National Institute for Health and Care Excellence

Final

Cystic Fibrosis: diagnosis and management

Appendix J

Main appendix document

GRADE tables

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FINAL

Developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologist

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

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Appendix J: GRADE Tables

J.1 Diagnosis of cystic fibrosis

Not applicable to this review.

J.2 Information and support

Not applicable to this review.

J.3 Service delivery

J.3.1 Service configuration

J.3.1.1 Home-based care

Table 1: Clinical evidence profile: Comparison 1.1. Home versus hospital care for the administration of IV antibiotics in people with CF experiencing an acute pulmonary exacerbation

Quality assessment							No of treatments		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Home care for the administration of IV antibiotics	Hospital care for the administration of IV antibiotics	Relative (95% CI)	Absolute	Quality	Importance
Lung function: change in FEV_1 % predicted (follow-up 21 days; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of treatments		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Home care for the administration of IV antibiotics	Hospital care for the administration of IV antibiotics	Relative (95% CI)	Absolute	**Quality**	**Importance**
1 (Wolter 1997)	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	13[a]	18[a]	-	MD 3 lower (13.61 lower to 7.61 higher)	VERY LOW	CRITICAL
Lung function: change in FEV_1 % predicted (follow-up mean 18 days; range of scores: 0-100; Better indicated by higher values)												
1 (Donati 1987)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	31[b]	32[b]	-	MD 5.60 lower (12.29 lower to 1.09 higher)[c]	VERY LOW	CRITICAL
Lung function: change in FEV_1 % predicted (follow-up 15 days; range of scores: 0-100; Better indicated by higher values)												
1 (Esmond 2006)	observational studies	serious[5]	no serious inconsistency	no serious indirectness	serious[4]	none	15[d]	15[d]	-	MD 3.1 lower (6.93 lower to 0.73 higher)	VERY LOW	CRITICAL
Patients starting next course of antibiotics more than 12 weeks after completing the previous course (proxy outcome for time to next exacerbation) (follow-up mean 18 days)												

Quality assessment							No of treatments		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Home care for the administration of IV antibiotics	Hospital care for the administration of IV antibiotics	Relative (95% CI)	Absolute	**Quality**	**Importance**
1 (Bosworth 1997)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	13/27 (48.1 %)[e]	28/32 (87.5%)[e]	RR 0.55 (0.36 to 0.83)		VERY LOW	CRITICAL
Weight (change) kg (follow-up 18 days; Better indicated by higher values)												
1 (Donati 1987)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	37[b]	37[b]	-	MD 1.10 lower (4.29 lower to 2.09 higher) [a]	VERY LOW	CRITICAL
Weight change (kg) (follow-up ≤10 days post treatment; Better indicated by higher values)												
1 (Wolter 1997)	observational studies	serious[2]	no serious inconsistency	no serious indirectness	very serious[7]	none	13[a]	18[a]	-	MD 0.5 lower (8.06 lower to 7.06 higher)	VERY LOW	IMPORTANT
BMI (follow-up 15 days; Better indicated by higher values)												
1 (Esmond	observational studies	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	15[d]	15[d]	-	MD 0.2 lower (0.63	VERY LOW	IMPORTANT

Quality assessment							No of treatments		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Home care for the administration of IV antibiotics	Hospital care for the administration of IV antibiotics	Relative (95% CI)	Absolute	Quality	Importance
2006)										lower to 0.23 higher)		
Change in quality of life – CF-QOL-Physical (follow-up 15 days; range of scores: 0-100; Better indicated by higher values)												
1 (Esmond 2006)	observational studies	serious[5]	no serious inconsistency	no serious indirectness	very serious[3, f]	none	15[d]	15[d]	-	MD 2.2 lower (13.21 lower to 8.81 higher)	VERY LOW	IMPORTANT
Change in quality of life – CF-QOL-Social (follow-up 15 days; range of scores: 0-100; Better indicated by higher values)												
1 (Esmond 2006)	observational studies	serious[5]	no serious inconsistency	no serious indirectness	very serious[3, f]	none	15[d]	15[d]	-	MD 3.4 lower (18.87 lower to 12.07 higher)	VERY LOW	IMPORTANT
Change in quality of life – CF-QOL-Treatment (follow-up 15 days; range of scores: 0-100; Better indicated by higher values)												
1 (Esmond 2006)	observational studies	serious[5]	no serious inconsistency	no serious indirectness	very serious[3, f]	none	15[d]	15[d]	-	MD 2 lower (17.15 lower to 13.15 higher)	VERY LOW	IMPORTANT

Quality assessment							No of treatments		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Home care for the administration of IV antibiotics	Hospital care for the administration of IV antibiotics	Relative (95% CI)	Absolute	Quality	Importance
Change in quality of life – CF-QOL-Symptoms (follow-up 15 days; range of scores: 0-100; Better indicated by higher values)												
1 (Esmond 2006)	observational studies	serious[5]	no serious inconsistency	no serious indirectness	serious[4, f]	none	15[d]	15[d]	-	MD 17.1 lower (31.25 to 2.95 lower)	VERY LOW	IMPORTANT
Change in quality of life – CF-QOL-Emotional (follow-up 15 days; range of scores: 0-100; Better indicated by higher values)												
1 (Esmond 2006)	observational studies	serious[5]	no serious inconsistency	no serious indirectness	very serious[3, f]	none	15[d]	15[d]	-	MD 4.2 higher (8.67 lower to 17.07 higher)	VERY LOW	IMPORTANT
Change in quality of life – CF-QOL-Future (follow-up 15 days; range of scores: 0-100; Better indicated by higher values)												
1 (Esmond 2006)	observational studies	serious[5]	no serious inconsistency	no serious indirectness	very serious[3, f]	none	15[d]	15[d]	-	MD 5.5 lower (17.96 lower to 6.96 higher)	VERY LOW	IMPORTANT
Change in quality of life – CF-QOL-Relationships (follow-up 15 days; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of treatments		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Home care for the administration of IV antibiotics	Hospital care for the administration of IV antibiotics	Relative (95% CI)	Absolute	**Quality**	**Importance**
1 (Esmond 2006)	observational studies	serious[5]	no serious inconsistency	no serious indirectness	very serious[3, f]	none	15[d]	15[d]	-	MD 7.4 higher (5.6 lower to 20.4 higher)	VERY LOW	IMPORTANT
Change in quality of life – CF-QOL-Body image (follow-up 15 days; range of scores: 0-100; Better indicated by higher values)												
1 (Esmond 2006)	observational studies	serious[5]	no serious inconsistency	no serious indirectness	very serious[3, f]	none	15[d]	15[d]	-	MD 0.9 higher (13.92 lower to 15.72 higher)	VERY LOW	IMPORTANT
Change in quality of life – CF-QOL-Career (follow-up 15 days; range of scores: 0-100; Better indicated by higher values)												
1 (Esmond 2006)	observational studies	serious[5]	no serious inconsistency	no serious indirectness	very serious[3, f]	none	15[d]	15[d]	-	MD 8.3 higher (5.76 lower to 22.36 higher)	VERY LOW	IMPORTANT

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; CF-QOL: cystic fibrosis quality of life questionnaire; FEV_1: forced expiratory volume in 1 second; IV: intravenous; MD: mean difference; RR: risk ratio
1 Cross-over trial
2 The quality of the evidence was downgraded by 1 as this is an open-label study
3 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 clinical MIDs.

4 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 clinical MID
5 The quality of the evidence was downgraded by 1 as there is a high-risk of bias in relation to the comparability of the groups
6 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
7 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
a Number of people in each group not reported
b Number of people included in the analysis in each group unclear
c The mean difference was calculated by the NGA technical team after calculating mean change from baseline and related SD in each group (using the mean and SE at baseline and follow-up and assuming a correlation of 0.75)
d There were 15 people in each group, but the total N of people is 28. Two people had both home care and hospital care.
e There were 19 people in the home group, 21 people in the hospital group (40 in total)
f Imprecision for quality of life was assessed using a clinical MID of 5 because the study by Esmond et al. used the CFQOL questionnaire (Gee et al. 2000)

Table 2: Clinical evidence profile: Comparison 1.2. Home versus hospital care for the administration of IV AB in people with CF and chronic pulmonary infection with *P aeruginosa*

Quality assessment							**No of treatments**		**Effect**			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Home care for the administration of IV antibiotics	Hospital care for the administration of IV AB	Relative (95% CI)	Absolute	**Quality**	**Importance**
Lung function: Change in FEV_1 % predicted (follow-up 14 days; range of scores: 0-100; Better indicated by higher values)												
1 (Riethmueller 2002)	observational studies	serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	29[a]	27 [a]	-	MD 2 higher (9.81 lower to 13.81 higher)	VERY LOW	CRITICAL
Nutritional status: change in weight (kg) (follow-up 14 days; Better indicated by higher values)												

Quality assessment							No of treatments		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Home care for the administration of IV antibiotics	Hospital care for the administration of IV AB	Relative (95% CI)	Absolute	**Quality**	**Importance**
1 (Riethmueller 2002)	observational studies	serious [1]	no serious inconsistency	no serious indirectness	very serious[3]	none	29[a]	28[a]	-	MD 0 higher (4.38 lower to 4.38 higher)	VERY LOW	IMPORTANT
Nutritional status: change in weight for height (%) (follow-up 14 days; Better indicated by higher values)												
1 (Riethmueller 2002)	observational studies	serious [1]	no serious inconsistency	no serious indirectness	serious[4]	none	29[a]	28[a]	-	MD 1 lower (4.64 lower to 2.64 higher)	VERY LOW	IMPORTANT

Abbreviations: CI: confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; IV: intravenous; MD: mean difference
1 The quality of the evidence was downgraded by 1 due to high risk of bias in relation to the comparability of the groups
2 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 clinical MIDs
3 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
4 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
a Number of people included in the analysis in each group unclear

J.3.1.2 CF centre care

Table 3: Clinical evidence profile: Comparison 2.1. CF centre care versus shared care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CF centre care	Shared care (UK equivalent)	Relative (95% CI)	Absolute		
Change in FEV_1 (% predicted) (follow-up 1 year; range of scores: 0-100; Better indicated by higher values)												
1 (Van Kool wijk 2002)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41	41	-	MD 0.5 lower (3.05 lower to 2.05 higher)	VERY LOW	CRITICAL
First to last FEV_1 (% per year) (follow-up 3 years; range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2008)	observational studies	very serious [2]	no serious inconsistency	no serious indirectness	serious[3]	none	67	30	-	MD 2.4 lower (5.72 lower to 0.92 higher)	VERY LOW	CRITICAL
Slope FEV_1 (% per year) (follow-up 3 years; range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2008)	observational studies	very serious 2	no serious inconsistency	no serious indirectness	serious3	none	67	30	-	MD 2.2 lower (5.37 lower to 0.97 higher)	VERY LOW	CRITICAL
BMI (follow-up 1 year; Better indicated by higher values)												
1 (Van Kool wijk 2002)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41	41	-	MD 0.12 lower (0.44 lower to	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CF centre care	Shared care (UK equivalent)	Relative (95% CI)	Absolute	**Quality**	**Importance**
										0.2 higher)		
Quality of life: CFQ-Teen - Physical (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	serious[3, a]	none	24	10	-	MD 17.8 lower (30.28 to 5.32 lower)	VERY LOW	IMPORTANT
Quality of life: CFQ-Teen - Role (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	serious[3, a]	none	24	10	-	MD 10.4 lower (26.45 lower to 5.65 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Teen - Vitality (range of scores: 0-100; Better indicated by lower values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	serious[3, a]	none	24	10	-	MD 18.2 lower (32.5 to 3.9 lower)	VERY LOW	IMPORTANT
Quality of life: CFQ-Teen - Emotional (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	serious[3, a]	none	24	10	-	MD 5.5 lower (18.35 lower to 7.35 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Teen - Social (range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CF centre care	Shared care (UK equivalent)	Relative (95% CI)	Absolute	**Quality**	**Importance**
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	serious[3, a]	none	24	10	-	MD 17.6 lower (26.71 to 8.49 lower)	VERY LOW	IMPORTANT
Quality of life: CFQ-Teen - Body (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	very serious[5, a]	none	24	10	-	MD 4.5 lower (21.56 lower to 12.56 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Teen - Eating (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	very serious[5, a]	none	24	10	-	MD 4.5 lower (21.56 lower to 12.56 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Teen - TB (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	very serious[5, a]	none	24	10	-	MD 9.6 lower (28.01 lower to 8.81 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Teen - Health (range of scores: 0-100; Better indicated by higher values)												
1 (Tho	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	serious[3, a]	none	24	10	-	MD 14.8 lower (31.75	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CF centre care	Shared care (UK equivalent)	Relative (95% CI)	Absolute		
mas 2006)										lower to 2.15 higher)		
Quality of life: CFQ-Teen - Weight (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	serious[3, a]	none	24	10	-	MD 12.5 lower (29.45 lower to 4.45 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Teen - Respiratory (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	serious[3, a]	none	24	10	-	MD 4.5 lower (15.25 lower to 6.25 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Teen - Digestion (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	serious[3, a]	none	24	10	-	MD 7.9 lower (17.14 lower to 1.34 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Child - Physical (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	very serious[5, a]	none	46	37	-	MD 1.2 lower (10.97 lower to	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CF centre care	Shared care (UK equivalent)	Relative (95% CI)	Absolute	**Quality**	**Importance**
										8.57 higher)		
Quality of life: CFQ-Child - Emotional (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	no serious imprecision [a]	none	46	37	-	MD 1.3 higher (5.13 lower to 7.73 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Child - Social (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	serious[3, a]	none	46	37	-	MD 1.7 lower (9.46 lower to 6.06 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Child - Body (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	serious[3, a]	none	46	37	-	MD 2.8 lower (13.64 lower to 8.04 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Child - Eating (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious 4	no serious inconsistency	no serious indirectness	very serious5, a	none	46	37	-	MD 0.5 lower (11.94 lower to 10.94 higher)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CF centre care	Shared care (UK equivalent)	Relative (95% CI)	Absolute	Quality	Importance
Quality of life: CFQ-Child - TB (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	serious [3, a]	none	46	37	-	MD 4.7 higher (5.88 lower to 15.28 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Child - Respiratory (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	serious [3, a]	none	46	37	-	MD 3.9 higher (5.69 lower to 13.49 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Child - Digestion (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	serious [3, a]	none	46	37	-	MD 4 higher (8.38 lower to 16.38 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Parent - Physical (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	serious [3, a]	none	45	35	-	MD 2.5 higher (6.96 lower to 11.96 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Parent - Vitality (range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CF centre care	Shared care (UK equivalent)	Relative (95% CI)	Absolute	Quality	Importance
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	no serious imprecision [a]	none	45	35	-	MD 0.7 lower (7.78 lower to 6.38 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Parent - Emotional (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	serious [3, a]	none	45	35	-	MD 1.1 higher (7.52 lower to 9.72 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Parent - Body (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	very serious [5, a]	none	45	35	-	MD 3 higher (9.12 lower to 15.12 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Parent - Eating (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	serious [3, a]	none	45	35	-	MD 7.5 lower (20.22 lower to 5.22 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Parent - TB (range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CF centre care	Shared care (UK equivalent)	Relative (95% CI)	Absolute	**Quality**	**Importance**
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	serious[3, a]	none	45	35	-	MD 6.2 lower (14.63 lower to 2.23 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Parent - Health (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	very serious[5, a]	none	45	35	-	MD 1.1 higher (8.6 lower to 10.8 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Parent - Weight (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	very serious[5, a]	none	45	35	-	MD 0.8 lower (16.4 lower to 14.8 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Parent - Respiratory (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	very serious[5, a]	none	45	35	-	MD 0.5 lower (10.33 lower to 9.33 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Parent - Digestion (range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CF centre care	Shared care (UK equivalent)	Relative (95% CI)	Absolute	Quality	Importance
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	serious[3, a]	none	45	35	-	MD 0.6 lower (8.76 lower to 7.56 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-Parent - School function (range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2006)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	very serious[5, a]	none	45	35	-	MD 0.60 lower (11.63 lower to 10.43 higher)	VERY LOW	IMPORTANT

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; CFQ: cystic fibrosis questionnaire; FEV_1: forced expiratory volume in 1 second; IV: intravenous; MD: mean difference

1 The quality of the evidence was downgraded by 2 because of the differences between groups.

2 The quality of the evidence was downgraded by 2 due to high risk of bias in relation to the selection of the population and high loss to follow-up

3 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID

4 The quality of the study was downgraded by 2 due to high risk of bias in relation to comparability of the groups, and significant differences at follow-up between groups

5 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 clinical MIDs

a Imprecision for quality of life was assessed using a clinical MID of 8.5 because the paper by Thomas et al. uses the CFQ- Teen, CFQ-Child and CFQ-Parent (Quittner et al. 2005)

Table 4: Clinical evidence profile: Comparison 2.2. CF centre care versus local care (below CF Trust recommendations)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CF Centre	Local care (below CF Trust recs)	Relative (95% CI)	Absolute	Quality	Importance
Change in lung function: FEV_1 (% predicted) (follow-up 1 years; range of scores: 0-100; Better indicated by higher values)												
1 (Van Koolwijk 2002)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	serious2	none	41	23	-	MD 2.7 higher (0.55 lower to 5.95 higher)	VERY LOW	CRITICAL
Lung function: First to last FEV_1 (% per year) (follow-up 3 years; range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2008)	observational studies	very serious [3]	no serious inconsistency	no serious indirectness	serious[2]	none	67	11	-	MD 5.7 lower (10.99 to 0.41 lower)	VERY LOW	CRITICAL
Slope FEV_1 (% per year) (follow-up 3 years; range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2008)	observational studies	very serious [3]	no serious inconsistency	no serious indirectness	serious[2]	none	67	11	-	MD 3.3 lower (6.13 to 0.47 lower)	VERY LOW	CRITICAL
BMI (follow-up 1 year; Better indicated by higher values)												
1 (Van Koolwijk 2002)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41	23	-	MD 0.09 lower (0.42 lower to 0.24 higher)	VERY LOW	IMPORTANT

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; IV: intravenous; MD: mean difference

1 The quality of the evidence was downgraded by 2 because of the differences between groups.
2 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 clinical MID
3 The quality of the evidence was downgraded by 2 due to high risk of bias in relation to the selection of the population and high loss to follow-up

Table 5: Clinical evidence profile: Comparison 2.3. CF centre care versus general clinic (non-CF)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CF specialist clinic	General (not CF) clinic	Relative (95% CI)	Absolute	**Quality**	**Importance**
Patient satisfaction with care overall (Better indicated by higher values)												
1 (Walters 1994)	observational studies	serious [1]	no serious inconsistency	no serious indirectness	Not calculable	none	N= 686 overall (not disaggregated by group)		-	MD 0.44 higher (0.29 higher to 0.58 higher)	VERY LOW	CRITICAL

Abbreviations: CI: confidence interval; CF: cystic fibrosis; MD: mean difference
1 The quality of the evidence was downgraded by 1 because the authors did not control the analysis for any of the confounding factors

J.3.1.3 Shared care

Table 6: Clinical evidence profile: Comparison 3.1. Local care (below CF Trust recommendations) versus shared care (UK equivalent)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Local care (below CF Trust recs)	Shared care (UK equivalent)	Relative (95% CI)	Absolute	**Quality**	**Importance**
Lung function: change in FEV_1 % predicted (follow-up 1 years; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Local care (below CF Trust recs)	Shared care (UK equivalent)	Relative (95% CI)	Absolute	Quality	Importance
1 (Van Kool wijk 2002)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	23	41	-	MD 3.2 lower (6.84 lower to 0.44 higher)	VERY LOW	CRITICAL
Lung function: First to last FEV_1 (% per year) (follow-up 1 year; range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2008)	observational studies	very serious [3]	no serious inconsistency	no serious indirectness	serious[2]	none	11	30	-	MD 3.3 higher (2.59 lower to 9.19 higher)	VERY LOW	CRITICAL
Lung function: Slope FEV_1 (% per year) (follow-up 1 year; range of scores: 0-100; Better indicated by lower values)												
1 (Thomas 2008)	observational studies	very serious [3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11	30	-	MD 1.1 higher (2.69 lower to 4.89 higher)	VERY LOW	CRITICAL
Nutritional status: change in BMI (follow-up 1 year; Better indicated by higher values)												
1 (Van Kool wijk 2002)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23	41	-	MD 0.03 lower (0.43 lower to 0.37 higher)	VERY LOW	IMPORTANT

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; MD: mean difference
1 The quality of the evidence was downgraded by 2 because of the differences between groups.

