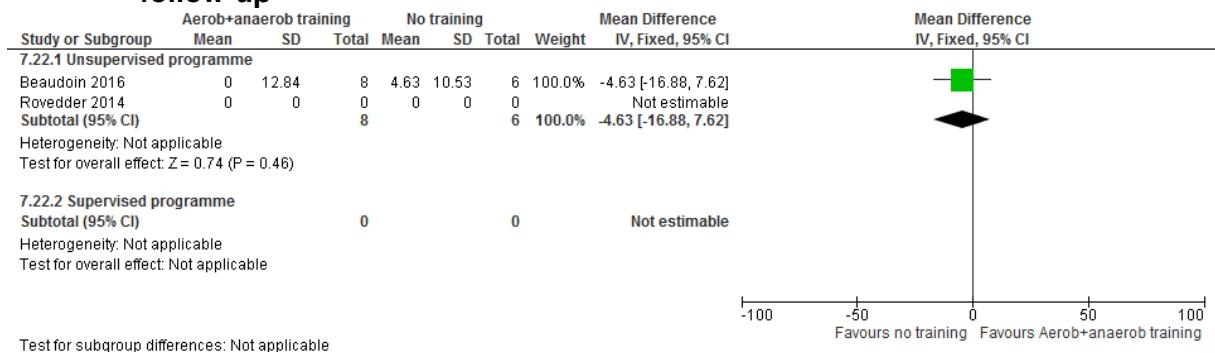
Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Figure 364: Change in quality of life – CFQ-R digestion symptoms at 3 months follow-up
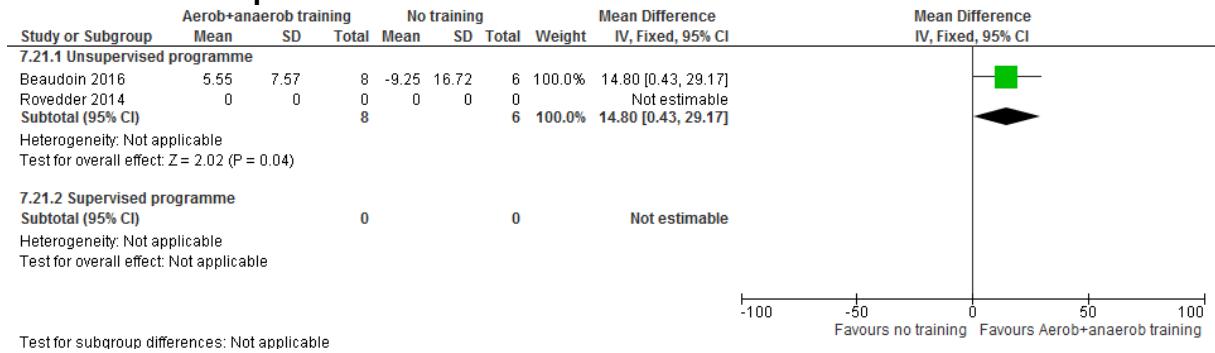

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Comparison 6. Combined inspiratory muscle training (IMT), resistance and aerobic training *versus* no exercise programme

Figure 365: Change in FEV$_1$ (litres) at 2 months follow-up (range of scores: 0-100)
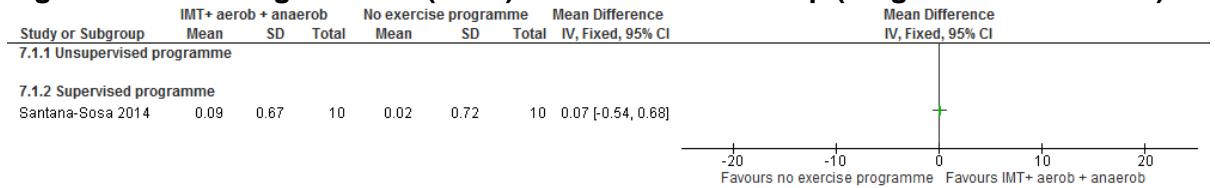

Abbreviations: CI: confidence interval; FEV$_1$: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 366: Change in forced vital capacity (litres) at 2 months follow-up (range of scores: 0-100)
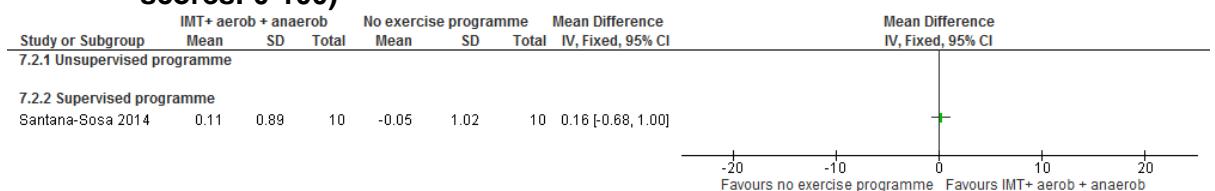

Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 367:   Change in weight (kg) at 2 months follow-up
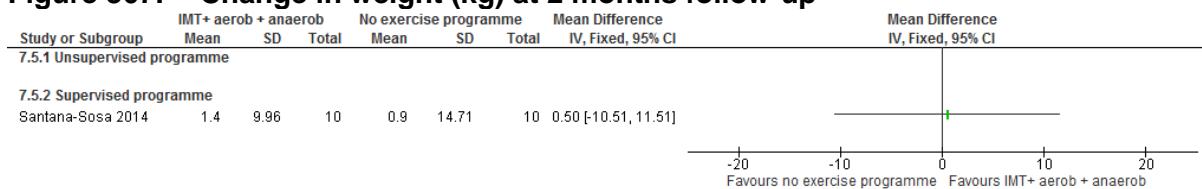
	IMT+ aerob + anaerob			No exercise programme			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
7.5.1 Unsupervised programme								
7.5.2 Supervised programme								
Santana-Sosa 2014	1.4	9.96	10	0.9	14.71	10	0.50 [-10.51, 11.51]	

Favours no exercise programme   Favours IMT+ aerob + anaerob

Abbreviations: kg: kilograms; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 368:   Change in quality of life (CFQ-R children's) at 2 months follow-up (range of scores: 0-100)

	IMT+ aerob + anaerob			No exercise programme				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
8.7.1 Unsupervised programme									
Subtotal (95% CI)			0			0		Not estimable	
Heterogeneity: Not applicable									
Test for overall effect: Not applicable									
8.7.2 Supervised programme									
Santana-Sosa 2014	37.8	10.12	10	36.4	9.8	10	100.0%	1.40 [-7.33, 10.13]	
Subtotal (95% CI)			10			10	100.0%	1.40 [-7.33, 10.13]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.31 (P = 0.75)									
Total (95% CI)			10			10	100.0%	1.40 [-7.33, 10.13]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.31 (P = 0.75)									
Test for subgroup differences: Not applicable									

Favours no exercise programme   Favours IMT+ aerob + anaerob

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Comparison 7. Physical activity: higher amount or longer duration *versus* lower amount or shorter duration

Figure 369:   Need of hospitalization (proxy outcome for time to next exacerbation) at 12 months follow-up

	Higher		Lower		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
8.8.1 >= 30 mins vs <30 mins						
Cox 2015	16	33	19	28	0.71 [0.46, 1.10]	
8.8.2 >=30 mins for >10 mins bouts vs less						
Cox 2015	8	21	26	40	0.59 [0.32, 1.06]	

Favours more PA   Favours less PA
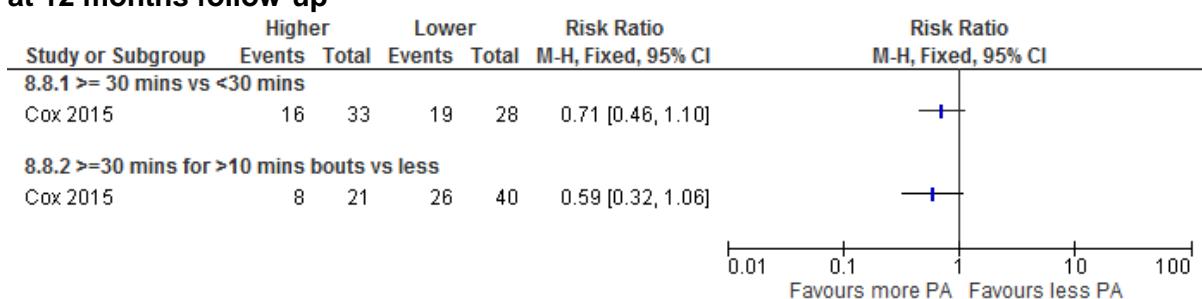
Abbreviations: M-H: Mantel-Haenszel; CI: confidence interval; PA: physical activity

I.21   Psychosocial assessment

Not applicable to this review.