2 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 clinical MID
3 The quality of the evidence was downgraded by 2 due to high risk of bias in relation to the selection of the population and high loss to follow-up

Table 7: Clinical evidence profile: Comparison 3.2. Shared care (above UK equivalent) versus shared care (UK equivalent)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Shared care (above UK equivalent)	Shared care (UK equivalent)	Relative (95% CI)	Absolute		
Lung function: First to last FEV_1 (% per year) (follow-up 3 years; range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2008)	observational studies	very serious [1]	no serious inconsistency	serious[2]	serious[3]	none	19	30	-	MD 0.5 lower (5.63 lower to 4.63 higher)	VERY LOW	CRITICAL
Lung function: Slope FEV_1 (% per year) (follow-up 3 years; range of scores: 0-100; Better indicated by higher values)												
1 (Thomas 2008)	observational studies	very serious [1]	no serious inconsistency	serious[2]	serious[3]	none	19	30	-	MD 2.1 lower (6.52 lower to 2.32 higher)	VERY LOW	CRITICAL

Abbreviations: CI: confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; MD: mean difference
1 The quality of the evidence was downgraded by 2 due to high risk of bias in relation to the selection of the population and high loss to follow-up
2 The quality of the evidence was downgraded by 1 because 1 of the comparators is not representative of current UK practice
3 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 clinical MID

J.3.1.4 Telemedicine

Table 8: Clinical evidence profile: Comparison 4.1. Telemedicine home monitoring programme + diary records versus usual care

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Home monitoring program with diary and usual care	Usual care	Relative (95% CI)	Absolute	Quality	Importance
Change in FEV 1 (% predicted) (follow-up 4 years; range of scores: 0-100; Better indicated by higher values)												
1 (Finkelstein 1992)	observational studies	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	25	-	MD 8 lower (17.01 lower to 1.01 higher)[3]	VERY LOW	CRITICAL

Abbreviations: CI: confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; MD: mean difference
1 The quality of the evidence was downgraded by 1 due lo unclear comparability between groups
2 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 clinical MID

Table 9: Clinical evidence profile: Comparison 4.2. Telemedicine versus usual care

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Telemedicine	Usual care	Relative (95% CI)	Absolute	Quality	Importance
Change in quality of life– CFQOL body (Follow-up: 6 months; range of scores: 0-100; Better indicated by lower values)												
1 (Wilkinson 2008)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	Not calculable	none	4 Significant improvement at 6	3	-	Not estimable	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Telemedicine	Usual care	Relative (95% CI)	Absolute	**Quality**	**Importance**
							months, p=0.02					

Abbreviations: CI: confidence interval; CFQOL: cystic fibrosis quality of life questionnaire
1 The quality of the evidence was downgraded by 2 because of incomplete reporting and high-loss to follow-up

J.3.2 Multidisciplinary teams

Not applicable, as no evidence was found for this review.

J.4 Transition

Not applicable to this review.

J.5 Complications of cystic fibrosis

Not applicable to this review.

J.6 Pulmonary monitoring

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

Monitoring technique 1. Non-invasive microbiological investigation

No evidence was found.

Monitoring technique 2. Invasive microbiological investigation

No evidence was found.

Table 10: Clinical evidence profile: Monitoring technique 3. Lung physiological function test (FEV_1% predicted at baseline) for prognosis of pulmonary exacerbations and FEV_1 percent predicted at 10 years

Prognostic factors	No of studies	Design	Setting	No of patients	Result (adjRR, MD)	Quality	Notes	Importance
Pulmonary exacerbations (defined as hospitalizations treated with IV AB) (Follow-up: 10 years; Better indicated by lower values)								
FEV_1 % predicted, 5-point decrease	1 (Sanders 2015)	Cohort study	CF centres in Europe	60	adjRR: 1.19 (95% CI: 1.10 to 1.30)[1]	⊕⊕⊕⊖ MODERATE[1]	Multiple Poisson model adjusted for sex, genotype, FEV_1 and mucoid ***P aeruginosa*** status at time of chest CT. p-value ≤0.001	CRITICAL
Change/ decline in FEV_1 % predicted (Follow-up: 10 years; Better indicated by lower values)								
FEV_1 % predicted, 5-point decrease	1 (Sanders 2015)	Cohort study	CF centres in Europe	60	MD: -4.47 (95% CI: -6.48 to -2.76)	⊕⊕⊕⊖ MODERATE[1]	Multiple linear model adjusted for sex, genotype, FEV_1 and mucoid ***P aeruginosa*** status at time of chest CT. p-value ≤0.001	CRITICAL

Abbreviations: adjRR: adjusted rate ratio; CF: cystic fibrosis; CI: confidence interval; CT: computerised tomography; FEV_1: forced expiratory volume in 1 second; MD: mean difference
1 The quality of the evidence was downgraded by 1 due to no adjustments for the confounder of concurrent treatment with immunomodulatory and/or mucolytic agents.

Table 11: Clinical evidence profile: Monitoring technique 4. Chest CT scan for prognosis of pulmonary exacerbations and FEV_1% predicted at 10 years

Prognostic factors	No of studies	Design	Setting	No of patients	Result (adjRR, MD)	Quality	Notes	Importance
Pulmonary exacerbations (defined as hospitalizations treated with IV AB) (Follow-up: 10 years; Better indicated by lower values)								
Brody chest CT score, 1-point increase	1 (Sanders 2015)	Cohort study	CF centres in Europe	60	adjRR: 1.39 (95% CI: 1.15 to 1.67)	⊕⊕⊕⊖ MODERATE[1]	Multiple Poisson model adjusted for sex, genotype, FEV_1 and mucoid ***P aeruginosa*** status at time of chest CT. p-value ≤0.001	CRITICAL
Change/ decline in FEV_1 % predicted (Follow-up: 10 years; Better indicated by lower values)								
Brody chest CT score, 1-point increase	1 (Sanders 2015)	Cohort study	CF centres in Europe	60	MD: -4.76 (95% CI: -7.80 to -1.72)	⊕⊕⊕⊖ MODERATE[1]	Multiple linear model adjusted for sex, genotype, FEV_1 and mucoid ***P aeruginosa*** status at time of chest CT. p-value ≤0.003	CRITICAL

Abbreviations: adjRR: adjusted rate ratio; CF: cystic fibrosis; CI: confidence interval; CT: computerised tomography; FEV_1: forced expiratory volume in 1 second; MD: mean difference
1 The quality of the evidence was downgraded by 1 due to no adjustments for the confounder of concurrent treatment with immunomodulatory and/or mucolytic agents

Table 12: Clinical evidence profile: Comparison 1. FEV_1% predicted versus chest CT scan for prognosis of pulmonary exacerbations and FEV_1% predicted at 10 years

Quality assessment							No of patients	Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)		Difference between tests P-value		
								FEV_1 % predicted, 5-point decrease	Brody chest CT score, 1-point increase			
Pulmonary exacerbations (defined as hospitalizations treated with IV AB) (Follow-up: 10 years; Better indicated by lower values)												
1 (Sanders 2015)	Cohort study	serious risk of bias[1]	no serious inconsistency	no serious indirectness	Not calculable[2]	none	60	adjRR: 1.19 (95% CI 1.10 to 1.30)[2]	adjRR: 1.39 (95% CI 1.15 to 1.67)[2]	RR = 0.86*; p-value =0.037 By Chi-Square test[2]	MODERATE	CRITICAL
Change/ decline in FEV_1 % predicted (Follow-up: 10 years; Better indicated by lower values)												
1 (Sanders 2015)	Cohort study	serious risk of bias[1]	no serious inconsistency	no serious indirectness	Not calculable[2]	none	60	Mean difference: -4.47 (95% CI: -6.48 to -2.76)	Mean difference: -4.76 (95% CI: -7.80 to -1.72)	MD: 0.29*; p-value = 0.4 By F test[2]	MODERATE	CRITICAL

Abbreviations: AB: antibiotics; adjRR: adjusted rate ratio; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IV: intravenous; MD: mean difference
** Calculated by NGA technical team*
1 The quality of the evidence was downgraded by 1 due to no adjustments for the confounder of concurrent treatment with immunomodulatory and/or mucolytic agents
2 Imprecision is not calculable, as the result is reported narratively only

J.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.

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

Monitoring strategy 1. Invasive microbiological investigations and/or imaging techniques in addition to non-invasive microbiological investigations and/or lung function test VERSUS non-invasive microbiological investigations

Table 13: Clinical evidence profile: Comparison 1. BAL monitoring versus standard monitoring

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BAL monitoring**	**Standard monitoring**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
FEV_1 (follow-up 5 years; measured with: z score; Better indicated by higher values)												
1 (Wainwright 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	No serious imprecision	none	80	77	-	MD 0.15 lower (0.58 lower to 0.28 higher)	MODERATE	CRITICAL
Clearance of *P aeruginosa* following 1 or 2 courses of eradication therapy (Follow up: 5 years; Better indicated by higher values)												
1 (Wainwright 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	38/39 (97.4 %)	39/43 (90.7%)	RR 1.07 (0.96 to 1.2)	63 more per 1000 (from 36 fewer to 181 more)	MODERATE	CRITICAL
Weight (follow-up 5 years; measured with: z scores; Better indicated by higher values)												
1 (Wainwright 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	80	77	-	MD 0.06 higher (0.21 lower to 0.32 higher)	LOW	IMPORTANT
Height (follow-up 5 years; measured with: z scores; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BAL monitoring**	**Standard monitoring**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1 (Wainwright 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	80	77	-	MD 0.06 higher (0.23 to 0.35 lower)	MODERATE	IMPORTANT
BMI (follow-up 5 years; measured with: z scores, BMI calculated as weight in kg divided by height in meters squared.; Better indicated by higher values)												
1 (Wainwright 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	80	77	-	MD 0.02 higher (0.25 lower to 0.3 higher)	MODERATE	IMPORTANT

Abbreviations: BAL: bronchoalveolar lavage; BMI: body mass index; FEV_1: forced expiratory volume in 1 second; MD: mean difference; RR: risk ratio
[1] The quality of the evidence was downgraded by 1 due to serious indirectness as intervention in BAL monitoring group does not reflect that of current clinical practice.
[2] The quality of the evidence was downgraded by 1 due to serious imprecision as 95% CI crossed 1 default MID.

Monitoring strategy 2. Invasive microbiological investigations and/or imaging techniques in addition to non-invasive microbiological investigations and/or lung function test VERSUS lung function test

No evidence was found for this strategy.

Monitoring strategy 3. Invasive microbiological investigations and/or imaging techniques in addition to non-invasive microbiological investigations and/or lung function test VERSUS non-invasive microbiological investigations and lung function test

No evidence was found for this strategy.

J.7 Airway clearance techniques

Comparison 1. Manual physiotherapy versus no airway clearance techniques

No evidence was found for this comparison.

Table 14: Clinical evidence profile: Comparison 2. Manual physiotherapy techniques versus oscillating devices

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Manual physiotherapy	Oscillating device	Relative (95% CI)	Absolute	Quality	Importance
Lung function - FEV_1 (follow-up mean 8.8 days; measured with: % change from baseline; range of scores: 0-100; Better indicated by higher values)												
1 (Homnick 1998)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22	22	-	MD 7.9 lower (31.04 lower to 15.24 higher)	VERY LOW	IMPORTANT
Lung function - FEV_1 (follow-up mean 1 months; measured with: % change from baseline; range of scores: 0-100; Better indicated by higher values)												
1 (Padman 1999)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	6	6	-	MD 2.59 higher (6.3 lower to 11.48 higher)	VERY LOW	IMPORTANT
Lung Function - FVC (follow-up mean 2 weeks; measured with: % change from baseline; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Manual physiotherapy	Oscillating device	Relative (95% CI)	Absolute		
1 (Homnick 1998)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	22	22	-	MD 2.9 higher (14.21 lower to 20.01 higher)	VERY LOW	IMPORTANT

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; MD: mean difference
1 The quality of the evidence was downgraded by 2 due to selection bias and attrition bias.
2 The quality of the evidence was downgraded by 1 due to serious imprecision as 95% CI crossed 1 default MID
3 The quality of the evidence was downgraded by 2 due to attrition bias and reporting bias
4 The quality of the evidence was downgraded by 2 due to very serious imprecision as 95% CI crossed 2 default MIDs

Table 15: Clinical evidence profile: Comparison 3. Manual physiotherapy versus high frequency chest wall oscillation (HFCWO)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Manual physiotherapy techniques	HFCWO	Relative (95% CI)	Absolute		
Sputum weight (dry) (follow-up 1-2 weeks; measured with: grams; Better indicated by higher values)												
1 (Warwick 2004)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	12	-	MD 0.13 lower (0.42 lower to 0.16 higher)	LOW	CRITICAL
Sputum weight (wet) (follow-up 1-2 weeks; measured with: grams; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Manual physiotherapy techniques	HFCWO	Relative (95% CI)	Absolute		
1 (Warwick 2004)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	12	-	MD 4.04 lower (10.77 lower to 2.69 higher)	LOW	CRITICAL

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; HFCWO: high frequency chest wall oscillation; MD: mean difference
1 The quality of the evidence was downgraded by 1 due to lack of blinding.
2 The quality of the evidence was downgraded by 1 due to serious imprecision because the 95% CI crossed 1 default MID

Table 16: Clinical evidence profile: Comparison 4. Positive expiratory pressure (PEP) versus no airway clearance technique

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PEP	No airway clearance technique	Relative (95% CI)	Absolute		
Sputum dry weight (follow-up mean 2 days; measured with: grams; Better indicated by higher values)												
1 (Placidi 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	17	17	-	MD 0.03 lower (0.48 lower to 0.42 higher)	LOW	CRITICAL
Sputum wet weight (follow-up mean 2 days; measured with: grams; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PEP**	**No airway clearance technique**	**Relative (95% CI)**	**Absolute**		
1 (Placidi 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	17	17	-	MD 1.8 higher (1.72 lower to 5.32 higher)	MODERATE	CRITICAL
Lung function - FEV_1 (follow-up mean 2 days; measured with: % predicted; range of scores: 0-100; Better indicated by lower values)												
1 (Braggion 1995)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	16	16	-	MD 2.1 higher (11.73 lower to 15.93 higher)	VERY LOW	IMPORTANT
Lung function - FEV_1 (follow-up mean 2 days; measured with: litres; Better indicated by higher values)												
1 (Placidi 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	17	17	-	MD 0.01 higher (0.18 lower to 0.2 higher)	LOW	IMPORTANT
Lung Function FVC (follow-up mean 2 days; measured with: % predicted; range of scores: 0-100; Better indicated by higher values)												
1 (Braggion 1995)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[1]	none	16	16	-	MD 1.2 higher (12.88 lower to 15.28 higher)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PEP**	**No airway clearance technique**	**Relative (95% CI)**	**Absolute**		
Lung function - FVC (follow-up mean 2 days; measured with: litres; Better indicated by higher values)												
1 (Placidi 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	17	17	-	MD 0.05 higher (0.35 lower to 0.45 higher)	LOW	IMPORTANT
Oxygen saturation - Spo2 (follow-up mean 2 days; measured with: %; range of scores: 0-100; Better indicated by higher values)												
1 (Placidi 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	17	17	-	MD 0.3 higher (0.58 lower to 1.18 higher)	MODERATE	IMPORTANT

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; MD: mean difference; SpO2: peripheral capillary oxygen saturation

1 The quality of the evidence was downgraded by 2 due to very serious imprecision as 95% CI crossed 2 default MIDs

2 The quality of the evidence was downgraded by 1 due to serious imprecision as 95% Ci crossed 1 default MID

3 The quality of the evidence was downgraded by 2 due to lack of blinding, attrition bias and reporting bias.

4 The quality of the evidence was downgraded by 2 due to very serious imprecision as 95% CI crossed 2 clinical MIDs

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

No evidence was found for this comparison.

Table 17: Clinical evidence profile: Comparison 6. Positive expiratory pressure (PEP) versus oscillating devices

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PEP	Oscillating device	Relative (95% CI)	Absolute	Quality	Importance
Patient preference: self-withdrawal due to lack of perceived effectiveness (follow-up mean 1 years; Better indicated by lower values)												
1 (McIlwaine 2001)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/20 (0%)	5/20 (25%)	RR 0.09 (0.01 to 1.54)	227 fewer per 1000 (from 248 fewer to 135 more)	VERY LOW	CRITICAL
Hospitalizations for respiratory exacerbations (follow-up mean 13 months; measured with: number per participant; Better indicated by lower values)												
1 (Newbold 2005)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	21	21	-	MD 0.4 lower (0.92 lower to 0.12 higher)	LOW	CRITICAL
Lung function - FEV_1 (follow-up 2-4 weeks; measured with: % change from baseline; range of scores: 0-100; Better indicated by higher values)												
1 (Padman 1999)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[4]	none	6	6	-	MD 4.08 higher (4.66 lower to 12.82 higher)	VERY LOW	IMPORTANT
Lung function - FEV_1 (follow-up mean 6-12 months; measured with: % change from baseline; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PEP**	**Oscillating device**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1 (McIlwaine 2001)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	17	13	-	MD 9.71 higher (2.12 lower to 21.54 higher)	LOW	IMPORTANT
Lung function - FEV_1 (follow-up 1-2 years; measured with: % change from baseline; range of scores: 0-100; Better indicated by higher values)												
3 (McIlwaine 2013, Newbold 2005, Tannenbaum 2005)	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[4]	none	78	82	-	MD 2.82 lower (6.36 lower to 0.72 higher)	LOW	IMPORTANT
Lung function - FVC (follow-up mean 1 years; measured with: % change from baseline; range of scores: 0-100; Better indicated by higher values)												
3 (McIlwaine 2001, McIlwaine 2013, Newbold 2005)	randomised trials	serious[6]	serious[7]	no serious indirectness	no serious imprecision	none	80	80	-	MD -0.44 lower (6.66 lower to 5.78 higher)	LOW	IMPORTANT
Lung function - FVC (follow-up 2-4 weeks; measured with: % predicted; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PEP	Oscillating device	Relative (95% CI)	Absolute		
1 (van Winden 1998)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	22	22	-	MD 2 lower (4.09 lower to 0.09 higher)	MODERATE	IMPORTANT
Quality of life – CFQ-R: physical domain (follow-up mean 1 years; range of scores: 0-100; Better indicated by higher values)												
1 (McIlwaine 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision [8]	none	51	56	-	MD 2.2 higher (1.32 lower to 5.72 higher)	HIGH	IMPORTANT
Quality of life – CFQ-R: treatment burden (follow-up mean 1 years; range of scores: 0-100; Better indicated by higher values)												
1 (McIlwaine 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision [8]	none	51	56	-	MD 1.05 higher (6.35 lower to 8.45 higher)	HIGH	IMPORTANT
Quality of life – CFQ-R: respiratory domain (follow-up mean 1 years; range of scores: 0-100; Better indicated by higher values)												
1 (McIlwaine 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8,9]	none	51	56	-	MD 2.79 higher (3.68 lower to 9.26 higher)	MODERATE	IMPORTANT

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; MD: mean difference; PEP: positive expiratory pressure; RR: risk ratio

1 The quality of the evidence was downgraded by 1 due to reporting bias.
2 The quality of the evidence was downgraded by 2 due to very serious imprecision as 95% CI crossed 2 default MIDs.
3 The quality of the evidence was downgraded by 1 due to differences in baseline characteristics (pulmonary function values) between both groups.
4 The quality of the evidence was downgraded by 1 due to serious imprecision as 95% CI crossed 1 default MID
5 The quality of the evidence was downgraded by 2 due to attrition bias and reporting bias.
6 Taking into account weighting in a meta-analysis and the likely contribution from each component, the quality of the evidence was downgraded by 1 due differences in baseline participant characteristics.
7 The quality of the evidence was downgraded by 1 due to serious heterogeneity (I-squared inconsistency statistic of 69%) and no plausible explanation was found with sensitivity analysis.
8 Clinical MID=8.5 was used to assess imprecision because the CFQ-R questionnaire (Quittner et al. 2009) was used
9 The quality of the evidence was downgraded by 1 as 95% CI crossed 1 clinical MID

Table 18: Clinical evidence profile: Comparison 7. Positive expiratory pressure (PEP) compared to High Frequency Chest Wall Oscillation (HFCWO)

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PEP**	**HFCWO**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Sputum volume (follow-up mean 1 weeks; measured with: ml ; Better indicated by higher values)												
1 (Grzincich 2008)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23	23	-	MD 1.8 higher (3 lower to 6.6 higher)	LOW	CRITICAL
Respiratory exacerbations: number of patients (follow-up mean 1 years; Better indicated by lower values)												
1 (McIlwaine 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	26/43 (60.5%)	40/48 (83.3%)	RR 0.73 (0.55 to 0.95)	225 fewer per 1000 (from 42 fewer to 375 fewer)	MODERATE	CRITICAL
Pulmonary exacerbations (patients requiring antibiotics) (follow-up mean 1 years ; Better indicated by lower values)												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PEP**	**HFCWO**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1 (McIlwaine 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	26/42 (61.9%)	40/46 (87%)	RR 0.71 (0.55 to 0.93)	254 fewer per 1000 (from 61 fewer to 391 fewer)	MODERATE	CRITICAL
Lung function - FEV_1 (follow-up 1 weeks; measured with: % predicted; range of scores: 0-100; Better indicated by higher values)												
2 (Braggion 1995; Grzincich 2008)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	39	39	-	MD 0.67 higher (8.04 lower to 9.38 higher)	VERY LOW	IMPORTANT
Lung Function - FEV_1 (follow-up 1-2 weeks; measured with: % predicted; range of scores: 0-100; Better indicated by higher values)												
1 (Darbee 2005)	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[4]	none	15	15	-	MD 3 lower (20.54 lower to 14.54 higher)	VERY LOW	IMPORTANT
Lung function — FEV_1 (follow-up 1 years; measured with: change from baseline in FEV_1 % predicted; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PEP**	**HFCWO**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1 (McIlwaine 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	42	46	-	MD 3.59 lower (9.29 lower to 2.11 higher)	MODERATE	IMPORTANT
Lung function - FVC (follow-up 1-2 weeks; measured with: % predicted; Better indicated by higher values)												
1 (Darbee 2005)	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[7]	none	15	15	-	MD 3 lower (16.6 lower to 10.6 higher)	VERY LOW	IMPORTANT
Lung function - FVC (follow-up 1 weeks; measured with: % predicted; range of scores: 0-100; Better indicated by higher values)												
2 (Braggion 1995, Grzincich 2008)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	39	39	-	MD 0.66 higher (7.4 lower to 8.71 higher)	MODERATE	IMPORTANT
Lung function - FVC (follow-up 1 years; measured with: change from baseline in % predicted; range of scores: 0-100; Better indicated by higher values)												
1 (McIlwaine	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	42	46	-	MD 5 lower (10.3 lower	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PEP	HFCWO	Relative (95% CI)	Absolute	Quality	Importance
2013)										to 0.3 higher)		

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; HFCWO: high frequency chest wall oscillation; MD: mean difference; PEP: positive expiratory pressure; RR: risk ratio
1 The quality of the evidence was downgraded by 1 as risk of bias could not be fully assessed from abstract paper which did not discuss method in detail.
2 The quality of the evidence was downgraded by 1 due to serious imprecision as 95% CI crossed 1 default MID.
3 Taking into account weighting in a meta-analysis and the likely contribution from each component, the quality of the evidence was downgraded by 1 as risk of bias could not be fully assessed from abstract paper which did not discuss method in detail.
4 The quality of the evidence was downgraded by 2 due to very serious imprecision as 95% CI crossed 2 clinical MIDs.
5 The quality of the evidence was downgraded by 1 due to selection bias.
6 The quality of the evidence was downgraded by 1 due to serious imprecision as 95% CI crossed 1 clinical MID
7 The quality of the evidence was downgraded by 2 due to very serious imprecision as 95% CI crossed 2 default MIDs

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.