I.22 Cross-infection control

I.22.1 Outpatient care

Comparison 1. Cohort segregation by clinic times *versus* no cohort segregation

Figure 370:   10 year incidence of P. Aeruginosa infections at 10 years follow-up

Study or Subgroup	Cohort segregation Events	Total	No cohort segregation Events	Total	Risk Ratio M-H, Fixed, 95% CI
Hayes 2010	13	21	14	18	0.80 [0.52, 1.21]
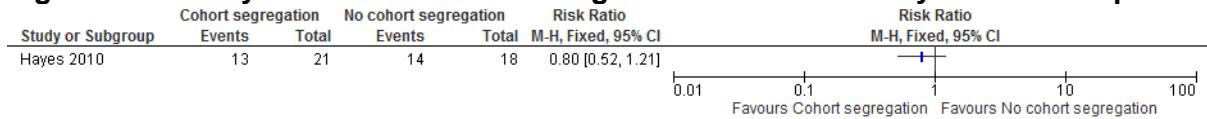
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

4-year prevalence of MRSA at 4 years follow-up

Data could not be plotted

4-year prevalence of non-mucoid PA at 4 years follow-up

Data could not be plotted

4-year prevalence of mucoid PA at 4 years follow-up

Data could not be plotted

Staff compliance at 4 years follow-up

Data could not be plotted

Comparison 2. Cohort segregation by location *versus* no cohort segregation

Annual incidence of new growths of PA at 9 years follow-up

Data could not be plotted

Figure 371:   Yearly prevalence of chronic P. Aeruginosa infections at 9 years follow-up

Study or Subgroup	Cohort segregation Events	Total	No cohort segregation Events	Total	Odds Ratio M-H, Fixed, 95% CI
Lee 2004	326	1803	237	966	0.68 [0.56, 0.82]

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 372:   Yearly prevalence of intermittent P. Aeruginosa infections at 9 years follow-up

Study or Subgroup	Cohort segregation Events	Total	No cohort segregation Events	Total	Odds Ratio M-H, Fixed, 95% CI
Lee 2004	622	1083	253	966	3.80 [3.15, 4.59]

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Comparison 3. Combination of protective equipment + individual segregation *versus* incomplete protective equipment + incomplete individual segregation

4-month prevalence of PA infections at 5 years follow-up

Data could not be plotted

4-month prevalence of MRSA infections at 5 years follow-up

Data could not be plotted

I.22.2   Inpatient care

Comparison 4. Cohort segregation by location *versus* no cohort segregation

Annual incidence of B. Cepacia Complex at 1 year follow-up

Data could not be plotted

Figure 373:   5-month incidence of hospital-associated colonization of P. Cepacia at 5 months follow-up

Study or Subgroup	Cohort segregation Events	Total	No cohort segregation Events	Total	Odds Ratio M-H, Fixed, 95% CI
Thomassen 1986	6	235	24	308	0.31 [0.12, 0.77]
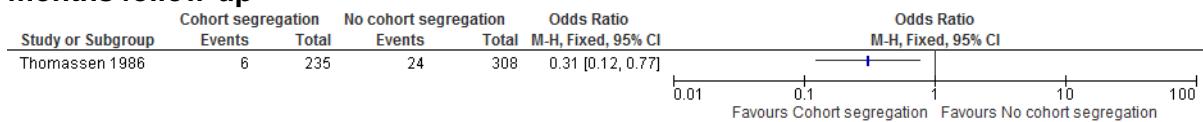
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Comparison 5. Individual segregation by location *versus* usual care

Patients' satisfaction

Data could not be plotted

Parents' satisfaction

Data could not be plotted

I.22.3   Combined inpatient and outpatient care

Comparison 6. Cohort segregation *versus* no cohort segregation

Figure 374:   Monthly incidence of multiply resistant PA strain at 1 month follow-up

Study or Subgroup	Cohort segregation Events	Total	No cohort segregation Events	Total	Odds Ratio M-H, Fixed, 95% CI
Hoiby 1989	5	77	22	107	0.27 [0.10, 0.74]

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

### Figure 375:   Annual incidence of intermittent PA at 1 year follow-up

Study or Subgroup	Cohort segregation Events	Total	No cohort segregation Events	Total	Odds Ratio M-H, Fixed, 95% CI
Frederiksen 1999	9	40	15	45	0.58 [0.22, 1.53]
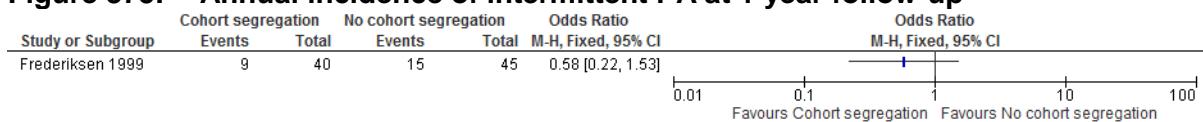
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 376:   Annual incidence of chronic PA at 1 year follow-up

Study or Subgroup	Cohort segregation Events	Total	No cohort segregation Events	Total	Odds Ratio M-H, Fixed, 95% CI
Frederiksen 1999	7	69	15	75	0.45 [0.17, 1.19]