Table 19: Clinical evidence profile: Comparison 12. Oscillating device versus High Frequency Chest Wall Oscillation (HFCWO)

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oscillating device**	**HFCWO**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Lung function - FEV_1 (follow-up 2-4 weeks; measured with: % predicted; range of scores: 0-100; Better indicated by higher values)												
1 (Oerman n 2001)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24	24	-	MD 1.6 lower (3.44 lower to 0.24 higher)	MODERATE	IMPORTANT
Lung function - FVC (follow-up 2-4 weeks; measured with: % predicted; range of scores: 0-100; Better indicated by higher values)												
1 (Oerman n 2001)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	24	24	-	MD 1.4 lower (3.07 lower to 0.27 higher)	LOW	IMPORTANT

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; HFCWO: high frequency chest wall oscillation; MD: mean difference

1 The quality of the evidence was downgraded by 1 due to reporting bias.

2 The quality of the evidence was downgraded by 1 due to serious imprecision as 95% CI crossed 1 default MID.

Comparison 13. High Frequency Chest Wall Oscillation (HFCWO) versus no clearance technique

No evidence was retrieved for this comparison.

Table 20: Clinical evidence profile: Comparison 14. Non-invasive ventilation (NIV) versus no airway clearance technique

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NIV	No airway clearance technique	Relative (95% CI)	Absolute	Quality	Importance
Lung function - FEV_1 (follow-up 6 weeks; measured with: % predicted; range of scores: 0-100; Better indicated by higher values)												
1 (Young 2008)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	7	8	-	MD 1 higher (8.62 lower to 10.62 higher)	LOW	IMPORTANT
Lung function - FVC (follow-up 6 weeks; measured with: % predicted; range of scores: 0-100; Better indicated by higher values)												
1 (Young 2008)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	7	8	-	MD 4 higher (10.3 lower to 18.3 higher)	LOW	IMPORTANT
Oxygen saturation (nocturnal) (follow-up 6 weeks; measured with: %; range of scores: 0-100; Better indicated by higher values)												
1 (Young 2008)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	7	8	-	MD 3 higher (1.12 lower to 7.12 higher)	MODERATE	IMPORTANT
Quality of life – CF-QOL chest symptom score (follow-up 6 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (Young 2008)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,4]	none	7	8	-	MD 7 higher (11.73 lower to	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NIV**	**No airway clearance technique**	**Relative (95% CI)**	**Absolute**		
										25.73 higher)		
Quality of life - CF-QOL traditional dyspnoea index score (follow-up 6 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (Young 2008)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4,5]	none	7	8	-	MD 2.9 higher (0.71 to 5.09 higher)	MODERATE	IMPORTANT

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; MD: mean difference; NIV: non-invasive ventilation
1 The quality of the evidence was downgraded by 2 due to very serious imprecision as 95% CI crossed 2 clinical MIDs
2 The quality of the evidence was downgraded by 2 due to very serious imprecision as 95% CI crossed 2 default MIDs
3 The quality of the evidence was downgraded by 1 due to serious imprecision as 95% CI crossed 1 default MID
4 Clinical MID=5 was used to assess imprecision for quality of life because the CF QOL questionnaire (Gee et al. 2000) was used
5 The quality of the evidence was downgraded by 1 due to serious imprecision as 95% CI crossed 1 clinical MID

J.8 Mucoactive agents

J.8.1 Mannitol

Table 21: Clinical evidence profile: Comparison 1.1. Mannitol versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mannitol	Control	Relative (95% CI)	Absolute		
FEV_1 % predicted (repeated measures, change from baseline) (follow-up 2 weeks; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mannitol	Control	Relative (95% CI)	Absolute	Quality	Importance
1 (Jaques 2008)	randomised trials[1]	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	36		-	MD 3.95 higher (0.96 to 6.94 higher)	LOW	CRITICAL
FEV_1 % predicted (repeated measures, change from baseline) (follow-up 2 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	361	239	-	MD 2.98 higher (1.04 to 4.92 higher)	MODERATE	CRITICAL
FEV_1 % predicted (repeated measures, change from baseline) (follow-up 4 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	361	239	-	MD 3.26 higher (1.16 to 5.35 higher)	LOW	CRITICAL
FEV_1 % predicted (repeated measures, change from baseline) (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	361	239	-	MD 3.89 higher (1.69 to 6.08 higher)	LOW	CRITICAL
FEV_1 % predicted in children and young people (repeated measures, change from baseline) (follow-up 2 months; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mannitol	Control	Relative (95% CI)	Absolute	Quality	Importance
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	Total number of children and young people: 258 (Number in each group not reported)		-	MD 2.64 higher (0.73 lower to 6.02 higher)	LOW	CRITICAL
FEV_1 % predicted in children and young people (repeated measures, change from baseline) (follow-up 4 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	Total number of children and young people: 258 (Number in each group not reported)		-	MD 1.34 higher (2.42 lower to 5.10 higher)	LOW	CRITICAL
FEV_1 % predicted in children and young people (repeated measures, change from baseline) (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	Total number of children and young people: 258 (Number in each group not reported)		-	MD 3.03 higher (0.78 lower to 6.84 higher)	LOW	CRITICAL
FEV_1 % predicted in adults (repeated measures, change from baseline) (follow-up 2 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	Total number of adults: 317 (Number in each group not reported)		-	MD 3.72 higher (0.82 to 6.64 higher)	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mannitol	Control	Relative (95% CI)	Absolute	Quality	Importance
FEV_1 % predicted in adults (repeated measures, change from baseline) (follow-up 4 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	Total number of adults: 317 (Number in each group not reported)		-	MD 4.23 higher (0.98 to 7.48 higher)	LOW	CRITICAL
FEV_1 % predicted in adults (repeated measures, change from baseline) (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	Total number of adults: 317 (Number in each group not reported)		-	MD 5.74 higher (2.36 to 9.13 higher)	LOW	CRITICAL
Time to first protocol defined pulmonary exacerbation (follow-up: 6 months)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[4]	none	0/361 (0%)	0/239 (0%)	HR 0.7 (0.48 to 1.02)	-	LOW	CRITICAL
Number of children and young people with protocol defined exacerbations (proxy for time to next exacerbation) (follow-up: 6 months)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[5]	none	No. participants with exacerbations	No. participants with exacerbation	RR 0.62 (0.35 to 1.09)	-	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mannitol	Control	Relative (95% CI)	Absolute	Quality	Importance
							not reported. Total N of participants: 154	s not reported. Total N of participants: 105				
Number of adults with protocol defined exacerbations (proxy for time to next exacerbation) (follow-up: 6 months)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[5]	none	No. participants with exacerbations not reported. Total N of participants: 207	No. participants with exacerbations not reported. Total N of participants: 134	RR 0.76 (0.52 to 1.13)	-	LOW	CRITICAL
Number of patients needing additional IV antibiotics (follow-up 6 months)												
2 (Aitken 2012,	randomised trials	no serious risk of bias	serious[6]	serious[2]	serious[5]	none	165/361 (45.7%)	134/239 (56.1%)	RR 0.81 (0.63 to 1.04)	107 fewer per 1000 (from 28 fewer to 168 fewer)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mannitol	Control	Relative (95% CI)	Absolute	Quality	Importance
Bilton 2011)								56%		106 fewer per 1000 (from 28 fewer to 168 fewer)		
Quality of life – CFQOL respiratory domain (change from baseline) (follow-up 4 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	serious[7]	serious[2]	serious[3]	none	292	215	-	MD 1.66 lower (5.66 lower to 2.34 higher)	VERY LOW	IMPORTANT
Quality of life – CFQOL respiratory domain (change from baseline) (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	very serious[8]	very serious2	very serious[9]	none	268	197	-	MD 1.53 lower (12.11 lower to 9.05 higher)	VERY LOW	IMPORTANT
Quality of life – CFQOL vitality domain (change from baseline) (follow-up 4 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	None	207	154	-	MD 3.42 higher (0.21 lower to 7.04 higher)	LOW	IMPORTANT
Quality of life – CFQOL vitality domain (change from baseline) (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mannitol	Control	Relative (95% CI)	Absolute	Quality	Importance
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	None	187	138	-	MD 4.84 higher (0.86 to 8.82 higher)	LOW	IMPORTANT
Quality of life – CFQOL physical domain (change from baseline) (follow-up 4 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	None	291	214	-	MD 1.8 lower (4.72 lower to 1.11 higher)	MODERATE	IMPORTANT
Quality of life – CFQOL physical domain (change from baseline) (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	serious[10]	serious[2]	very serious[9]	none	268	197	-	MD 0.66 higher (6.2 lower to 7.52 higher)	VERY LOW	IMPORTANT
Quality of life – CFQOL emotion domain (change from baseline) (follow-up 4; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	None	292	214	-	MD 2.11 lower (4.56 lower to 0.34 higher)	MODERATE	IMPORTANT
Quality of life - CFQOL emotion domain (change from baseline) (follow-up 6 weeks; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mannitol	Control	Relative (95% CI)	Absolute	Quality	Importance
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	None	269	196	-	MD 1.27 lower (3.74 lower to 1.2 higher)	MODERATE	IMPORTANT
Quality of life – CFQOL eating domain (change from baseline) (follow-up 4 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	None	292	213	-	MD 0.81 higher (1.96 lower to 3.58 higher)	MODERATE	IMPORTANT
Quality of life – CFQOL eating domain (change from baseline) (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	None	269	197	-	MD 0.68 higher (2.29 lower to 3.65 higher)	MODERATE	IMPORTANT
Quality of life – CFQOL health domain (change from baseline) (follow-up 4 weeks; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	None	208	152	-	MD 0.43 lower (4.18 lower to 3.32 higher)	MODERATE	IMPORTANT
Quality of life – CFQOL health domain (change from baseline) (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mannitol	Control	Relative (95% CI)	Absolute	Quality	Importance
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	None	186	139	-	MD 0.21 lower (4.14 lower to 3.72 higher)	MODERATE	IMPORTANT
Quality of life – CFQOL social domain (change from baseline) (follow-up 4 weeks; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	None	292	212	-	MD 1.2 lower (3.7 lower to 1.3 higher)	MODERATE	IMPORTANT
Quality of life – CFQOL social domain (change from baseline) (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	very serious[11]	serious[2]	serious[3]	None	268	197	-	MD 1.56 lower (6.66 lower to 3.54 higher)	VERY LOW	IMPORTANT
Quality of life – CFQOL body domain (change from baseline) (follow-up 4 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	None	290	210	-	MD 3.1 lower (6.49 lower to 0.29 higher)	LOW	IMPORTANT
Quality of life - CFQOL body domain (change from baseline) (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mannitol	Control	Relative (95% CI)	Absolute	Quality	Importance
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	None	266	195	-	MD 1.19 lower (4.51 lower to 2.13 higher)	MODERATE	IMPORTANT
Quality of life - CFQOL role domain (change from baseline) (follow-up 4 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	None	207	151	-	MD 1.22 higher (2.21 lower to 4.66 higher)	MODERATE	IMPORTANT
Quality of life - CFQOL role domain (change from baseline) (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	serious[12]	serious[2]	serious[3]	None	186	138	-	MD 1.30 lower (45.79 lower to 3.19 higher)	VERY LOW	IMPORTANT
Quality of life - CFQOL digestion domain (change from baseline) (follow-up 4 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	292	213	-	MD 1.49 lower (4.77 lower to 1.78 higher)	MODERATE	IMPORTANT
Quality of life - CFQOL digestion domain (change from baseline) (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mannitol	Control	Relative (95% CI)	Absolute	Quality	Importance
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	None	268	197	-	MD 1.07 lower (5.04 lower to 2.9 higher)	LOW	IMPORTANT
Quality of life - CFQOL weight domain (change from baseline) (follow-up 4 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	None	207	153	-	MD 4.23 lower (10.28 lower to 1.83 higher)	LOW	IMPORTANT
Quality of life - CFQOL weight domain (change from baseline) (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	None	186	139	-	MD 3.27 lower (9.84 lower to 3.31 higher)	LOW	IMPORTANT
Adverse events: haemoptysis (mild) (follow-up 2 weeks)												
1 (Jaques 2008)	randomised trials[1]	no serious risk of bias	no serious inconsistency	serious[2]	not calculable[a]	None	18 (0%)	18 (0%)	RR not estimable[b]	0 events in each group	MODERATE	IMPORTANT
Adverse events: haemoptysis (severe) (follow-up 2 weeks)												
				serious[2]		None	18				VERY LOW	

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mannitol	Control	Relative (95% CI)	Absolute	Quality	Importance
1 (Jaques 2008)	randomised trials[1]	no serious risk of bias	no serious inconsistency		very serious[9]		2(5.3%)	2(5.3%)	RR 1 (0.15 to 6.74)	0 fewer per 1000 (from 45 fewer to 302 more)		IMPORTANT
Adverse events: Bronchospasm (mild) (follow-up 6 months)												
1 (Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	not calculable[a]	None	0/177 (0%)	0/118 (0%)	RR not estimable[b]	0 events in each group	MODERATE	IMPORTANT
Adverse events: Haemoptysis (mild) (follow-up 6 months)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[9]	None	6/361 (1.7%)	2/239 (0.84%)	RR 1.73 (0.26 to 11.62)	6 more per 1000 (from 6 fewer to 89 more)	VERY LOW	IMPORTANT
								0.9%		7 more per 1000 (from 7 fewer to 96 more)		
Adverse events: Bronchospasm (moderate) (follow-up 6 months)												
1 (Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[9]	None	1/177 (0.56%)	0/118 (0%)	RR 2.01 (0.03 to 133.11)	-	VERY LOW	IMPORTANT
Adverse events: Haemoptysis (moderate) (follow-up 6 months)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mannitol	Control	Relative (95% CI)	Absolute	Quality	Importance
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[9]	None	10/361 (2.8%)	1/239 (0.42%)	RR 4.66 (0.5 to 43.49)	15 more per 1000 (from 2 fewer to 178 more)	VERY LOW	IMPORTANT
								0.4%		15 more per 1000 (from 2 fewer to 170 more)		
Adverse events: Bronchospasm (severe) (follow-up 6 months)												
1 (Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[9]	none	1/177 (0.56%)	0/118 (0%)	RR 2.01 (0.03 to 133.11)	-	VERY LOW	IMPORTANT
Adverse events: Haemoptysis (severe) (follow-up 6 months)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[9]	none	3/361 (0.83%)	1/239 (0.42%)	RR 1.55 (0.13 to 18.99)	2 more per 1000 (from 4 fewer to 75 more)	VERY LOW	IMPORTANT
								0.4%		2 more per 1000 (from 3 fewer to 72 more)		
Adverse events: Bronchospasm in children and young people (follow-up 6 months)												
1 (Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	not calculable[a]	None	0/63 (0%)	0/42 (0%)	RR not estimable[b]	0 events in each group	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mannitol	Control	Relative (95% CI)	Absolute	Quality	Importance
Adverse events in adults: Bronchospasm in adults (follow-up 6 months)												
1 (Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[9]	None	No. participants with bronchospasm not reported. Total N of participants: 114	No. participants with bronchospasm not reported. Total N of participants: 76	RR 3.35 (0.16 to 71.50)	-	VERY LOW	IMPORTANT
Adverse events: Haemoptysis in children and young people (follow-up 6 months)												
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[9]	none	No. participants with haemoptysis not reported. Total N of participants: 154	No. participants with haemoptysis not reported. Total N of participants: 105	RR 5.48 (0.69 to 43.50)	-	VERY LOW	IMPORTANT
Adverse events: Haemoptysis in adults (follow-up 6 months)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mannitol	Control	Relative (95% CI)	Absolute	Quality	Importance
2 (Aitken 2012, Bilton 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[9]	none	No. participants with haemoptysis not reported. Total N of participants: 207	No. participants with haemoptysis not reported. Total N of participants: 134	RR 1.83 (0.64 to 5.23)	-	VERY LOW	IMPORTANT

Abbreviations: CFQOL: cystic fibrosis quality of life questionnaire; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; HR: hazard ratio; MD: mean difference; RR: risk ratio
1 Cross-over design
2 The quality of the evidence was downgraded by 1 as the participants in the trial underwent a tolerance test at screening. Those who failed were not entered in the study, and this limits the generalisability of the results to the general CF population.
3 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID
4 The quality of the evidence was downgraded by 1, as the 95% CI crossed the null effect
5 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID
6 The quality of the evidence was downgraded by 1 due to moderate heterogeneity (I2=59%)
7 The quality of the evidence was downgraded by 1 due to moderate heterogeneity (I2=37%).
8 The quality of the evidence was downgraded by 2 due to high heterogeneity (I2=89%)
9 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs
10 The quality of the evidence was downgraded by 1 due to high heterogeneity (I2=77%). It was not downgraded further as both studies showed no differences between groups.
11 The quality of the evidence was downgraded by 2 due to high heterogeneity (I2=70%). Studies show conflicting results.
12 The quality of the evidence was downgraded by 1 due to moderate heterogeneity (I2=41%)
a Imprecision not calculable because risk ratio could not be estimated as there were 0 events in each group
b Risk ratio not estimable because there were 0 events in each group

Table 22: Clinical evidence profile: Comparison 1.2.1. Mannitol versus Dornase alfa

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mannitol	Dornase alfa	Relative (95% CI)	Absolute		
FEV_1 (% change from baseline) - Up to 3 months (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Minasian 2010)	randomised trials[1]	serious [2]	no serious inconsistency	serious[3]	serious[4]	none	20		-	MD 2.8 higher (4.8 lower to 10.4 higher)	VERY LOW	CRITICAL

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference
1 Cross-over design
2 The quality of the evidence was downgraded by 1 because this is an open trial, and there is high risk of incomplete reporting
3 The quality of the evidence was downgraded by 1 as the participants in the trial underwent a tolerance test at screening. Those who fail were not entered in the study, and this limits the generalisability of the results to the general CF population
4 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MIDs

Table 23: Clinical evidence profile: Comparison 1.2.2. Mannitol + Dornase alfa versus Dornase alfa alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mannitol + dornase alfa *versus*	Dornase alfa alone	Relative (95% CI)	Absolute		
FEV_1 (% change from baseline) (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Minasian 2010)	randomised trials1	serious [2]	no serious inconsistency	serious[3]	very serious[4]	none	20		-	MD 4.3 lower (14.1 lower to 5.5 higher)	VERY LOW	CRITICAL

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference
1 Cross-over design

2 The quality of the evidence was downgraded by 1 because this is an open trial, and there is high risk of incomplete reporting
3 The quality of the evidence was downgraded by 1 as the participants in the trial underwent a tolerance test at screening. Those who fail were not entered in the study, and this limits the generalisability of the results to the general CF population
4 The quality of the evidence was downgraded by 2 as the CI crossed 2 clinical MIDs

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.

J.8.2 Dornase alfa

Table 24: Clinical evidence profile: Comparison 2.1. Dornase alfa versus placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dornase alfa	Placebo	Relative (95% CI)	Absolute	**Quality**	**Importance**
Lung function: relative mean % change in FEV_1 (follow-up 10 days; range of scores: 0-100; Better indicated by higher values)												
Shah 1996	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[7]	none	20	21	-	MD 13.17 higher (0.70 to 25.64 higher)	VERY LOW	CRITICAL
Lung function: relative mean % change in FEV_1 (follow-up 1 months; range of scores: 0-100; Better indicated by higher values)												
4 (Laube 1996, Ramsey 1993a, Ranasinha 1993,	randomised trials	very serious [3]	very serious[4]	no serious indirectness	serious[7]	none	121	127	-	MD 9.52 higher (0.59 to 18.46 higher)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dornase alfa	Placebo	Relative (95% CI)	Absolute	**Quality**	**Importance**
Shah 1995)												
Lung function: relative mean % change in FEV_1 (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
2 (Amin 2011, McCoy 1996)	randomised trials[5]	very serious [6]	no serious inconsistency	no serious indirectness	serious[7]	none	175	144	-	MD 6.7 higher (3.72 to 9.67 higher)	VERY LOW	CRITICAL
Lung function: relative mean % change in FEV_1 (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Fuchs 1994)	randomised trials	serious [8]	no serious inconsistency	no serious indirectness	serious[7]	none	322	325	-	MD 5.8 higher (4.41 to 7.19 higher)	LOW	CRITICAL
subgroup analysis based on disease severity: participants with moderate disease FEV_1 relative mean % change in FEV_1 (follow-up 1 months; range of scores: 0-100; Better indicated by higher values)												
3 (Laube 1996, Ramsey 1993a, Ranasinha 1993)	randomised trials	very serious [9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	90	93	-	MD 14.32 higher (10.81 to 17.83 higher)	LOW	CRITICAL
subgroup analysis based on disease severity: participants with severe disease FEV_1 relative mean % change in FEV_1 (follow-up 1 months; Better indicated by higher values)												
1 (Shah 1995)	randomised trials	very serious [10]	no serious inconsistency	no serious indirectness	serious[7]	none	31	34	-	MD 2.8 lower (8.76 lower to 3.16 higher)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dornase alfa	Placebo	Relative (95% CI)	Absolute	Quality	Importance
subgroup analysis based on disease severity: participants with acute pulmonary exacerbation mean % change in FEV_1 (follow-up 1 months; range of scores: 0-100; Better indicated by higher values)												
1 (Wilmott 1996)	randomised trials	very serious[11]	no serious inconsistency	no serious indirectness	very serious[2]	none	43	37	-	MD 1 higher (13.93 lower to 15.93 higher)	VERY LOW	CRITICAL
Lung function: absolute mean % change in FEV_1 (follow-up 2 years; range of scores: 0-100; Better indicated by higher values)												
1 (Quan 2001)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	204	206	-	MD 3.24 higher (1.03 to 5.45 higher)	MODERATE	CRITICAL
Number of people experiencing exacerbations (follow-up 6 month)												
1 (Fuchs 1994)	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[12]	none	71/322 (22%)	89/325 (27.4%)	RR 0.81 (0.61 to 1.06)	52 fewer per 1000 (from 107 fewer to 16 more)	LOW	CRITICAL
Number of people experiencing exacerbations (follow-up 2 years)												
1 (Quan 2001)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[12]	none	40/236 (16.9%)	56/234 (23.9%)	RR 0.71 (0.49 to 1.02)	69 fewer per 1000 (from 122 fewer to 5 more)	MODERATE	CRITICAL
Number of days of IV antibiotic use (follow-up 3 months; Better indicated by lower values)												
1 (McCoy 1996)	randomised trials	serious[13]	no serious inconsistency	no serious indirectness	very serious[14]	none	158	162	-	MD 2.96 lower (7.29 lower to 1.37 higher)	VERY LOW	CRITICAL
Adverse events: haemoptysis (follow-up 1 months)												
2 (Rana	randomised trials				very serious[14]	none	4/71 (5.6%)	3/70 (4.3%)		10 more per 1000 (from	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dornase alfa	Placebo	Relative (95% CI)	Absolute		
sinha 1993, Shah 1995)		very serious [15]	no serious inconsistency	no serious indirectness					RR 1.23 (0.20 to 7.63)	34 fewer to 284 more)		
								4.3%		10 more per 1000 (from 34 fewer to 285 more)		
Adverse events: haemoptysis (follow-up 6 months)												
1 (Fuchs 1994)	randomised trials	serious [8]	no serious inconsistency	no serious indirectness	very serious[14]	none	17/322 (5.3%)	21/325 (6.5%)	RR 0.82 (0.44 to 1.52)	12 fewer per 1000 (from 36 fewer to 34 more)	VERY LOW	IMPORTANT
Adverse events: voice alteration (follow-up 1 months)												
3 (Ramsey 1993a, Ranasinha 1993, Shah 1995)	randomised trials	very serious [16]	very serious[17]	no serious indirectness	very serious[14]	none	13/115 (11.3%)	3/118 (2.5%)	RR 2.79 (0.03 to 278.07)	46 more per 1000 (from 25 fewer to 1000 more)	VERY LOW	IMPORTANT
								0%		-		
Adverse events: voice alteration (follow-up 3 months)												
1 (McCoy 1996)	randomised trials	serious [13]	no serious inconsistency	no serious indirectness	no serious imprecision	none	28/158 (17.7%)	10/162 (6.2%)	RR 2.87 (1.44 to 5.71)	115 more per 1000 (from 27 more to 291 more)	MODERATE	IMPORTANT
Adverse events: voice alteration (follow-up 6 months)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dornase alfa	Placebo	Relative (95% CI)	Absolute		
1 (Fuchs 1994)	randomised trials	serious [8]	no serious inconsistency	no serious indirectness	very serious[14]	none	12/322 (3.7%)	7/325 (2.2%)	RR 1.73 (0.69 to 4.34)	16 more per 1000 (from 7 fewer to 72 more)	VERY LOW	IMPORTANT
Adverse events: voice alteration (follow-up 2 years)												
1 (Quan 2001)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[14]	none	26/236 (11%)	27/234 (11.5%)	RR 0.95 (0.57 to 1.59)	6 fewer per 1000 (from 50 fewer to 68 more)	LOW	IMPORTANT
Quality of life: change in QFQ-R parents (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Amin 2011)	randomised trials[5]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	17		-	MD 5.45 lower (15.23 lower to 4.33 higher)	MODERATE	IMPORTANT
Quality of life: change in QFQ-R 14+ (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Amin 2011)	randomised trials[5]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	17		-	MD 5.21 lower (15.5 lower to 5.08 higher)	MODERATE	IMPORTANT

Abbreviations: CFQ-R: cystic fibrosis questionnaire revised; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IV: intravenous; MD: mean difference; RR: risk ratio

1 The quality of the evidence was downgraded by due to unclear sequence generation, allocation concealment, blinding and reporting

2 The quality of the evidence was downgraded by 2 as the CI crossed 2 clinical MIDs

3 The quality of the evidence was downgraded by 2 due to unclear sequence generation, blinding, allocation concealment and reporting in 3 of the trials, and unclear blinding and reporting in the fourth trial

4 The quality of the evidence was downgraded by 1 due to high heterogeneity (I2=88%) . See sensitivity analysis.

5 Amin 2011: cross-over trial

6 The quality of the evidence was downgraded by 1 due to unclear sequence generation, blinding, allocation concealment and reporting in the 1 of the trial

7 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID

8 The quality of the evidence was downgraded by 1 due to unclear blinding, allocation, concealment and reporting

9 The quality of the evidence was downgraded by 2 due to unclear sequence generation, blinding, allocation concealment and reporting in 2 of the trials, and unclear blinding and reporting in the third trial

10 The quality of the evidence was downgraded by 2 due to unclear sequence generation, blinding, allocation concealment and reporting

11 The quality of the evidence was downgraded by 2 due to unclear sequence generation, blinding, allocation concealment and reporting
12 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID
13 The quality of the evidence was downgraded by 2 due to unclear randomization, blinding, allocation concealment and reporting
14 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs
15 The quality of the evidence was downgraded by 2 due to unclear sequence generation, blinding, allocation concealment and reporting in both trials
16 The quality of the evidence was downgraded by 2 due to unclear blinding, allocation concealment and reporting in 2 of the trials, and unclear blinding and reporting in the third trial
17 The quality of the evidence was downgraded by 1 due to high heterogeneity (I2=85%)

Table 25: Clinical evidence profile: Comparison 2.2. Dornase alfa versus nebulized sodium chloride

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dornase alfa	Nebulised sodium chloride	Relative (95% CI)	Absolute	Quality	Importance
Lung function: mean % change in FEV_1 (follow-up 3 weeks; range of scores: 0-100; Better indicated by higher values)												
1 Ballman 1998	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	48		-	MD 1.6 higher (7.96 lower to 11.16 higher)	VERY LOW	CRITICAL
Lung function: mean % change in FEV_1 (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1 Suri 2001	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	14		-	MD 8 higher (2 to 14 higher)	LOW	CRITICAL
Number of days inpatient treatment (follow-up 3 months; Better indicated by lower values)												
1 Suri 2001	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14		-	MD 0.4 lower (2.32 lower to 1.52 higher)	MODERATE	CRITICAL

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference
1 Cross-over study
2 The quality of the evidence was downgraded by 1 due to unclear blinding, allocation, concealment and reporting
3 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 clinical MIDs
4 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID

Comparison 2.3. Dornase alfa versus acetylcysteine

No evidence was found for this comparison.

J.8.3 Nebulised sodium chloride

Table 26: Clinical evidence profile: Comparison 3.1. Nebulised sodium chloride (> 3% concentration) versus placebo (0.9% to 0.12%) or low-concentration (≤ 3%)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High concentration (>3% sodium chloride)	Low concentration(≤3% sodium chloride)	Relative (95% CI)	Absolute	Quality	Importance
Failed to regain pre-exacerbation FEV_1% predicted (follow-up: at hospital discharge; range of scores: 0-100; Better indicated by higher values)												
1 (Dentice 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	17/67 (25.4%)	28/65 (43.1%)	RR 0.59 (0.36 to 0.97)	177 fewer per 1000 (from 13 fewer to 276 fewer)	MODERATE	CRITICAL
Lung function: % change in FEV_1 (follow-up 2 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (Gupta 2012)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	15	15	-	MD 14.35 lower (27.8 to 0.9 lower)	MODERATE	CRITICAL
Lung function: % change in FEV_1 (follow-up 4 weeks; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High concentration (>3% sodium chloride)	Low concentration(≤3% sodium chloride)	Relative (95% CI)	Absolute	Quality	Importance
2 (Gupta 2012, Mainz 2016)	randomised trials[2]	very serious[3]	very serious[4]	no serious indirectness	very serious[5]	none	75	78	-	MD 4.92 lower (17.69 lower to 7.86 higher)	VERY LOW	CRITICAL
Lung function: % change in FEV_1 (follow-up 12 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (Elkins 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	76	73	-	MD 4.1 higher (0.08 lower to 8.28 higher)	MODERATE	CRITICAL
Lung function: % change in FEV_1 (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (Elkins 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	75	65	-	MD 5.37 higher (1.03 to 9.71 higher)	MODERATE	CRITICAL
Lung function: % change in FEV_1 (follow-up 36 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (Elkins	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[1]	none	69	65	-	MD 3.63 higher	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High concentration (>3% sodium chloride)	Low concentration(≤3% sodium chloride)	Relative (95% CI)	Absolute	Quality	Importance
2006)		risk of bias								(1.56 lower to 8.82 higher)		
Lung function: % change in FEV_1 (follow-up 48 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (Elkins 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	68	66	-	MD 2.31 higher(2.72 lower to 7.34 higher)	MODERATE	CRITICAL
Time to first pulmonary exacerbation (follow-up: > 1 year)												
2 (Dentice 2016, Rosenfeld 2012)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	225	228	HR 0.92 (0.74 to 1.14)	-	MODERATE	CRITICAL
Number of days of treatment for a pulmonary exacerbation (follow-up 48 weeks; Better indicated by lower values)												
1 (Rosendfeld	randomised trials	no serious risk	no serious inconsistency	no serious indirectness	no serious imprecision	none	158	163	-	MD 1.11 higher (0.89	HIGH	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High concentration (>3% sodium chloride)	Low concentration(≤3% sodium chloride)	Relative (95% CI)	Absolute	Quality	Importance
2012)		of bias								to 1.33 higher)		
Change in quality of life following treatment – CFQOL, physical domain (follow-up 7 days; range of scores: 0-100; Better indicated by higher values)												
1 (Dentice 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	67	65	-	MD 2.00 higher (3.12 lower to 7.12 higher)	MODERATE	IMPORTANT
Change in quality of life following treatment – CFQOL, burden domain (follow-up 7 days; range of scores: 0-100; Better indicated by higher values)												
1 (Dentice 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	67	65	-	MD 0.00 higher (4.78 lower to 4.78 higher)	HIGH	IMPORTANT
Change in quality of life following treatment – CFQOL, health domain (follow-up 7 days; range of scores: 0-100; Better indicated by higher values)												
1 (Dentice	randomised trials	no serious risk	no serious inconsistency	no serious indirectness	serious[1]	none	67	65	-	MD 2.00 lower (8.15 lower	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High concentration (>3% sodium chloride)	Low concentration(≤3% sodium chloride)	Relative (95% CI)	Absolute	Quality	Importance
2016)		of bias								to 4.15 higher)		
Change in quality of life following treatment – CFQOL, respiratory domain (follow-up 7 days; range of scores: 0-100; Better indicated by higher values)												
1 (Dentice 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	67	65	-	MD 1.00 higher (4.99 lower to 6.99 higher)	MODERATE	IMPORTANT
Change in quality of life following treatment – CFQOL, physical domain (at hospital discharge; range of scores: 0-100; Better indicated by higher values)												
1 (Dentice 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	67	65	-	MD 2.00 higher (4.15 lower to 8.15 higher)	MODERATE	IMPORTANT
Change in quality of life following treatment – CFQOL, burden domain (at hospital discharge; range of scores: 0-100; Better indicated by higher values)												
1 (Dentice	randomised trials	no serious risk	no serious inconsistency	no serious indirectness	serious[1]	none	67	65	-	MD 2.00 higher (4.04 lower	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High concentration (>3% sodium chloride)	Low concentration(≤3% sodium chloride)	Relative (95% CI)	Absolute	Quality	Importance
2016)		of bias								to 8.04 higher)		
Change in quality of life following treatment — CFQOL, health domain (at hospital discharge; range of scores: 0-100; Better indicated by higher values)												
1 (Dentice 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	67	65	-	MD 2.00 higher (4.99 lower to 8.99 higher)	MODERATE	IMPORTANT
Change in quality of life following treatment – CFQOL, respiratory domain (at hospital discharge; range of scores: 0-100; Better indicated by higher values)												
1 (Dentice 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	67	65	-	MD 2.00 lower (8.67 lower to 4.67 higher)	MODERATE	IMPORTANT
Quality of life: CFQ parent, CFQ-R respiratory (follow-up 4 week; range of scores: 0-100; Better indicated by higher values)												
1 (Amin 2010)	randomised trials[7]	no serious risk	no serious inconsistency	no serious indirectness	serious[1]	none	20		-	MD 5.9 higher (3.1 lower	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High concentration (>3% sodium chloride)	Low concentration(≤3% sodium chloride)	Relative (95% CI)	Absolute		
		of bias								to 14.9 higher)		
Quality of life: CFQ 14+, CFQ-R respiratory (follow-up 4 weeks; Better indicated by higher values)												
1 (Amin 2010)	randomised trials[7]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	20		-	MD 5.2 higher (7 lower to 17.4 higher)	LOW	IMPORTANT
Change in quality of life: CFQ-R parents (follow-up 48 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (Elkins 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	34	33	-	MD 1.13 lower (7.49 lower to 5.23 higher)	LOW	IMPORTANT
Change in quality of life: CFQ-R 14+ (follow-up 48 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (Elkins 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	46	46	-	MD 7.77 higher(1.86 to 13.68 higher)	MODERATE	IMPORTANT
Change in quality of life: CFQ-R respiratory domain (follow-up 48 weeks; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High concentration (>3% sodium chloride)	Low concentration(≤3% sodium chloride)	Relative (95% CI)	Absolute	Quality	Importance
1 (Rosenfeld 2012)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	158	163	-	MD 3.3 higher (0 to 6.6 higher)	MODERATE	IMPORTANT

Abbreviations: CFQ-R: cystic fibrosis questionnaire revised; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; HR: hazard ratio, MD: mean difference; RR: risk ratio
1 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID
2 Mainz 2016: Cross-over study
3 The quality of the study was downgraded by 1 due to unclear risk of bias in relation to random sequence generation, allocation concealment and selective reporting in 1 study
4 The quality of the evidence was downgrade by 2 due to serious inconsistency (I2=77%)
5 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 clinical MIDs
6 The quality of the evidence was downgraded by 1 as the 95% CI crossed the null effect
7 Amin 2010: cross-over study

Comparison 3.2. Nebulised sodium chloride versus acetylcysteine

No evidence was found for this comparison.

J.8.4 Acetylcysteine

Table 27: Clinical evidence profile: Comparison 4. Acetylcysteine versus placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acetylcysteine	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Lung function: change in FEV_1 (% predicted) (follow-up 4 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (Skov 2015)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10	9	-	MD 3.51 higher (0.65 lower to 7.67 higher)	VERY LOW	CRITICAL
Lung function: change in FEV_1 (% predicted) (follow-up 12 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (Ratjen 1985)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	10	11	-	MD 5 higher (10.84 lower to 20.84 higher)	LOW	CRITICAL
Lung function: change in FEV_1 (% predicted) (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (Conrad 2015)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	36	34	-	MD 4.4 higher (0.83 to 7.97 higher)	MODERATE	CRITICAL
Inflammatory markers: change in sputum IL-8 (log10) (follow-up 24 weeks; Better indicated by lower values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acetylcysteine	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1 (Conrad 2015)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	not calculable[4]	none	36	34	-	MD 0.19 higher (0.03 lower to 0.42 higher)	HIGH	IMPORTANT
Incidence of pulmonary exacerbations (follow-up 24 weeks)												
1 (Conrad 2015)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	15/36 (41.7%)	17/34 (50%)	RR 0.83 (0.5 to 1.39)	85 fewer per 1000 (from 250 fewer to 195 more)	LOW	CRITICAL
Quality of life: QFQ-R respiratory (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (Conrad 2015)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	36	34	-	MD 0.34 lower (6.3 lower to 5.62 higher)	LOW	IMPORTANT

Abbreviations: CFQ-R: cystic fibrosis questionnaire revised; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IL-8: interleukin 8; MD: mean difference; RR: risk ratio

1 The quality of the evidence was downgraded by 1 as this is an open trial, and there was unclear randomization and allocation concealment.

2 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID

3 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 clinical MIDs

4 Imprecision not calculable, as SD for the control group was not available in the study

J.9 Pulmonary infection – prophylaxis

Table 28: Clinical evidence profile: Comparison 1. Continuous oral Flucloxacillin versus antibiotics 'as required'

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Continuous oral Flucloxacillin, antibiotic prophylaxis**	**Antibiotics as required**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Number of children from whom *S aureus* isolated at least once (follow-up mean 1 years)												
1 (Chatfield 1991)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	9/45 (20%)	19/51 (37.3 %)	RR 0.54 (0.27 to 1.06)	171 fewer per 1000 (from 272 fewer to 22 more)	VERY LOW	IMPORTANT
Number of children from whom *S aureus* isolated at least once (follow-up mean 2 years)												
2 (Chatfield 1991, Weaver 1994)	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/69 (18.8%)	34/80 (42.5 %)	RR 0.44 (0.25 to 0.77)	238 fewer per 1000 (from 98 fewer to 319 fewer)	LOW	IMPORTANT
								48.3%		270 fewer per 1000 (from 111		

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous oral Flucloxacillin, antibiotic prophylaxis	Antibiotics as required	Relative (95% CI)	Absolute		
										fewer to 362 fewer)		
Number of children from whom *S aureus* isolated at least once (follow-up mean 3 years)												
1 (Chatfield 1991)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/54 (22.2%)	28/65 (43.1 %)	RR 0.52 (0.29 to 0.91)	207 fewer per 1000 (from 39 fewer to 306 fewer)	VERY LOW	IMPORTANT
Number of children from whom *P aeruginosa* isolated at least once (follow-up mean 1 years)												
1 (Chatfield 1991)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[4]	none	6/44 (13.6%)	3/51 (5.9%)	RR 2.32 (0.62 to 8.73)	78 more per 1000 (from 22 fewer to 455 more)	VERY LOW	CRITICAL
Number of children from whom *P aeruginosa* isolated at least once (follow-up mean 2 years)												
2 (Chatfield 1991, Weav	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	very serious[4]	none	9/69 (13%)	14/80 (17.5 %)	RR 0.74 (0.34 to 1.61)	45 fewer per 1000 (from 115	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous oral Flucloxacillin, antibiotic prophylaxis	Antibiotics as required	Relative (95% CI)	Absolute		
er 1994)										fewer to 107 more)		
								21.7%		56 fewer per 1000 (from 143 fewer to 132 more)		
Number of children from whom *P aeruginosa* isolated at least once (follow-up mean 3 years)												
1 (Chatfield 1991)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[4]	none	9/54 (16.7%)	14/66 (21.2 %)	RR 0.79 (0.37 to 1.67)	45 fewer per 1000 (from 134 fewer to 142 more)	VERY LOW	CRITICAL
Number of children requiring admission due to pulmonary exacerbations (annualised rates) (follow-up mean 3 years)												
2 (Chatfield 1991, Weaver 1994)	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	very serious[4]	none	19/58 (32.8%)	22/66 (33.3 %)	RR 0.98 (0.59 to 1.62)	7 fewer per 1000 (from 137 fewer to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous oral Flucloxacillin, antibiotic prophylaxis	Antibiotics as required	Relative (95% CI)	Absolute		
										207 more)		

Abbreviations: CI: confidence interval; RR: risk ratio
1 The quality of the evidence was downgraded by 2 as this is an open trial, and there was unclear risk of bias for the domains randomisation, allocation concealment, incomplete outcome data, and selective reporting
2 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID
3 The quality of the evidence was downgraded by 2 as both studies were open trials, and there was unclear risk of bias for the domains randomisation, allocation concealment, incomplete outcome data, and selective reporting for 1 of the trials
4 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs

Table 29: Clinical evidence profile: Comparison 2. Continuous oral Cephalexin versus antibiotics 'as required'