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 377:   6-month incidence of B. Cepacia at 6 months follow-up

Study or Subgroup	Cohort segregation Events	Total	No cohort segregation Events	Total	Odds Ratio M-H, Fixed, 95% CI
Whiteford 1995	1	93	5	109	0.23 [0.03, 1.97]
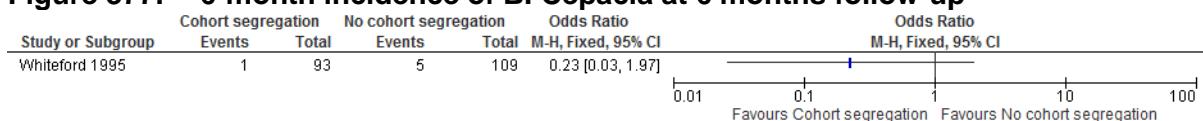
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Annual incidence of Burkholderia species infection at 1 year follow-up

Data could not be plotted

Figure 378:   Monthly prevalence of multiply resistant PA strain at 1 month follow-up

Study or Subgroup	Cohort segregation Events	Total	No cohort segregation Events	Total	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Hoiby 1989	44	119	39	119	1.20 [0.71, 2.05]	

Favours Cohort segregation   Favours No cohort segregation
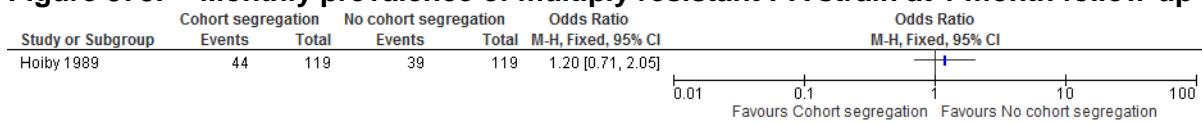
*Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel*

Prevalence of AES-1 (PA epidemic strain) at 2 years follow-up

Data could not be plotted

Figure 379:   Annual prevalence of chronic PA infection at 1 year follow-up

Study or Subgroup	Cohort segregation Events	Total	No cohort segregation Events	Total	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Jones 2005	184	228	156	216	1.61 [1.03, 2.51]	

Favours Cohort segregation   Favours No cohort segregation
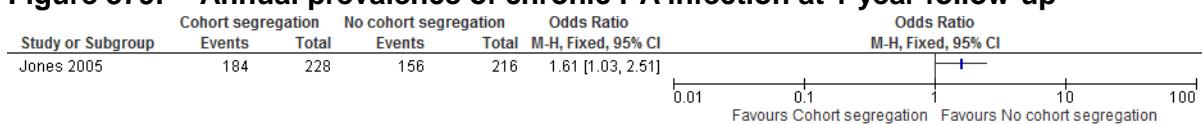
Abbreviations: M-H: Mantel-Haenszel; CI: confidence interval

Figure 380:   Annual prevalence of transmissible PA infection at 1 year follow-up

Study or Subgroup	Cohort segregation Events	Total	No cohort segregation Events	Total	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Jones 2005	35	228	28	216	1.22 [0.71, 2.08]	

Favours Cohort segregation   Favours No cohort segregation
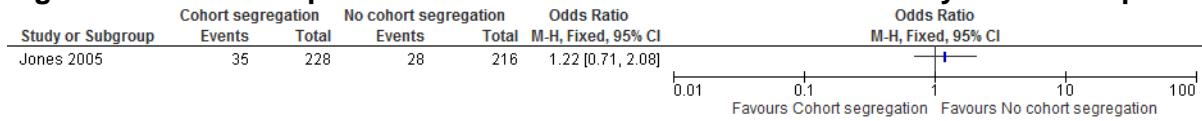
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Annual prevalence of chronic infection with transmissible PA strain at 1 year follow-up

Data could not be plotted

Comparison 7. Complete cohort segregation *versus* incomplete cohort segregation

Annual incidence of Burkholderia species at 1 year follow-up

Data could not be plotted

Comparison 8. Individual segregation *versus* usual care

Patient satisfaction

Data could not be plotted

Comparison 9. Cohort segregation + individual segregation *versus* cohort segregation

Yearly prevalence of B. Cepacia complex infection at 1 year follow-up

Data could not be plotted

Yearly prevalence of Burkholderia species at 5 years follow-up

Data could not be plotted

Comparison 10. Cohort segregation + individual segregation + protective equipment *versus* usual care

Annual incidence of B. Cepacia complex infection at 1 year follow-up

Data could not be plotted

Comparison 11. Cohort segregation + individual segregation *versus* usual care

Patient satisfaction

Data could not be plotted