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous oral Cephalexin, antibiotic prophylaxis	Antibiotics as required	Relative (95% CI)	Absolute		
Number of children from whom *S aureus* isolated at least once (follow-up mean 1 years; assessed with: Respiratory cultures)												
1 (Stutman 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/75 (14.7%)	36/77 (46.8%)	RR 0.31 (0.17 to 0.57)	323 fewer per 1000 (from 201 fewer	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Continuous oral Cephalexin, antibiotic prophylaxis**	**Antibiotics as required**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
										to 388 fewer)		
Number of children from whom *S aureus* isolated at least once (follow-up mean 2 years; assessed with: Respiratory cultures)												
1 (Stutman 2002)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/87 (21.8%)	52/79 (65.8%)	RR 0.33 (0.22 to 0.51)	441 fewer per 1000 (from 323 fewer to 513 fewer)	MODERATE	IMPORTANT
Number of children from whom *S aureus* isolated at least once (follow-up mean 3 years; assessed with: Respiratory cultures)												
1 (Stutman 2002)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25/77 (32.5%)	44/64 (68.8%)	RR 0.42 (0.29 to 0.59)	399 fewer per 1000 (from 282 fewer to 488 fewer)	MODERATE	IMPORTANT
Number of children from whom *S aureus* isolated at least once (follow-up mean 4 years; assessed with: Respiratory cultures)												
1 (Stutman	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25/71 (35.2%)	47/56 (83.9%)	RR 0.42 (0.3 to 0.59)	487 fewer per 1000 (from	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Continuous oral Cephalexin, antibiotic prophylaxis**	**Antibiotics as required**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
2002)										344 fewer to 587 fewer)		
Number of children from whom *S aureus* isolated at least once (follow-up mean 5 years; assessed with: Respiratory cultures)												
1 (Stutman 2002)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/58 (34.5%)	34/40 (85%)	RR 0.41 (0.28 to 0.59)	502 fewer per 1000 (from 349 fewer to 612 fewer)	LOW	IMPORTANT
Number of children from whom *S aureus* isolated at least once (follow-up mean 6 years; assessed with: Respiratory cultures)												
1 (Stutman 2002)	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/25 (28%)	14/18 (77.8 %)	RR 0.36 (0.18 to 0.71)	498 fewer per 1000 (from 226 fewer to 638 fewer)	LOW	IMPORTANT
Lung function: FEV_1 litres (follow-up mean 6 years; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Continuous oral Cephalexin, antibiotic prophylaxis**	**Antibiotics as required**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1 (Stutman 2002)	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[8]	none	68	51	-	MD 2.3 lower (13.59 lower to 8.99 higher)	VERY LOW	IMPORTANT
Any pulmonary exacerbations (follow-up mean 6 years; measured with: %; Better indicated by lower values)												
1 (Stutman 2002)	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[9]	none	68	51	-	MD 4.9 lower (22.24 lower to 12.44 higher)	VERY LOW	CRITICAL
Number of children requiring admission due to pulmonary exacerbations (annualised rates) (follow-up mean 6 years; assessed with: not reported)												
1 (Stutman 2002)	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[9]	none	5/68 (7.4%)	4/51 (7.8%)	RR 0.94 (0.26 to 3.32)	5 fewer per 1000 (from 58 fewer to 182 more)	VERY LOW	CRITICAL
Adherence to treatment (follow-up mean 6 years; measured with: Parents self-report; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous oral Cephalexin, antibiotic prophylaxis	Antibiotics as required	Relative (95% CI)	Absolute	Quality	Importance
1 (Stutman 2002)	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	Not calculable[10]	none	68	51	-	MD 5 higher (0 to 0 higher)	MODERATE	IMPORTANT
Minor adverse events - generalised rash (follow-up mean 6 years; measured with: Parents self-report; Better indicated by lower values)												
1 (Stutman 2002)	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	68	51	-	MD 0.4 higher (0.07 lower to 0.87 higher)	MODERATE	IMPORTANT
Minor adverse events - nappy rash (follow-up mean 6 years; measured with: Parents self-report; Better indicated by lower values)												
1 (Stutman 2002)	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	68	51	-	MD 0.9 higher (1.06 lower to 2.86 higher)	MODERATE	IMPORTANT
Minor adverse events - increased stool frequency (follow-up mean 6 years; measured with: Parents self-report; Better indicated by lower values)												
1 (Stutman 2002)	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	68	51	-	MD 0.2 higher (2.18 lower	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Continuous oral Cephalexin, antibiotic prophylaxis**	**Antibiotics as required**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
										to 2.58 higher)		
Number of children from whom *P aeruginosa* identified at least once (follow-up mean 1 years)												
1 (Stutman 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[9]	none	27/75 (36%)	24/77 (31.2%)	RR 1.15 (0.74 to 1.81)	47 more per 1000 (from 81 fewer to 252 more)	VERY LOW	CRITICAL
Number of children from whom *P aeruginosa* identified at least once (follow-up mean 2 years)												
1 (Stutman 2002)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[11]	none	38/87 (43.7%)	40/79 (50.6%)	RR 0.86 (0.62 to 1.19)	71 fewer per 1000 (from 192 fewer to 96 more)	LOW	CRITICAL
Number of children from whom *P aeruginosa* identified at least once (follow-up mean 3 years)												
1 (Stutman	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[9]	none	45/77 (58.4%)	38/64 (59.4%)	RR 0.98 (0.75 to 1.3)	12 fewer per 1000 (from	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Continuous oral Cephalexin, antibiotic prophylaxis**	**Antibiotics as required**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
2002)										148 fewer to 178 more)		
Number of children from whom *P aeruginosa* identified at least once (follow-up mean 4 years)												
1 (Stutman 2002)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[11]	none	46/71 (64.8%)	33/56 (58.9%)	RR 1.1 (0.83 to 1.45)	59 more per 1000 (from 100 fewer to 265 more)	LOW	CRITICAL
								58.9%		59 more per 1000 (from 100 fewer to 265 more)		
Number of children from whom *P aeruginosa* identified at least once (follow-up mean 5 years)												
1 (Stutman	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[11]	none	41/58 (70.7%)	22/40 (55%)	RR 1.29 (0.93	159 more per 1000	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Continuous oral Cephalexin, antibiotic prophylaxis**	**Antibiotics as required**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
2002)									to 1.78)	(from 38 fewer to 429 more)		
Number of children from whom *P aeruginosa* identified at least once (follow-up mean 6 years)												
1 (Stutman 2002)	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	serious[11]	none	22/25 (88%)	12/18 (66.7%)	RR 1.32 (0.92 to 1.89)	213 more per 1000 (from 53 fewer to 593 more)	VERY LOW	CRITICAL

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference; RR: risk ratio
1 This study was assessed by the Cochrane review Smyth 2014 as low risk of bias. However, the quality of the evidence was downgraded by 1 for this outcome, as the losses to follow up are over 20% (n=152; N=209).
2 This study was assessed by the Cochrane review Smyth 2014 as low risk of bias. However, the quality of the evidence was downgraded by 1 for this outcome, as the losses to follow up are over 20% (n=166; N=209).
3 This study was assessed by the Cochrane review Smyth 2014 as low risk of bias. However, the quality of the evidence was downgraded by 1 for this outcome, as the losses to follow up are over 20% (n=141; N=209).
4 This study was assessed by the Cochrane review Smyth 2014 as low risk of bias. However, the quality of the evidence was downgraded by 1 for this outcome, as the losses to follow up are over 20% (n=127; N=209).
5 This study was assessed by the Cochrane review Smyth 2014 as low risk of bias. However, the quality of the evidence was downgraded by 2 for this outcome, as the losses to follow up are over 50% (n=98; N=209).
6 This study was assessed by the Cochrane review Smyth 2014 as low risk of bias. However, the quality of the evidence was downgraded by 2 for this outcome, as the losses to follow up are over 50% (n=43; N=209).
7 This study was assessed by the Cochrane review Smyth 2014 as low risk of bias. However, the quality of the evidence was downgraded by 1 for this outcome, as the losses to follow up are over 20% (n=119; N=209).

8 The quality of the evidence was downgraded by 2, as the 95% CI crossed 2 clinical MIDs
9 The quality of the evidence was downgraded by 2, as the 95% CI crossed 2 default MIDs
10 Imprecision is not calculable with the data reported
11 The quality of the evidence was downgraded by 1, as the 95% CI crossed 1 default MID for dichotomous outcomes

J.10 Pulmonary infection – acute

J.10.1 *Pseudomonas aeruginosa*

J.10.1.1 Antimicrobial treatment for pulmonary exacerbations due to *P aeruginosa*

Table 30: Clinical evidence profile: Comparison 1. Single IV agents compared for pulmonary exacerbations with *P aeruginosa*

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single IV agent	Single IV agent	Relative (95% CI)	Absolute	Quality	Importance
FEV_1 (absolute change) (follow-up 2 weeks; measured with: litres ; Better indicated by higher values) [ceftazidime versus aztreonam]												
2 (Elborn 1992, Salh 1992)	randomised trials	serious [1]	serious[2]	no serious indirectness	no serious imprecision	none	23	23	-	MD 0.06 lower (0.44 lower to 0.32 higher)	LOW	CRITICAL

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference
1 The quality of the evidence was downgraded by 1 as 4 participants received both drugs in Salh 1992 study,
2 The quality of the evidence was downgraded by 1 due to serious heterogeneity (chi-squared p<0.1, I-squared inconsistency statistic of 50%-74.99%)

Table 31: Clinical evidence profile: Comparison 2. Single IV antibiotic (with placebo) vs combination IV antibiotic for pulmonary exacerbations with *P aeruginosa*

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single IV antibiotic (with placebo)**	**Combination IV antibiotic**	**Relative (95% CI)**	**Absolute**		
FEV_1 % predicted (absolute change) (follow-up 10 days; Better indicated by higher values) [tobramycin + placebo *versus* tobramycin + ceftazidime]												
1 (Master 2001)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	47	51	-	MD 2.2 lower (6.63 lower to 2.23 higher)	LOW	CRITICAL
FEV_1% predicted (relative change) (follow-up 2 weeks; Better indicated by higher values) [tobramycin + placebo *versus* IV piperacillin + tobramycin]												
1(Macfarlane 1985)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	4	5	-	MD 4.2 lower (26.5 lower to 18.1 higher)	VERY LOW	CRITICAL
FEV_1% predicted (relative change) (follow-up 2 weeks; Better indicated by higher values) [tobramycin + placebo *versus* piperacillin + tobramycin]												
1(Macfarlane 1985)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	4	5	-	MD 7.95 higher (8.78 lower to 24.68 higher)	VERY LOW	CRITICAL
Adverse effects - sensitivity reaction (follow-up 2 weeks; assessed with: number of participants) [tobramycin + placebo *versus* piperacillin all regimens]												
1(Macfarlane 1985)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	0/8 (0%)	3/10 (30%)	RR 0.17 (0.01	249 fewer per 1000	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single IV antibiotic (with placebo)	Combination IV antibiotic	Relative (95% CI)	Absolute		
									to 2.96)	(from 297 fewer to 588 more)		
Adverse effects - Number of hospital admissions due to tinnitus (follow-up 2 weeks) [tobramycin + placebo *versus* tobramycin + ceftazidime]												
1(Master 2001)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[6]	none	2/47 (4.3%)	2/51 (3.9%)	RR 1.09 (0.16 to 7.4)	4 more per 1000 (from 33 fewer to 251 more)	VERY LOW	IMPORTANT
Adverse effects - serum creatinine (follow-up 2 weeks; Better indicated by lower values) [tobramycin + placebo *versus* tobramycin + ceftazidime]												
1(Master 2001)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[6]	none	21	23	-	MD 4 lower (9.38 lower to 1.38 higher)	VERY LOW	IMPORTANT
Adverse effects - serum NAG (follow-up 2 weeks; Better indicated by lower values) [tobramycin + placebo *versus* tobramycin + ceftazidime]												
1(Master 2001)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	23	-	MD 2.1 lower (3.46 lower to 0.74 lower)	MODERATE	IMPORTANT

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference; NAG: N-acetyl glucosamide; RR: risk ratio
1 The quality of the evidence was downgraded by 1 as each participant contributed to multiple treatment episodes.
2 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID

3 The quality of the evidence was downgraded by 1 due to attrition bias (2 participants withdrew and did not contribute to analysis) and 1 participant received 2 treatment courses.
4 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 clinical MIDs
5 The quality of the evidence was downgraded by 1 due to very serious imprecision as 95%CI crossed 1 default MIDs
6 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs

Table 32: Clinical evidence profile: Comparison 3. Single IV antibiotic *versus* combination IV antibiotic for pulmonary exacerbations with *P aeruginosa*

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single IV antibiotic**	**Combination IV antibiotic**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Eradication: number of people in whom pseudomonas isolates were eradicated at end of course (follow-up 10 days) [Piperacillin *versus* piperacillin + tobramycin]												
1(McCarty 1988)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	5/19 (26.3%)	12/19 (63.2%)	RR 0.42 (0.18 to 0.95)	366 fewer per 1000 (from 32 fewer to 518 fewer)	LOW	CRITICAL
FEV_1 (relative change) (follow-up 10 - 14 days; measured with: %; Better indicated by higher values) [ceftazidime *versus* tobramycin + ticarcillin]												
1 (Gold 1985)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious imprecision[4]	none	17	13	-	MD 19.6 lower (38.26 to 0.94 lower)	LOW	CRITICAL
FEV_1 (absolute change) (follow-up 12 days; measured with: ml ; Better indicated by higher values) [Colistin *versus* colistin & "other"]												
1 (Conway	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious	none	36	35	-	MD 160 lower	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single IV antibiotic	Combination IV antibiotic	Relative (95% CI)	Absolute	Quality	Importance
1997)					imprecision					(309.72 to 10.28 lower)		
FEV_1 % predicted (absolute change) (follow-up: 14 days; Better indicated by higher values) [ceftazidime *versus* tobramycin + piperacillin]												
1 (De Boeck 1989)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[6]	none	11	10	-	MD 1 higher (8.85 lower to 10.85 higher)	VERY LOW	CRITICAL
Time to readmission (follow-up: 24 to 26 months; Better indicated by lower values) [ceftazidime *versus* tobramycin + piperacillin]												
1 (De Boeck 1989)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[7]	none	9	10	-	MD 1 lower (5.52 lower to 3.52 higher)	VERY LOW	IMPORTANT
Number of admissions, requiring IV antibiotics or death (follow-up 3 months) [ceftazidime *versus* tobramycin + ticarcillin]												
1 (Wesley 1988)	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[7]	none	7/12 (58.3%)	5/10 (50%)	RR 1.17 (0.53 to 2.55)	85 more per 1000 (from 235 fewer to 775 more)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single IV antibiotic	Combination IV antibiotic	Relative (95% CI)	Absolute	Quality	Importance
Mortality (follow-up 4 months) [ceftazidime *versus* tobramycin & ticarcillin]												
1 (De Boeck 1989)	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	serious[10]	none	1/10 (10%)	1/11 (9.1%)	RR 1.1 (0.08 to 15.36)	9 more per 1000 (from 84 fewer to 1000 more)	LOW	IMPORTANT
Mortality (follow-up 12 weeks) [Colistin *versus* colistin + "other"]												
1 (Conway 1997)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[10]	none	0/36 (0%)	1/35 (2.9%)	RR 0.32 (0.01 to 7.7)	19 fewer per 1000 (from 28 fewer to 191 more)	VERY LOW	IMPORTANT
Adverse effects: liver transaminase enzyme elevation (follow-up 10-14 days) [ceftazidime *versus* tobramycin + ticarcillin]												
2 (Gold 1987 and Wesley 1988)	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[7]	none	4/29a (13.8%)	2/23[a,b] (8.7%)	RR 1.53 (0.33 to 7.11)	46 more per 1000 (from 58 fewer to 531 more)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single IV antibiotic	Combination IV antibiotic	Relative (95% CI)	Absolute	Quality	Importance
Adverse effects: neurological adverse effects (follow-up 12 days) [Colistin *versus* combination anti-pseudo]												
1 (Conway 1997)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	33/35 (94.3%)	36/36 (100 %)	RR 0.94 (0.86 to 1.04)	60 fewer per 1000 (from 140 fewer to 40 more)	LOW	IMPORTANT
Adverse effects: rash (follow-up 10 days) [piperacillin *versus* piperacillin + tobramycin]												
1 (McCarty 1988)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	0/8 (0%)	1/9 (11.1 %)	RR 0.37 (0.02 to 7.99)	70 fewer per 1000 (from 109 fewer to 777 more)	VERY LOW	IMPORTANT
Adverse effects: fever (follow-up 10 days) [piperacillin *versus* piperacillin + tobramycin]												
1 (McCarty 1988)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	1/8 (12.5%)	1/9 (11.1 %)	RR 1.12 (0.08 to 15.19)	13 more per 1000 (from 102 fewer to	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single IV antibiotic	Combination IV antibiotic	Relative (95% CI)	Absolute	Quality	Importance
										1000 more)		
Adverse effects: proteinuria (follow-up 10 - 14 days) [ceftazidime *versus* tobramycin+ticarcillin]												
1 (Gold 1985)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[7]	none	1/17[a] (5.9%)	1/17[a] (5.9%)	RR 1 (0.07 to 14.72)	0 fewer per 1000 (from 55 fewer to 807 more)	VERY LOW	IMPORTANT
Adverse effects: renal toxicity - Change in blood urea (mmol/l) (follow-up 12 days; Better indicated by lower values) [colistin *versus* combination anti-pseudo]												
1 (Conway 1997)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[12]	none	36	35	-	MD 0.26 lower (0.93 lower to 0.41 higher)	VERY LOW	IMPORTANT
Adverse effects: renal toxicity - Change in serum creatinine (mmol/l) (follow-up 12 days; Better indicated by lower values) [colistin *versus* combination anti-pseudo]												
1 (Conway 1997)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[7]	none	36	35	-	MD 8.85 higher (0.66 lower to	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single IV antibiotic	Combination IV antibiotic	Relative (95% CI)	Absolute		
										18.36 higher)		

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IV: intravenous; MD: mean difference; mmol/ l: millimoles per litre; RR: risk ratio
a Gold 1985: total of 34 treatment observations in N=30
b Wesley 1988: total of 23 observations in N=13
1 The quality of the evidence was downgraded by 2 due to no blinding and 3 participants were included twice in analysis
2 Minimal important difference for this outcome (MID) = any difference is clinically significant
3 The quality of the evidence was downgraded by 1 due to no blinding.
4 The quality of the evidence was downgraded by 1 as 95% CI crossed 1 clinical MID
5 The quality of the evidence was downgraded by 2 due to single blinding and 18 participants were enrolled twice.
6 The quality of the evidence was downgraded by 2 due as 95%CI crossed 2 clinical MIDs.
7 The quality of the evidence was downgraded by 2 as 95% CI crossed 2 default MIDs
8 The quality of the evidence was downgraded by 1 as 13 participants received 23 courses of treatment.
9 The quality of the evidence was downgraded by 1 due to multiple enrolment of participants (40 participants contribute to 46 treatment episodes).
10 The quality of the evidence was downgraded by 1, as the 95% CI crossed the null effect (mortality could either decrease or increase)
11 The quality of the evidence was downgraded by 1 due lack of blinding in 1 trial, and because some participants were enrolled twice
12 The quality of the evidence was downgraded by 1 as 95% CI crossed 1 default MID

Table 33: Clinical evidence profile: Comparison 4. Combination IV antibiotics *versus* combination IV antibiotics for pulmonary exacerbations with *P aeruginosa*

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination IV AB	combination IV AB	Relative (95% CI)	Absolute		
Eradication of pathogen (follow-up 2 weeks) [aztreonam + amikacin *versus* ceftazidime + amikacin]												
1(Schaad 1989)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	17/28[a] (60.7%)	16/28[a] (57.1 %)	RR 1.06 (0.69	34 more per 1000 (from	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination IV AB**	**combination IV AB**	**Relative (95% CI)**	**Absolute**		
									to 1.65)	177 fewer to 371 more)		
FEV_1 % predicted (absolute change) (follow-up 2 weeks; Better indicated by lower values) [aztreonam + *versus* ceftazidime + amikacin]												
1 Schaad (1989)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	24[a]	25[a]	-	MD 4 higher (0.25 lower to 8.25 higher)	LOW	CRITICAL
FEV_1 % predicted (absolute change) (follow-up 2 - 4 weeks[b]; Better indicated by higher values) [meropenem + tobramycin *versus* ceftazidime + tobramycin]												
1 (Blumer 2005)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	47	50	-	MD 2.7 higher (0.76 lower to 6.16 higher)	LOW	CRITICAL
FEV_1 % predicted (relative % change) (follow-up 2-4 weeks[b]; Better indicated by higher values) [meropenem + tobramycin *versus* ceftazidime + tobramycin]												
1 (Blumer 2005)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	47	50	-	MD 9.4 higher (8.44 lower to 27.24 higher)	VERY LOW	CRITICAL
Adverse effects - Rash (follow-up 2 weeks) [aztreonam + amikacin *versus* ceftazidime + amikacin]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination IV AB**	**combination IV AB**	**Relative (95% CI)**	**Absolute**		
1 (Schaad 1989)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[6]	none	0/28a (0%)	2/28a (7.1%)	RR 0.2 (0.01 to 3.99)	57 fewer per 1000 (from 71 fewer to 214 more)	VERY LOW	IMPORTANT
Adverse effects - Liver transaminases - AST & ALT (follow-up 2 weeks) [aztreonam + amikacin *versus* ceftazidime + amikacin]												
1 (Schaad 1989)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[6]	none	4/28 (14.3%)	2/28 (7.1%)	RR 2 (0.4 to 10.05)	71 more per 1000 (from 43 fewer to 646 more)	VERY LOW	IMPORTANT
Adverse effects - Thrombocytopenia (follow-up 2 weeks) [aztreonam + amikacin *versus* ceftazidime + amikacin]												
1 (Schaad 1989)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[6]	none	3/28 (10.7%)	0/28 (0%)	RR 7 (0.38 to 129.55)	-	VERY LOW	IMPORTANT

Abbreviations: AST: aminotransferase, ALT: alanine aminotransferase; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IV: intravenous; MD: mean difference; RR: risk ratio
a total of 56 treatment courses were randomised, N=42 participants
b 2 to 4 weeks after discontinuation of 2 week course.
1 The quality of the evidence was downgraded by 1 due to attrition bias (clinical outcomes available for only around 50% of participants).
2 The quality of the evidence was downgraded by 2, as the 95% CI crossed the null effect and the CI was very wide
3 The quality of the evidence was downgraded by 1 as 95% CI crossed 1 clinical MID.
4 The quality of the evidence was downgraded by 1 due to attrition bias (some data missing).
5 The quality of the evidence was downgraded by 2 as 95% CI crossed 2 clinical MIDs.
6 The quality of the evidence was downgraded by 2 as 95% CI crossed 2 default MIDs.

Table 34: Clinical evidence profile: Comparison 5. Combination of 2 IV antibiotics + inhaled antibiotic *versus* 2 IV antibiotics without inhaled antibiotic for pulmonary exacerbations with *P aeruginosa*

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**2 IV antibiotic + inhaled antibiotic**	**2 IV without inhaled antibiotic**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Eradication of *P aeruginosa* - (follow-up 15 days) [IV ceftazidime + IV amikacin + inhaled amikacin versusversus IV ceftazidime + IV amikacin]												
1(Schaad 1987)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/40 (75%)	18/44 (40.9 %)	RR 1.83 (1.23 to 2.73)	340 more per 1000 (from 94 more to 708 more)	MODERATE	CRITICAL
Adverse effects: raised liver transaminases (follow-up: 4 to 6 weeks) [IV ceftazidime + IV amikacin + inhaled amikacin versusversus IV ceftazidime + IV amikacin]												
1 (Schaad 1987)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/30 (16.7%)	6/24 (25%)	RR 0.67 (0.23 to 1.92)	82 fewer per 1000 (from 192 fewer to 230 more) 82 fewer per 1000 (from 192 fewer to 230 more)	VERY LOW	IMPORTANT

Abbreviations: CI: confidence interval; IV: intravenous; RR: risk ratio
1 The quality of the evidence was downgraded by 1 as 18 participants were recruited twice and 6 participants enrolled 3 times.

2 The quality of the evidence was downgraded by 2 due to serious imprecision as 95% CI crossed 2 default MIDs.

Table 35: Clinical evidence profile: Comparison 6. Combination of IV ceftazidime + IV tobramycin *versus* oral ciprofloxacin for pulmonary exacerbations with *P aeruginosa*

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV ceftazidime + IV tobramycin	oral ciprofloxacin	Relative (95% CI)	Absolute	Quality	Importance
Eradication of *P aeruginosa* (follow-up 2 weeks)												
1 (Richard 1997)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/40 (75%)	12/49 (24.5 %)	RR 2.55 (1.49 to 4.39)	380 more per 1000 (from 120 more to 830 more)	MODERATE	CRITICAL
Adverse effects - Treatment-related events (follow-up 2 weeks)												
1(Richard 1997)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/53 (18.9%)	9/55 (16.4 %)	RR 1.15 (0.51 to 2.61)	25 more per 1000 (from 80 fewer to 263 more)	VERY LOW	IMPORTANT

Abbreviations: CI: confidence interval; IV: intravenous; RR: risk ratio
1 The quality of the evidence was downgraded by 1 due to no blinding.
2 The quality of the evidence was downgraded by 2 as 95% CI crossed 2 default MIDs.

J.10.1.2 Antimicrobial treatment for acute infection with *P aeruginosa*

Table 36: Clinical evidence profile: Comparison 7. Oral ciprofloxacin + inhaled colistin *versus* inhaled tobramycin for acute infection with *P aeruginosa*

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral ciprofloxacin + inhaled colistin**	**inhaled tobramycin**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Adverse events: severe cough (follow-up 3 months)												
1 (Proesmans 2013)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/29 (0%)	1/29 (3.4%)	RR 0.33 (0.01 to 7.86)	23 fewer per 1000 (from 34 fewer to 237 more)	VERY LOW	IMPORTANT

Abbreviations: CI: confidence interval; RR: risk ratio
1 The quality of the evidence was downgraded by 1 due to no blinding. Blinding was not possible due to route of administration (oral versus inhaled).
2 The quality of the evidence was downgraded by 2 due to very serious imprecision as 95% CI crossed 2 default MIDs.

Table 37: Clinical evidence profile: Comparison 8. Inhaled colistin + oral ciprofloxacin *versus* inhaled tobramycin + oral ciprofloxacin for acute infection with *P aeruginosa*

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inhaled colistin + oral ciprofloxacin	inhaled tobramycin + oral ciprofloxacin	Relative (95% CI)	Absolute		
Relative change in % predicted FEV_1 from baseline (follow-up 54 days; Better indicated by higher values)												
1 (Taccetti 2012)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	60	68	-	MD 2.4 lower (5.885 lower to 1.0855 higher)	VERY LOW	CRITICAL
Treatment failure: trial discontinuation due to lack of compliance (follow-up 28 days)												
1(Taccetti 2012)	randomised trials	serious [1]	no serious inconsistency	serious[3]	very serious[4]	none	11/105 (10.5%)	13/118 (11%)	RR 0.95 (0.45 to 2.03)	6 fewer per 1000 (from 61 fewer to 113 more)	VERY LOW	IMPORTANT
Adverse events: vomiting (follow-up 28 days)												
1(Taccetti 2012)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[5]	none	1/105 (0.95%)	2/118 (1.7%)	RR 0.56 (0.05 to 6.11)	7 fewer per 1000 (from 16 fewer to 87 more)	VERY LOW	IMPORTANT

Adverse events: photosensitivity (follow-up 28 days)												
1(Taccetti 2012)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[5]	none	1/105 (0.95%)	0/118 (0%)	RR 3.37 (0.14 to 81.79)	-	VERY LOW	IMPORTANT
Adverse events: wheeze (follow-up 28 days)												
1(Taccetti 2012)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[5]	none	0/105 (0%)	1/118 (0.85 %)	RR 0.37 (0.02 to 9.09)	5 fewer per 1000 (from 8 fewer to 69 more)	VERY LOW	
Adverse events leading to trial discontinuation - pulmonary exacerbation during early eradication treatment (follow-up 28 days)												
1(Taccetti 2012)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[4]	none	4/105 (3.8%)	5/118 (4.2%)	RR 0.9 (0.25 to 3.26)	4 fewer per 1000 (from 32 fewer to 96 more)	VERY LOW	IMPORTANT

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IV: intravenous; RR: risk ratio
1 The quality of the evidence was downgraded by 1 due to serious imprecision as there was no blinding (open-label).
2 The quality of the evidence was downgraded by 2 due to serious imprecision as 95% CI crossed 2 clinical MIDs.
3 The quality of the evidence was downgraded due to indirect outcome for discontinuation due to adverse events. It is unclear if discontinuation is due to adverse events or other factors.
4 The quality of the evidence was downgraded by 2, as the 95% CI crossed the null effect and the CI was very wide
5 The quality of the evidence was downgraded by 2 due to serious imprecision as 95% CI crossed 2 default MIDs.

J.10.2 *Staphylococcus aureus*

Not applicable, as studies were identified for inclusion.

J.10.3 *Burkholderia cepacia* complex

Not applicable, as studies were identified for inclusion.

J.10.4 Non-tuberculous *mycobacteria*

Not applicable, as studies were identified for inclusion.

J.10.5 Non-identified pathogen

Not applicable, as studies were identified for inclusion.

J.11 Pulmonary infection – chronic

J.11.1 *P Aeruginosa*

Table 38: Clinical evidence profile: Comparison 1. Aztreonam lysine versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aztreonam lysine	Placebo	Relative (95% CI)	Absolute		
Lung function: relative change in FEV_1% predicted (follow-up: 28 days; range of scores: 0-100; Better indicated by higher values)												
1 (Wainwright 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	76	81	-	MD 2.79 higher (0.48 TO 5.10 higher)	MODERATE	CRITICAL
Number of patients with 1 or more exacerbations												
NMA outcome												
Suppression of the organism: adjusted mean change sputum density (follow-up 28 days; measured with: log10 CFU/G; Better indicated by higher values)												
2 (Retsch-Bogart 2009, Wainwright 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	156	165	-	MD 1.40 lower (1.94 lower to 0.85 higher)	HIGH	IMPORTANT
Nutritional status (follow-up 28 days; measured with: % weight change (kg) ; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aztreonam lysine	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1 1 (Retsch-Bogart 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	80	84	-	MD 1 higher (0.33 to 1.67 higher)	HIGH	IMPORTANT
Quality of life: CFQ-R body image (follow-up 28 days; range of scores: 0-100; Better indicated by higher values)												
2 (Retsch-Bogart 2009, Wainwright 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	156	164	-	MD 2.44 higher (0.35 lower to 5.23 higher)	MODERATE	IMPORTANT
Quality of life: CFQ-R digestion (follow-up 28 days; range of scores: 0-100; Better indicated by higher values)												
2 (Retsch-Bogart 2009, Wainwright 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	156	165	-	MD 0.45 lower (3.53 lower to 2.63 higher)	HIGH	IMPORTANT
Quality of life: CFQ-R eating (follow-up 28 days; range of scores: 0-100; Better indicated by higher values)												
2 (Retsch-Bogart 2009, Wainwright 2011)	randomised trials	no serious risk of bias	very serious[2]	no serious indirectness	serious[1]	none	156	165	-	MD 4.99 higher (1.47 lower to 711.46higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-R emotional functioning (follow-up 28 days; range of scores: 0-100; Better indicated by higher values)												
2 (Retsch-Bogart 2009, Wainwright 2011)	randomised trials	no serious risk of bias	very serious[2]	no serious indirectness	serious[1]	none	156	164	-	MD 2.36 higher (3.13 lower to 7.84 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-R health perceptions (follow-up 28 days; range of scores: 0-100; Better indicated by higher values)												
2 (Retsch-Bogart 2009, Wainwright 2011)	randomised trials	no serious risk of bias	very serious[2]	no serious indirectness	serious[1]	none	134	138	-	MD 6.82higher (0.75 to 12.89 higher)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aztreonam lysine	Placebo	Relative (95% CI)	Absolute		
Quality of life: CFQ-R physical functioning (follow-up 28 days; range of scores: 0-100; Better indicated by higher values)												
2 (Retsch-Bogart 2009, Wainwright 2011)	randomised trials	no serious risk of bias	very serious[2]	no serious indirectness	serious[1]	none	156	164	-	MD 5.60 higher (0.96 lower to 12.15 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-R respiratory symptoms (follow-up 28 days; range of scores: 0-100; Better indicated by higher values)												
2 (Retsch-Bogart 2009, Wainwright 2011)	randomised trials	no serious risk of bias	very serious[2]	no serious indirectness	serious[1]	none	156	165	-	MD 4.81 higher (4.60 lower to 14.21 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-R role/school (follow-up 28 days; range of scores: 0-100; Better indicated by higher values)												
2 (Retsch-Bogart 2009, Wainwright 2011)	randomised trials	no serious risk of bias	very serious[2]	no serious indirectness	serious[1]	none	133	139	-	MD 2.97 higher (3.20lower to 9.13 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-R social functioning (follow-up 28 days; range of scores: 0-100; Better indicated by higher values)												
2 (Retsch-Bogart 2009, Wainwright 2011)	randomised trials	no serious risk of bias	No serious inconsistency	no serious indirectness	serious[1]	none	155	164	-	MD 3.54 higher (0.78 to 6.31 higher)	MODERATE	IMPORTANT
Quality of life: CFQ-R treatment burden (follow-up 28 days; range of scores: 0-100; Better indicated by higher values)												
2 (Retsch-Bogart 2009, Wainwright 2011)	randomised trials	no serious risk of bias	very serious[2]	no serious indirectness	very serious[3]	none	156	165	-	MD 0.36 lower (7.42 lower to 6.69 higher)	VERY LOW	IMPORTANT
Quality of life: CFQ-R vitality (follow-up 28 days; range of scores: 0-100; Better indicated by higher values)												
2 (Retsch-Bogart 2009,	randomised trials	no serious	serious[2]	no serious	serious[1]	none	134	138	-	MD 5.46 higher (0.16 to 10.76 higher)	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aztreonam lysine	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Wainwright 2011)		risk of bias		indirectness								
Quality of life: CFQ-R weight (follow-up 28 days; range of scores: 0-100; Better indicated by higher values)												
2 (Retsch-Bogart 2009, Wainwright 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	133	139	-	MD 2.58 higher (2.83 lower to 7.98 higher)	MODERATE	IMPORTANT
Minor adverse events: chest discomfort (follow-up 28 days)												
1 (Retsch-Bogart 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	5/80 (6.3%)	4/84 (4.8 %)	RR 1.31 (0.37 to 4.71)	15 more per 1000 (from 30 fewer to 177 more)	LOW	IMPORTANT
Minor adverse events: cough (follow-up 28 days)												
3 (McCoy 2009, Retsch-Bogart 2009, Wainwright 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	106/291 (36.4 %)	82/241 (34 %)	RR 1.09 (0.87 to 1.38)	31 more per 1000 (from 44 fewer to 129 more)	LOW	IMPORTANT
								34.2 %		31 more per 1000 (from 44 fewer to 130 more)		
Minor adverse events: headache (follow-up 28 days)												
2 (Retsch-Bogart 2009, Wainwright 2011)	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	very serious[4]	none	19/156 (12.2 %)	20/165 (12.1%)	RR 0.94 (0.34 to 2.61)	7 fewer per 1000 (from 80 fewer to 195 more)	VERY LOW	IMPORTANT
								12.1 %		7 fewer per 1000 (from 80		

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aztreonam lysine	Placebo	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 195 more)		
Major adverse events: dyspnoea (follow-up 28 days)												
1 (Retsch-Bogart 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	5/80 (6.3%)	8/84 (9.5%)	RR 0.66 (0.22 to 1.92)	32 fewer per 1000 (from 74 fewer to 88 more)	LOW	IMPORTANT
Major adverse events: haemoptysis (follow-up 28 days)												
2 (McCoy 2009, Retsch-Bogart 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	18/215 (8.4%)	15/160 (9.4%)	RR 0.86 (0.44 to 1.7)	13 fewer per 1000 (from 53 fewer to 66 more)	LOW	IMPORTANT
								9.4 %		13 fewer per 1000 (from 53 fewer to 66 more)		
Mortality (follow-up 28 days)												
1 (McCoy 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Not calculable	none	0/135 (0%)	0/76 (0%)	-	-	HIGH	IMPORTANT
Emergence of resistant organisms: persistent isolation of *S aureus* (follow-up 42 days)												
1 (Retsch-Bogart 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	2/74 (2.7%)	5/81 (6.2%)	RR 0.44 (0.09 to 2.19)	35 fewer per 1000 (from 56 fewer to 73 more)	MODERATE	IMPORTANT
Emergence of resistant organisms : persistent isolation of *B cepacia* (follow-up 42 days)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aztreonam lysine	Placebo	Relative (95% CI)	Absolute		
1 (Retsch-Bogart 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Not calculable	none	0/74 (0%)	0/81 (0%)	-		HIGH	IMPORTANT
Emergence of resistant organisms: persistent isolation of *S maltophilia* (follow-up 42 days)												
1 (Retsch-Bogart 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	2/74 (2.7%)	0/81 (0%)	RR 5.47 (0.27 to 112.04)	-	LOW	IMPORTANT
Emergence of resistant organisms: persistent isolation of *A xilosidans* (follow-up 42 days)												
1 (Retsch-Bogart 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	1/74 (1.4%)	2/81 (2.5%)	RR 0.55 (0.05 to 5.91)	11 fewer per 1000 (from 23 fewer to 121 more)	LOW	IMPORTANT

Abbreviations: CFQ-R: cystic fibrosis questionnaire revised; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference; RR: risk ratio
1 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID
2 The quality of the evidence was downgraded by 1 or by 2 due to the moderate of high heterogeneity in the different CFQ-R domains (eating I2=79%; emotional functioning I2=80%; health perceptions I2=62%; respiratory symptoms I2=85%; role/ school I2=73%; treatment burden I2=79%; vitality I2=40%)
3 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 clinical MIDs
4 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs
5 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID
6 The quality of the evidence was downgraded by 2 due to high heterogeneity (I2=62%)

Table 39: Clinical evidence profile: Comparison 2. Ciprofloxacin versus placebo

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ciprofloxacin**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Lung function: FEV_1												
Not reported												CRITICAL
Number of people with 1 or more exacerbations												
NMA outcome												CRITICAL
Nutritional status: weight (follow-up 6 to 12 months; measured with: kg; Better indicated by higher values)												
1 (Sheldon 1993)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	15	16	-	MD 4.4 higher (3.7 lower to 12.5 higher)	VERY LOW	IMPORTANT
Minor adverse events: gastrointestinal (follow-up 12 months)												
1 (Sheldon 1993)	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/20 (10%)	0/20 (0%)	RR 5 (0.26 to 98)	-	VERY LOW	IMPORTANT
Mortality (follow-up 12 months)												
1 (Sheldon 1993)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	1/20 (5%)	1/20 (5%)	RR 1 (0.07 to 14.9)	0 fewer per 1000 (from 47 fewer to 695 more)	LOW	IMPORTANT
Emergence of resistant organisms - isolation of resistant strains of *P aeruginosa* (follow-up 12 months)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ciprofloxacin	Placebo	Relative (95% CI)	Absolute		
1 (Sheldon 1993)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/15 (66.7%)	5/16 (31.3 %)	RR 2.13 (0.95 to 4.8)	353 more per 1000 (from 16 fewer to 1000 more)	VERY LOW	IMPORTANT
Emergence of resistant organisms - isolation of resistant strains of *S aureus* (follow-up 12 months)												
1 (Sheldon 1993)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[4]	none	4/15 (26.7%)	6/16 (37.5 %)	RR 0.71 (0.25 to 2.03)	109 fewer per 1000 (from 281 fewer to 386 more)	VERY LOW	IMPORTANT

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference; RR: risk ratio
1 The quality of the evidence was downgraded by 2 due to unclear blinding and reporting and high loss to follow-up
2 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID
3 The quality of the evidence was downgraded by 1 due to unclear blinding and reporting
4 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs
5 The quality of the evidence was downgraded by 2 as the 95% CI crossed the line of null effect, and the CI is very wide (trial underpowered to detect a difference)

Table 40: Clinical evidence profile: Comparison 3.1. Colistin versus placebo

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Colistin**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Lung function: change in FEV_1 % predicted (Follow-up: 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Jensen 1987)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious imprecision [2]	none	18	11		MD 6.00 (1.07 lower to 13.07 higher)	LOW	CRITICAL
Number of patients with 1 or more exacerbations												
NMA outcome												
Suppression of the organism: eradication of *P aeruginosa* from the sputum, at 3 months												
1 (Jensen 1987)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	Not calculable [3]	none	0/20 (0%)	0/20 (0%)	-	-	MODERATE	IMPORTANT
Emergence of resistant organisms - superinfection with other colistin-resistant organisms, during the 3 months trial												
1 (Jensen 1987)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	Not calculable [3]	none	0/20 (0%)	0/20 (0%)	-	-	MODERATE	IMPORTANT
Emergence of resistant organisms - resistance to colistin, during the 3 months trial												
1 (Jensen 1987)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	Not calculable [3]	none	0/20 (0%)	0/20 (0%)	-	-	MODERATE	IMPORTANT
Emergence of resistant organisms - resistance to other commonly used anti-pseudomonas txt, during the 3 months trial												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colistin	Placebo	Relative (95% CI)	Absolute		
1 (Jensen 1987)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	Not calculable [3]	none	0/20 (0%)	0/20 (0%)	-	-	MODERATE	IMPORTANT

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference
1 The quality of the evidence was downgrade by 1 due to unclear randomization, allocation and blinding methods. Poor reporting.
2 The quality of the evidence was downgraded by 1 due to serious imprecision, as the 95% CI crossed 1 clinical MID
3 Not calculable, as data reported narratively only.

Table 41: Clinical evidence profile: Comparison 3.2. Colistin inhalation powder versus colistin inhalation solution

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colistin inhalation powder (COLI DPI)	Colistin inhalation solution (COLI neb)	Relative (95% CI)	Absolute		
Lung function: % mean change in FEV_1% predicted (follow-up: 4 weeks; range of scores: 0-100; Better indicated by lower values)												
1 COLO/DPI/02/05	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16	15	-	MD 3.01 lower (18.71 lower to 12.69 higher)	VERY LOW	CRITICAL
Number of patients with 1 or more exacerbations												
NMA outcome												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colistin inhalation powder (COLI DPI)	Colistin inhalation solution (COLI neb)	Relative (95% CI)	Absolute	Quality	Importance
Minor adverse events: vomiting (follow-up 8 weeks)												
1 COLO/DPI/02/05	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/16 (12.5%)	0/15 (0%)	RR 4.71 (0.24 to 90.69)	-	VERY LOW	IMPORTANT
Minor adverse events: productive cough (follow-up 8 weeks)												
1 COLO/DPI/02/05	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/16 (12.5%)	1/15 (6.7%)	RR 1.88 (0.19 to 18.6)	59 more per 1000 (from 54 fewer to 1000 more)	VERY LOW	IMPORTANT
Minor adverse events: chest discomfort (follow-up 8 weeks)												
1 COLO/DPI/02/05	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/16 (25%)	2/15 (13.3%)	RR 1.88 (0.4 to 8.78)	117 more per 1000 (from 80 fewer to 1000 more)	VERY LOW	IMPORTANT
Serious adverse events - AE: dyspnoea (follow-up 8 weeks)												
1 COLO/DPI/02/05	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/16 (18.8%)	4/15 (26.7%)	RR 0.7 (0.19 to 2.63)	80 fewer per 1000 (from 216 fewer to 435 more)	VERY LOW	IMPORTANT

Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference; RR: risk ratio
1 The quality of the evidence was downgraded by 1 as this is an open trial, and the randomization is unclear

3 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 clinical MIDs
3 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs

Table 42: Clinical evidence profile: Comparison 3.3. Colistin versus tobramycin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Colistin**	**Tobramycin**	**Relative (95% CI)**	**Absolute**		
Lung function: mean % change in FEV_1 % predicted (follow-up: 1 to 3 months; range of scores: 0-100; Better indicated by higher values) [COLI nebulised versus TOBI nebulised]												
1 (Hodson 2002)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	59	50	-	MD 6.33 lower (12.7 lower to 0.04 higher)	VERY LOW	CRITICAL
Lung function: mean % change in FEV_1 % predicted (follow-up: 4 weeks; range of scores: 0-100; Better indicated by higher values) [COLI DPI versus TOBI nebulised]												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	183	191	-	MD 1.67 lower (5.43 lower to 2.09 higher)	LOW	CRITICAL
Lung function: mean % change in FEV_1 % predicted (follow-up: 12 weeks; range of scores: 0-100; Better indicated by higher values) [COLI DPI versus TOBI nebulised]												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	183	191	-	MD 2.63 lower (6.67 lower to 1.41 higher)	LOW	CRITICAL
Lung function: mean % change in FEV_1 % predicted (follow-up: 24 weeks; range of scores: 0-100; Better indicated by higher values) [COLI versus TOBI]												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Colistin**	**Tobramycin**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
2 (COLO/DPI/02/06, Schuster 2013)	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	No serious imprecision	none	306	352	-	MD 0.99 lower (0.95 to 1.03 higher)	LOW	CRITICAL
Number of patients with 1 or more exacerbations												
NMA outcome												
Time to next pulmonary exacerbation: time to first additional anti-pseudomal treatment (Better indicated by higher values) [COLI DPI versus TOBI nebulised)												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[5]	none	183	191	-	MD 3.49 higher (5.14 lower to 12.12 higher)	VERY LOW	CRITICAL
Suppression of the organism: change in sputum PA density Log10 CFU/ml (follow-up 4 weeks; Better indicated by higher values) [COLI nebulised versus TOBI nebulised]												
1 (Hodson 2002)	randomised trials	very serious1	no serious inconsistency	no serious indirectness	no serious imprecision	none	37	42	-	MD 0.32 higher (0.32 lower to 0.96 higher)	LOW	IMPORTANT
Nutritional status: BMI change (follow-up 24 weeks; measured with: kg; Better indicated by higher values)												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[6]	none	183	191	-	MD 0.09 lower (0.26 lower to 0.88 higher)	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colistin	Tobramycin	Relative (95% CI)	Absolute	Quality	Importance
Quality of life: change in CFQ-R physical (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values) [COLI DPI versus TOBI nebulised)												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	Not calculable [7]	none	183	191	P=0.353	MD 1.82 higher (0 to 0 higher)	MODERATE	IMPORTANT
Quality of life: change in CFQ-R vitality (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values) [COLI DPI versus TOBI nebulised)												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	Not calculable [7]	none	183	191	P=0.293	MD 2.27 higher (0 to 0 higher)	MODERATE	IMPORTANT
Quality of life: change in CFQ-R emotion (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values) [COLI DPI versus TOBI nebulised)												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	Not calculable [7]	none	183	191	P=0.244	MD 1.75 higher (0 to 0 higher)	MODERATE	IMPORTANT
Quality of life: change in CFQ-R eating (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values) [COLI DPI versus TOBI nebulised)												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	Not calculable [7]	none	181	191	P=0.925	MD 0.19 lower (0 to 0 higher)	MODERATE	IMPORTANT
Quality of life: change in CFQ-R treatment burden (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values) [COLI DPI versus TOBI nebulised)												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	Not calculable [7]	none	183	191	P=0.091	MD 2.87 higher (0 to 0 higher)	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colistin	Tobramycin	Relative (95% CI)	Absolute		
Quality of life: change in CFQ-R health perception (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values) [COLI DPI versus TOBI nebulised)												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	Not calculable [7]	none	183	191	P=0.159	MD 2.96 higher (0 to 0 higher)	MODERATE	IMPORTANT
Quality of life: change in CFQ-R social (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values) [COLI DPI versus TOBI nebulised)												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	Not calculable [7]	none	183	191	P=0.153	MD 0.92 higher (0 to 0 higher)	MODERATE	IMPORTANT
Quality of life: change in CFQ-R body image (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values) [COLI DPI versus TOBI nebulised)												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	Not calculable [7]	none	183	191	P=0.385	MD 1.85 higher (0 to 0 higher)	MODERATE	IMPORTANT
Quality of life: change in CFQ-R role (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values) [COLI DPI versus TOBI nebulised)												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	Not calculable [7]	none	183	191	P=0.607	MD 1.22 lower (0 to 0 higher)	MODERATE	IMPORTANT
Quality of life: change in CFQ-R weight (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values) [COLI DPI versus TOBI nebulised)												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	Not calculable [7]	none	183	191	P=0.461	MD 2.81 higher (0 to 0 higher)	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Colistin**	**Tobramycin**	**Relative (95% CI)**	**Absolute**		
Quality of life: change in CFQ-R respiratory (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values) [COLI DPI versus TOBI nebulised)												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	Not calculable [7]	none	183	191	P=0.756	MD 0.53 lower (0 to 0 higher)	MODERATE	IMPORTANT
Quality of life: change in CFQ-R digestion (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values) [COLI DPI versus TOBI nebulised)												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	Not calculable [7]	none	183	191	P=0.077	MD 3.22 higher (0 to 0 higher)	MODERATE	IMPORTANT
Minor adverse events: sputum (follow-up 4 weeks) [COLI nebulised versus TOBI nebulised]												
1 (Hodson 2002)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	8/62 (12.9%)	6/53 (11.3%)	RR 1.14 (0.42 to 3.08)	16 more per 1000 (from 66 fewer to 235 more)	VERY LOW	IMPORTANT
Minor adverse events: pharyngitis (follow-up 4 weeks) [COLI nebulised versus TOBI nebulised]												
1 (Hodson 2002)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	3/62 (4.8%)	7/53 (13.2%)	RR 0.37 (0.1 to 1.35)	83 fewer per 1000 (from 119 fewer to 46 more)	VERY LOW	IMPORTANT
Minor adverse events: cough (follow-up 4 weeks) [COLI nebulised versus TOBI nebulised]												
1 (Hodson 2002)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	11/62 (17.7%)	5/53 (9.4%)	RR 1.88 (0.7 to 5.07)	83 more per 1000 (from 28 fewer to 384 more)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colistin	Tobramycin	Relative (95% CI)	Absolute		
Minor adverse events: productive cough (follow-up 24 weeks) [COLI DPI versus TOBI nebulised)												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[8]	none	38/187 (20.3%)	44/193 (22.8%)	RR 0.89 (0.61 to 1.31)	25 fewer per 1000 (from 89 fewer to 71 more)	VERY LOW	IMPORTANT
Minor adverse events: chest discomfort (follow-up 24 weeks) [COLI DPI versus TOBI nebulised)												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[8]	none	26/187 (13.9%)	34/193 (17.6%)	RR 0.79 (0.49 to 1.26)	37 fewer per 1000 (from 90 fewer to 46 more)	VERY LOW	IMPORTANT
Minor adverse events: vomiting (follow-up 24 weeks) [COLI DPI versus TOBI nebulised)												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[8]	none	6/187 (3.2%)	8/193 (4.1%)	RR 0.77 (0.27 to 2.19)	10 fewer per 1000 (from 30 fewer to 49 more)	VERY LOW	IMPORTANT
Serious adverse events: patients with >1 serious AE (follow-up 4 weeks) [COLI nebulised versus TOBI nebulised]												
1 (Hodson 2002)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	7/62 (11.3%)	8/53 (15.1%)	RR 0.75 (0.29 to 1.93)	38 fewer per 1000 (from 107 fewer to 140 more)	VERY LOW	IMPORTANT
Serious adverse events: patients withdrawn (follow-up 24 weeks) [COLI DPI versus TOBI nebulised)												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/187 (11.8%)	5/193 (2.6%)	RR 4.54 (1.76 to 11.74)	92 more per 1000 (from 20 more to 278 more)	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colistin	Tobramycin	Relative (95% CI)	Absolute	Quality	Importance
Serious adverse events: haemoptysis (follow-up 24 weeks) [COLI nebulised versus TOBI nebulised]												
1 (Hodson 2002)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	20/187 (10.7%)	13/193 (6.7%)	RR 1.59 (0.81 to 3.1)	40 more per 1000 (from 13 fewer to 141 more)	VERY LOW	IMPORTANT
Serious adverse events: dyspnoea (follow-up 4 weeks) [COLI nebulised versus TOBI nebulised]												
1 (Hodson 2002)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	7/62 (11.3%)	5/53 (9.4%)	RR 1.2 (0.4 to 3.55)	19 more per 1000 (from 57 fewer to 241 more)	VERY LOW	IMPORTANT
Serious adverse events: dyspnoea (follow-up 24 weeks) [COLI DPI versus TOBI nebulised)												
1 (COLO/DPI/02/06)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[8]	none	49/187 (26.2%)	52/193 (26.9%)	RR 0.97 (0.7 to 1.36)	8 fewer per 1000 (from 81 fewer to 97 more)	VERY LOW	IMPORTANT
Emergence of resistant organisms: emergence of highly tobramycin-resistant *P aeruginosa* (follow-up 24 weeks) [COLI nebulised versus TOBI nebulised]												
1 (Hodson 2002)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	Not calculable	none	0/62 (0%)	0/53 (0%)	-	-	LOW	IMPORTANT

Abbreviations: CFQ-R: cystic fibrosis questionnaire revised; CI: confidence interval; COLI: colistin; DPI: dry powder for inhalation; FEV_1: forced expiratory volume in 1 second; MD: mean difference; RR: risk ratio; TOBI: tobramycin

1 The quality of the evidence was downgraded by 2 because this is an open trial, and risk of bias for randomisation and allocation concealment was unclear

2 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID

3 The quality of the evidence was downgraded by 1 because this is an open trial, and risk of bias for randomisation was unclear

4 The quality of the evidence was downgraded by 2 because both studies were open trials, and risk of bias for randomisation and allocation concealment was unclear

5 The quality of the evidence was downgraded by 2, as the 95% CI is very large and crossed the line of no effect

6 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID
7 Not calculable, p-value > 0.05
8 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs

Table 43: Clinical evidence profile: Comparison 4.1. Tobramycin versus placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Lung function: mean % change in FEV_1 % predicted (follow-up: 1 to 3 months; range of scores 1-100; Better indicated by higher values)												
4 (Galeva 2013, Konstan 2011/ EVOLVE trial, Lenoir 2007, Ramsey 1993)	randomised trials	serious[1]	serious[2]	No serious indirectness	no serious imprecision	none	257	259		MD 9.36 higher (5.01 to 13.70 higher)	LOW	CRITICAL
Number of patients with 1 or more exacerbations												
NMA outcome												CRITICAL
Suppression of the organism: eradication of the organism (negative culture) (follow-up 4 weeks)												
3 (Chuchalin 2007, Galeva 2013, Lenoir 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	71/217 (32.7%)	17/140 (12.1%)	RR 2.46 (1.20 to 5.04)	177 more per 1000 (from 24 more to 491 more)	HIGH	IMPORTANT
								14.3%		209 more per 1000 (from 92 more to 465 more)		

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Suppression of the organism: eradication of the organism (negative culture) (follow-up 6 weeks)												
1 (Lenoir 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	3/29 (10.3%)	3/30 (10%)	RR 1.03 (0.23 to 4.71)	3 more per 1000 (from 29 fewer to 578 more)	MODERATE	IMPORTANT
Suppression of the organism: eradication of the organism (negative culture) (follow-up 8 weeks)												
1 (Chuchalin 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	23/159 (14.5%)	10/83 (12%)	RR 1.2 (0.6 to 2.4)	24 more per 1000 (from 48 fewer to 169 more)	MODERATE	IMPORTANT
Suppression of the organism: eradication of the organism (negative culture) (follow-up 20 weeks)												
1 (Chuchalin 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	52/156 (33.3%)	13/79 (16.5%)	RR 2.03 (1.18 to 3.49)	169 more per 1000 (from 30 more to 410 more)	HIGH	IMPORTANT
Suppression of the organism: eradication of the organism (negative culture) (follow-up 24 weeks)												
1 (Chuchalin 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	38/159 (23.9%)	17/84 (20.2%)	RR 1.18 (0.71 to 1.96)	36 more per 1000 (from 59 fewer to 194 more)	MODERATE	IMPORTANT
Suppression of the organism: change in *P aeruginosa* sputum density log10 CFU/G (follow-up 4 weeks; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin	Placebo	Relative (95% CI)	Absolute		
1 (Galeva 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	29	26	-	MD 1.2 lower (2.03 to 0.37 lower)	MODERATE	IMPORTANT
Suppression of the organism: change in non-mucoid *P aeruginosa* sputum density log10 CFU/G (follow-up 4 weeks; Better indicated by higher values)												
1 (Konstan 2011/ EVOLVE trial)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	46	49	-	MD 1.76 lower (2.52 to 1 lower)	LOW	IMPORTANT
Suppression of the organism: change in mucoid *P aeruginosa* sputum density log10 CFU/G (follow-up 4 weeks; Better indicated by higher values)												
1 (Konstan 2011/ EVOLVE trial)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	46	49	-	MD 2.18 (2.97 to 1.39 lower)	LOW	IMPORTANT
Nutritional status: body weight change (follow-up 12 weeks; measured with: kg; Better indicated by higher values)												
1 (Lenoir 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	29	30	-	MD 0.23 higher (0.23 lower to 0.69 higher)	HIGH	IMPORTANT
Nutritional status: body weight change (follow-up 24 weeks; measured with: kg; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1 (Chuchalin 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	161	84	-	MD 0.75 higher (0.22 to 1.28 higher)	MODERATE	IMPORTANT
Minor adverse events: minor adverse events (any) (follow-up 4 weeks)												
2 (Galeva 2013, Konstan 2011/ EVOLVE trial)	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	serious[4]	none	31/75 (41.3%)	48/75 (64%)	RR 0.66 (0.49 to 0.89)	218 fewer per 1000 (from 70 fewer to 326 more)	VERY LOW	IMPORTANT
								42.3%		144 fewer per 1000 (from 47 fewer to 216 more)		
Minor adverse events: minor adverse events (any) (follow-up 24 weeks)												
1 (Chuchalin 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[7]	none	25/161 (15.5%)	13/85 (15.3 %)	RR 1.02 (0.55 to 1.88)	3 more per 1000 (from 69 fewer to 135 more)	LOW	IMPORTANT
Minor adverse events: auditory impairment (follow-up 4 weeks)												
1 (Galeva 2013)	randomised trials	no serious risk	no serious inconsistency	no serious indirectness	very serious[7]	none	3/29 (10.3%)	2/26 (7.7%)	RR 1.34 (0.24 to 7.43)	26 more per 1000 (from 58 fewer to 495 more)	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
		of bias										
Minor adverse events: auditory impairment (follow-up 24 weeks)												
1 (Ramsey 1999)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/152 (0%)	0/148 (0%)	-	-	HIGH	IMPORTANT
Minor adverse events: auditory impairment (follow-up 42 weeks)												
1 (Ramsey 1993)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/36 (0%)	0/35 (0%)	-	-	HIGH	IMPORTANT
Minor adverse events: cough (follow-up 4 weeks)												
2 (Galeva 2013, Konstan 2011/ EVOLVE trial)	randomised trials	very serious[6]	very serious[8]	no serious indirectness	very serious[7]	none	11/75 (14.7%)	13/75 (17.3 %)	RR 1.67 (0.08 to 36.11)	116 more per 1000 (from 159 fewer to 1000 more)	VERY LOW	IMPORTANT
								-		-		
Minor adverse events: tinnitus (follow-up 24 weeks)												
1 (Ramsey 1999)	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[4]	none	8/258 (3.1%)	0/262 (0%)	RR 17.26 (1 to	-	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin	Placebo	Relative (95% CI)	Absolute		
		risk of bias							297.54)			
Minor adverse events: headaches (follow-up 4 weeks)												
1 (Konstan 2011/ EVOLVE trial)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[7]	none	1/46 (2.2%)	1/49 (2%)	RR 0.36 (0.04 to 3.29)	13 fewer per 1000 (from 20 fewer to 47 more)	VERY LOW	IMPORTANT
Major adverse events: any (follow-up 4 weeks)												
2 (Galeva 2013, Konstan 2011/ EVOLVE trial)	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	very serious[7]	none	4/75 (5.3%)	8/75 (10.7%)	RR 0.52 (0.16 to 1.64)	51 fewer per 1000 (from 90 fewer to 68 more)	VERY LOW	IMPORTANT
								3.9%		19 fewer per 1000 (from 33 fewer to 25 more)		
Major adverse events: any (follow-up 24 weeks)												
1 (Chuchalin 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/161 (10.6%)	22/85 (25.9%)	RR 0.41 (0.23 to 0.73)	153 fewer per 1000 (from 70 fewer to 199 fewer)	HIGH	IMPORTANT
Major adverse events: haemoptysis (follow-up 4 weeks)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1 (Konstan 2011/ EVOLVE trial)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[7]	none	1/46 (2.2%)	1/49 (2%)	RR 1.07 (0.07 to 16.54)	1 more per 1000 (from 19 fewer to 317 more)	VERY LOW	IMPORTANT
Major adverse events: haemoptysis (follow-up 24 weeks)												
1 (Ramsey 1999)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	69/258 (26.7%)	81/262 (30.9 %)	RR 0.87 (0.66 to 1.13)	40 fewer per 1000 (from 105 fewer to 40 more)	MODERATE	IMPORTANT
Major adverse events: pneumothorax (follow-up 24 weeks)												
1 (Ramsey 1999)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[7]	none	1/258 (0.39%)	4/262 (1.5%)	RR 0.25 (0.03 to 2.26)	11 fewer per 1000 (from 15 fewer to 19 more)	LOW	IMPORTANT
Mortality (follow-up 4 weeks)												
1 (Konstan 2011/ EVOLVE trial)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	0/46 (0%)	1/49 (2%)	RR 0.35 (0.01 to 8.49)	13 fewer per 1000 (from 20 fewer to 153 more)	LOW	IMPORTANT
Mortality (follow-up 3 to 12 months)												
2 (Chuchalin 2007,	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[3]	none	1/419 (0.24%)	6/348 (1.7%)	RR 0.17 (0.03	14 fewer per 1000 (from 17	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Ramsey 1999)		risk of bias							to 1.09)	fewer to 2 more)		
Emergence of resistant organisms: frequency of Tobramycin-resistant *P aeruginosa* (follow-up 24 weeks)												
2 (Chuchalin 2007, Ramsey 1999)	randomised trials	no serious risk of bias	very serious[10]	no serious indirectness	serious[4]	none	86/376 (22.9%)	31/296 (10.5%)	RR 1.95 (0.86 to 4.42)	99 more per 1000 (from 15 fewer to 385 more)	VERY LOW	IMPORTANT
Emergence of resistant organisms: frequency of new isolates of drug resistant *B cepacia* (follow-up 24 weeks)												
1 (Ramsey 1999)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/258 (0%)	0/262 (0%)	-	-	HIGH	IMPORTANT
Emergence of resistant organisms: frequency of new isolates of drug resistant *S maltophilia* (follow-up 24 weeks)												
1 (Ramsey 1999)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[7]	none	3/258 (1.2%)	1/262 (0.38%)	RR 3.05 (0.32 to 29.1)	8 more per 1000 (from 3 fewer to 107 more)	LOW	IMPORTANT
Emergence of resistant organisms: frequency of new isolates of drug resistant *A xylosidans* (follow-up 24 weeks)												
1 (Ramsey 1999)	randomised trials	no serious risk	no serious inconsistency	no serious indirectness	very serious[7]	none	1/258 (0.39%)	1/262 (0.38%)	RR 1.02 (0.06 to 16.15)	0 more per 1000 (from 4 fewer to 58 more)	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
		of bias										
Emergence of resistant organisms: frequency of new isolates of drug resistant *aspergillus* (follow-up 24 weeks)												
1 (Ramsey 1999)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/196 (2%)	20/193 (10.4%)	RR 0.2 (0.07 to 0.57)	83 fewer per 1000 (from 45 fewer to 96 fewer)	HIGH	CRITICAL

Abbreviations: CFU/G: colony forming units per gram; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; kg: kilogrammes; MD: mean difference; RR: risk ratio
1 The quality of the evidence was downgraded by 1, as 1 of the trials had unclear risk of bias for the domains randomisation, allocation concealment, and blinding and another trial had unclear risk of bias for the domains randomisation, allocation concealment and high risk of bias for blinding
2 The quality of the evidence was downgraded by 1 due to moderate inconsistency (I2=51%). Sub-group analysis was not conducted, as all of the trials showed a beneficial effect of tobramycin
3 The quality of the evidence was downgraded by 1 as the 95% CI crossed the null effect
4 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID
5 The quality of the evidence was downgraded by 2 due to unclear risk of bias for the domains randomisation, allocation concealment and high risk of bias for blinding
6 The quality of the evidence was downgraded by 2, as the largest trial had unclear risk of bias for the domains randomisation, allocation concealment and high risk of bias for blinding
7 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs
8 The quality of the evidence was downgraded by 2 due to very serious inconsistency (I2=77%).
9 The quality of the evidence was downgraded by 2 as the 95% CI is very wide and it crossed the null effect. The study is underpowered to detect differences
10 The quality of the evidence was downgraded by 2 due to very serious inconsistency (I2=79%)

Table 44: Clinical evidence profile: Comparison 4.2. Tobramycin inhalation powder versus Tobramycin inhalation solution

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin inhalation powder (TOBI DPI)	Tobramycin inhalation solution (TOBI neb)	Relative (95% CI)	Absolute	Quality	Importance
Lung function: % mean change in FEV_1% predicted (follow-up: 4 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (Konstan 2011a/EAGER trial)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	308	209	-	MD 0.8 lower (3.90 lower to 2.30 higher)	LOW	IMPORTANT
Lung function: % mean change in FEV_1% predicted (follow-up: 20 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (Konstan 2011a/EAGER trial)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	308	209	-	MD 1.10 higher (2.33 lower to 4.53 higher)	LOW	IMPORTANT
Lung function: % mean change in FEV_1% predicted (follow-up: 24 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (Konstan 2011a/EAGER trial)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	308	209	-	MD 2.20 lower (1.11 to 5.51 lower)	LOW	IMPORTANT
Number of patients with 1 or more exacerbations												
NMA outcome												
Suppression of the organism: mean change in *P aeruginosa* sputum density log10 CFU (follow-up 4 weeks; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin inhalation powder (TOBI DPI)	Tobramycin inhalation solution (TOBI neb)	Relative (95% CI)	Absolute		
1 (Konstan 2011a/EAGER trial)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	308	209	-	MD 0.44 lower (0.79 to 0.09 lower)	MODERATE	IMPORTANT
Suppression of the organism: mean change in *P aeruginosa* sputum density log10 CFU (follow-up 20 weeks; Better indicated by higher values)												
1 (Konstan 2011a/EAGER trial)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	308	209	-	MD 0.84 lower (1.17 to 0.51 lower)	LOW	IMPORTANT
Adverse events: any mild or moderate adverse (follow-up 24 weeks)												
1 (Konstan 2011a/EAGER trial)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	226/308 (73.4%)	143/209 (68.4%)	RR 1.07 (0.96 to 1.2)	48 more per 1000 (from 27 fewer to 137 more)	MODERATE	IMPORTANT
Adverse events: any serious adverse (follow-up 24 weeks)												
1 (Konstan 2011a/E	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	84/308 (27.3%)	61/209 (29.2%)	RR 0.93 (0.71	20 fewer per 1000	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin inhalation powder (TOBI DPI)	Tobramycin inhalation solution (TOBI neb)	Relative (95% CI)	Absolute		
AGER trial)									to 1.24)	(from 85 fewer to 70 more)		
Mild adverse events: productive cough (follow-up 24 weeks)												
1 (Konstan 2011a/EAGER trial)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	56/308 (18.2%)	41/209 (19.6%)	RR 0.93 (0.64 to 1.33)	14 fewer per 1000 (from 71 fewer to 65 more)	VERY LOW	IMPORTANT
Mild adverse events: headache (follow-up 24 weeks)												
1 (Konstan 2011a/EAGER trial)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	35/308 (11.4%)	25/209 (12%)	RR 0.95 (0.59 to 1.54)	6 fewer per 1000 (from 49 fewer to 65 more)	VERY LOW	IMPORTANT
Mild adverse events: vomiting (follow-up 24 weeks)												
1 (Konstan 2011a/E	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	19/308 (6.2%)	12/209 (5.7%)	RR 1.07 (0.53	4 more per 1000 (from	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin inhalation powder (TOBI DPI)	Tobramycin inhalation solution (TOBI neb)	Relative (95% CI)	Absolute	Quality	Importance
AGER trial)									to 2.17)	27 fewer to 67 more)		
Serious adverse events: dyspnoea (follow-up 24 weeks)												
1 (Konstan 2011a/EAGER trial)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	48/308 (15.6%)	26/209 (12.4%)	RR 1.25 (0.8 to 1.95)	31 more per 1000 (from 25 fewer to 118 more)	VERY LOW	IMPORTANT
Serious adverse events: haemoptysis (follow-up 24 weeks)												
1 (Konstan 2011a/EAGER trial)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	40/308 (13%)	26/209 (12.4%)	RR 1.04 (0.66 to 1.66)	5 more per 1000 (from 42 fewer to 82 more)	VERY LOW	IMPORTANT

Abbreviations: CFU: colony forming units; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference; RR: risk ratio
1 The quality of the evidence was downgraded by 1 as this was an open trial, and randomisations was unclear
2 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID
3 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID
4 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs

Table 45: Clinical evidence profile: Comparison 4.3 Tobramycin versus Aztreonam lysine

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin	Aztreonam lysine	Relative (95% CI)	Absolute	Quality	Importance
Lung function: % change in FEV_1 % predicted (follow-up: 3 months; range of scores: 0-100; Better indicated by higher values) [TOBI nebulised *versus* AZLI inhaled]												
1 (Assael 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	132	136	-	MD 2.71 lower (2.88 to 2.54 lower)	MODERATE	CRITICAL
Number of patients with 1 or more exacerbations												
NMA outcome												
Suppression of the organism: adj mean change sputum density log10 PA CFU/G (follow-up 20 weeks; Better indicated by higher values) [TOBI nebulised *versus* AZLI inhaled]												
1 (Assael 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	97	97	-	MD 0.23 higher (0.3 lower to 0.76 higher)	LOW	IMPORTANT
Nutritional status: % adj mean weight change (follow-up 24 weeks; Better indicated by higher values) [TOBI nebulised *versus* AZLI inhaled]												
1 (Assael 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	132	136	-	MD 0.52 lower (1.68 lower to 0.64 higher)	LOW	IMPORTANT
Quality of life: CFQ-R respiratory, adj mean change (follow-up 20 weeks; Better indicated by higher values) [TOBI nebulised *versus* AZLI inhaled]												
1 (Assael 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	131	131	-	MD 4.1 lower (8.59 lower to 0.39 higher)	LOW	IMPORTANT
Minor adverse events: chest discomfort (follow-up 3 months) [TOBI nebulised *versus* AZLI inhaled]												
1 (Assael 2013)	randomised trials	serious[1]	no serious	no serious	very serious[4]	none	13/132 (9.8%)	14/136 (10.3%)	RR 0.96 (0.47	4 fewer per 1000 (from 55	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Tobramycin**	**Aztreonam lysine**	**Relative (95% CI)**	**Absolute**		
			inconsistency	indirectness					to 1.96)	fewer to 99 more)		
Minor adverse events: cough (follow-up 3 months) [TOBI nebulised *versus* AZLI inhaled]												
1 (Assael 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	104/132 (78.8%)	96/136 (70.6%)	RR 1.12 (0.97 to 1.28)	85 more per 1000 (from 21 fewer to 198 more)	LOW	IMPORTANT
Minor adverse events: headache (follow-up 3 months) [TOBI nebulised *versus* AZLI inhaled]												
1 (Assael 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	27/132 (20.5%)	29/136 (21.3%)	RR 0.96 (0.6 to 1.53)	9 fewer per 1000 (from 85 fewer to 113 more)	VERY LOW	IMPORTANT
Minor adverse events: vomiting (follow-up 3 months) [TOBI nebulised *versus* AZLI inhaled]												
1 (Assael 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	14/132 (10.6%)	14/136 (10.3%)	RR 1.03 (0.51 to 2.08)	3 more per 1000 (from 50 fewer to 111 more)	VERY LOW	IMPORTANT
Major adverse events: dyspnoea (follow-up 3 months) [TOBI nebulised *versus* AZLI inhaled]												
1 (Assael 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	21/132 (15.9%)	31/136 (22.8%)	RR 0.7 (0.42 to 1.15)	68 fewer per 1000 (from 132 fewer to 34 more)	LOW	IMPORTANT
Major adverse events: haemoptysis (follow-up 3 months) [TOBI nebulised *versus* AZLI inhaled]												
1 (Assael 2013)	randomised trials	serious[1]	no serious	no serious	serious[2]	none	21/132 (15.9%)	31/136 (22.8%)	RR 0.7 (0.42	68 fewer per 1000 (from 132	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin	Aztreonam lysine	Relative (95% CI)	Absolute		
			inconsistency	indirectness					to 1.15)	fewer to 34 more)		

Abbreviations: AZLI: aztreonam lysine; CFQ-R: cystic fibrosis questionnaire revised; CFU/g: colony forming units per gram; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference; RR: risk ratio; TOBI: tobramycin
1 The quality of the evidence was downgraded by 1 because this is an open trial
2 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID
3 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID
4 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs

Table 46: Clinical evidence profile: Comparison 5. Combination of fosfomycin + tobramycin *versus* placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of fosfomacyn + tobramycin	Placebo	Relative (95% CI)	Absolute		
Lung function: relative change in FEV_1% predicted (follow-up 4 weeks; range of scores: 0-100; Better indicated by higher values) [FTI 80/20 mg]												
1 (Trapnell 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	38	32	-	MD 7.5 higher (3.6 to 11.4 higher)	MODERATE	CRITICAL
Lung function: relative change in FEV_1% predicted (follow-up 4 weeks; range of scores: 0-100; Better indicated by higher values) [FTI 160/40 mg]												
1 (Trapnell 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	41	32	-	MD 6.2 higher (2.42 to 9.98 higher)	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of fosfomycin + tobramycin	Placebo	Relative (95% CI)	Absolute		
Suppression of the organism: sputum *P aeruginosa* density, log 10 CFU/g FTI 80/20 mg (follow-up 4 weeks; Better indicated by lower values) [FTI 80/20 mg]												
1 (Trapnell 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	38	32	-	MD 1.04 lower (1.82 to 0.26 lower)	LOW	IMPORTANT
Suppression of the organism: sputum *P aeruginosa* density, log 10 CFU/g FTI 160/40 mg (follow-up 4 weeks; Better indicated by lower values) [FTI 160/40 mg]												
1 (Trapnell 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	41	32	-	MD 0.28 lower (1.06 lower to 0.5 higher)	LOW	IMPORTANT

Abbreviations: CFU: colony forming units; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FTI: Fosfomycin/ tobramycin inhaled; MD: mean difference; mg: milligrams; RR: risk ratio

1 The quality of the evidence was downgraded by 1 due to unclear risk of bias for allocation concealment and data reporting

2 The quality of the evidence was downgraded by as the 95% CI crossed 1 clinical MID

3 The quality of the evidence was downgraded by as the 95% CI crossed 1 default MID

Table 47: Clinical evidence profile: Comparison 6. Continuous alternating therapy versus intermittent treatment: aztreonam lysine + tobramycin or placebo + tobramycin

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous alternating therapy: aztreonam lysine + tobramycin	Intermittent treatment: placebo + tobramycin	Relative (95% CI)	Absolute	Quality	Importance
Lung function: % change in FEV_1% predicted (follow-up 20 weeks[1]; range of scores: 0-100; Better indicated by higher values)												
1 (Flume 2016)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	42	46	-	MD 1.33 higher (1.05 to 1.61 higher)	MODERATE	CRITICAL
Time to next pulmonary exacerbation												
1 (Flume 2016)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	42	46	HR 0.89 (0.49 to 1.6)	-	LOW	CRITICAL
										-		
Quality of life: change in CFQ-R (follow-up 20 weeks[1]; range of scores: 0-100; Better indicated by higher values)												
1 (Flume 2016)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	42	46	-	MD 3.06 higher (2.35 to 3.77 higher)	LOW	
Minor adverse events: cough (follow-up 3 months)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous alternating therapy: aztreonam lysine + tobramycin	Intermitent treatment: placebo + tobramycin	Relative (95% CI)	Absolute	Quality	Importance
1 (Flume 2016)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	32/42 (76.2%)	20/46 (43.5%)	RR 1.75 (1.21 to 2.54)	326 more per 1000 (from 91 more to 670 more)	LOW	IMPORTANT
Serious adverse events: dyspnoea (follow-up 3 months)												
1 (Flume 2016)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	13/42 (31%)	24/46 (52.2%)	RR 0.59 (0.35 to 1.01)	214 fewer per 1000 (from 339 fewer to 5 more)	LOW	IMPORTANT
Serious adverse events (not treatment related) (follow-up 3 months)												
1 (Flume 2016)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[6]	none	21/42 (50%)	24/46 (52.2%)	RR 0.96 (0.64 to 1.44)	21 fewer per 1000 (from	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous alternating therapy: aztreonam lysine + tobramycin	Intermitent treatment: placebo + tobramycin	Relative (95% CI)	Absolute	**Quality**	**Importance**
										188 fewer to 230 more)		

Abbreviations: CFQ-R: cystic fibrosis questionnaire reviewed; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference; mg: milligrams; RR: risk ratio
1 Values at 4 ,12 and 20 weeks were averaged
2 The quality of the evidence was downgraded by 1 due to unclear allocation concealment, blinding, and data collection/ reporting
3 The quality of the evidence was downgraded by 1 as the 95% CI crossed the null effect line
4 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 clinical MID
5 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID
6 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs

J.11.2 S Aureus

Not applicable, as no relevant studies were identified for this pathogen.

J.11.3 *B Cepacia* Complex

Not applicable, as no relevant studies were identified for this pathogen.

J.11.4 *Aspergillus Fumigatus*

Table 48: Clinical evidence profile: Comparison 7. Itraconazole *versus* placebo

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Itraconazole**	**Placebo, 24-week treatment**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Lung function (follow-up mean 24 weeks; measured with: percentage change in FEV_1 predicted from baseline ; range of scores: 0-100; Better indicated by higher values)												
1 (Aaron 2012)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	18	17	-	MD 4.94 lower (15.33 lower to 5.45 higher)	VERY LOW	CRITICAL
Lung function (follow-up mean 48 weeks; measured with: percentage change in FEV_1 predicted from baseline; range of scores: 0-100; Better indicated by higher values)												
1 (Aaron 2012)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	18	17	-	MD 3.71 lower (-13.26 to 20.28)	VERY LOW	CRITICAL
Time to next pulmonary exacerbation (follow-up mean 24 weeks; Better indicated by lower values)												
1 (Aaron 2012)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4]	none	0/18 (0%)	0/17 (0%)	adjHR 1.34 (0.57 to 3.14)	-	VERY LOW	CRITICAL
proxy: number of patients with an exacerbation requiring antibiotics (follow-up mean 24 weeks; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Itraconazole	Placebo, 24-week treatment	Relative (95% CI)	Absolute		
1 (Aaron 2012)	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[5]	none	12/18 (66.7%)	7/18 (38.9%)	RR 1.71 (0.88 to 3.33)	276 more per 1000 (from 47 fewer to 906 more)	VERY LOW	IMPORTANT
proxy: number of patients with an exacerbation requiring AB (follow-up mean 48 weeks; Better indicated by lower values)												
1 (Aaron 2012)	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[5]	none	15/18 (83.3%)	11/18 (61.1%)	RR 1.36 (0.89 to 2.08)	220 more per 1000 (from 67 fewer to 660 more)	VERY LOW	IMPORTANT
proxy: number of patients with an exacerbation admitted to hospital (follow-up mean 24 weeks; Better indicated by lower values)												
1 (Aaron 2012)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[6]	none	3/18 (16.7%)	3/17 (17.6%)	RR 0.94 (0.22 to 4.05)	11 fewer per 1000 (from 138 fewer to 538 more)	VERY LOW	IMPORTANT
proxy: number of patients with an exacerbation admitted to hospital (follow-up mean 48 weeks; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Itraconazole	Placebo, 24-week treatment	Relative (95% CI)	Absolute		
1 (Aaron 2012)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[6]	none	4/18 (22.2%)	3/17 (17.6%)	RR 1.26 (0.33 to 4.82)	46 more per 1000 (from 118 fewer to 674 more)	VERY LOW	IMPORTANT
Quality of life – CFQ-R all domains (follow-up mean 24 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (Aaron 2012)	randomised trials	serious[1]	no serious inconsistency	serious[2]	not calculable[7]	none	18	17	-	No significant differences	VERY LOW	IMPORTANT
Quality of life - CFQ-R respiratory domain (follow-up mean 24 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (Aaron 2012)	randomised trials	serious[1]	no serious inconsistency	serious[2]	not calculable[7]	none	18 (mean: 3.76)	17 (mean: 4.77)	MD 1.01	p-value= 0.87	VERY LOW	IMPORTANT
Minor adverse events: increased dyspnoea (follow-up mean 24 weeks; Better indicated by lower values)												
1 (Aaron 2012)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[6]	none	2/18 (11.1%)	2/16 (12.5%)	RR 0.89 (0.14 to 5.6)	14 fewer per 1000 (from 108 fewer	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Itraconazole	Placebo, 24-week treatment	Relative (95% CI)	Absolute		
										to 575 more)		
Minor adverse events: rash (follow-up mean 24 weeks; Better indicated by lower values)												
1 (Aaron 2012)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[6]	none	2/18 (11.1%)	1/16 (6.3%)	RR 1.78 (0.18 to 17.8)	49 more per 1000 (from 51 fewer to 1000 more)	VERY LOW	IMPORTANT
Minor adverse events: hyperglycaemia (follow-up mean 24 weeks; Better indicated by lower values)												
1 (Aaron 2012)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[6]	none	1/18 (5.6%)	0/16 (0%)	RR 2.68 (0.12 to 61.58)	-	VERY LOW	IMPORTANT
Minor adverse events: flu-like illness (follow-up mean 24 weeks; Better indicated by lower values)												
1 (Aaron 2012)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[6]	none	3/18 (16.7%)	0/16 (0%)	RR 6.26 (0.35 to 112.7)	-	VERY LOW	IMPORTANT
Minor adverse events: diarrhoea (follow-up mean 24 weeks; Better indicated by lower values)												
1 (Aaron	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[6]	none	0/18 (0%)	1/16 (6.3%)	RR 0.3 (0.01 to 6.84)	44 fewer per 1000	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Itraconazole	Placebo, 24-week treatment	Relative (95% CI)	Absolute		
2012)										(from 62 fewer to 365 more)		
Minor adverse events: conjunctivitis (follow-up mean 24 weeks; Better indicated by lower values)												
1 (Aaron 2012)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[6]	none	0/18 (0%)	1/16 (6.3%)	RR 0.3 (0.01 to 6.84)	44 fewer per 1000 (from 62 fewer to 365 more)	VERY LOW	IMPORTANT
Major adverse events: haemoptysis (follow-up mean 24 weeks; Better indicated by lower values)												
1 (Aaron 2012)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[6]	none	2/18 (11.1%)	1/16 (6.3%)	RR 1.78 (0.18 to 17.8)	49 more per 1000 (from 51 fewer to 1000 more)	VERY LOW	IMPORTANT
Major adverse events: spontaneous pneumothorax (follow-up mean 24 weeks; Better indicated by lower values)												
1 (Aaron	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[6]	none	1/18 (5.6%)	0/17 (0%)	RR 2.84 (0.12 to 65.34)	-	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Itraconazole	Placebo, 24-week treatment	Relative (95% CI)	Absolute	Quality	Importance
2012)												

Abbreviations: CFQ-R: cystic fibrosis questionnaire reviewed; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MD: mean difference; RR: risk ratio
1 The quality of the evidence was downgraded by 1 due to unclear allocation, data reporting and sample size
2 The quality of the evidence was downgraded by 1 due to indirectness, as the therapeutic dosages were not achieved in 2/3 of the participants
3 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 clinical MIDs.
4 The quality of the evidence was downgraded by 2 as the 95% CI crossed the null effect and it is very wide. The study in underpowered to detect differences between groups.
5 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID.
6 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs
7 Not calculable, as no data was provided in the study.

J.12 Immunomodulatory agents

Table 49: Pairwise comparison from NMA. Macrolide antibiotics *versus* placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide antibiotics	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Rate of exacerbations after short-term (1-10 month) treatment												
3 (Equi 2002, Robinson 2012, Wolter 2002)	Randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	very serious[2]	none	114	112	Rate Ratio 0.75 (0.38 to 1.49)	Not calculable	VERY LOW	IMPORTANT

Abbreviations: CI: confidence interval
1 The quality of the evidence was downgraded by 2 due to very serious inconsistency between studies
2 The quality of the evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed 2 default MIDs

Table 50: Clinical evidence profile: Comparison 1. Fluticasone *versus* placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluticasone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Time to first exacerbation (follow-up 6 months)												
1 (Balfour-Lynn 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	41/84 (48.8%)[2]	40/87 (46%)[2]	HR 1.07 (0.68 to 1.6838)	23 more per 1000 (from 118 fewer to 186 more)	LOW	CRITICAL
Growth (change in height) (follow-up 12 months; measured with: SDS (standard deviation) score; Better indicated by higher values)												
1 (De Boeck 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	15	15	-	MD 0.37 lower (0.77 lower to 0.03 higher)	MODERATE	IMPORTANT
Growth (change in height) in paediatric participants (follow-up 8 months; measured with: cm; Better indicated by higher values)												
1 (Balfour-Lynn 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	42	38	-	MD 0.6 higher (0.46 lower to 1.66 higher)	MODERATE	IMPORTANT

Abbreviations: CI: confidence interval; HR: hazard ratio; MD: mean difference; SDS: standard deviation score
1 The quality of the evidence was downgraded by 2 as 95%CI crossed the null effect line, and it is very wide.
2 Calculated by the NGA technical team from percentage of participants in group with at least 1 exacerbation.
3 The quality of the evidence was downgraded by 1 because 95%CI crossed 1 default MID.

Table 51: Clinical evidence profile: Comparison 2. Prednisolone/ Prednisone *versus* placebo

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Prednisone/ Prednisolone**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Absolute change in weight (follow-up 12 weeks; measured with: kg; Better indicated by higher values) [2 mg prednisone]												
1 (Greally 1994)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13	12	-	MD 0.34 higher (2.32 lower to 3 higher)	VERY LOW	CRITICAL
Weight at 18 Years of Age - Boys - (measured with: Kg; Better indicated by higher values) [1 mg prednisone]												
1 (Lai 2000)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	34	21	-	MD 4.6 lower (9.69 lower to 0.49 higher)	VERY LOW	CRITICAL
Weight at 18 Years of Age - Boys (measured with: Kg; Better indicated by higher values) [2 mg prednisone]												
1 (Lai 2000)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[4]	3	21	-	MD 6.7 lower (11.59 lower to 1.81 lower)	MODERATE	CRITICAL
Weight at 18 Years of Age - Girls (measured with: Kg; Better indicated by higher values) [1 mg prednisone]												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prednisone/ Prednisolone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1 (Lai 2000)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	20	23	-	mean 0 higher (7.62 lower to 3.02 higher)	VERY LOW	CRITICAL
Weight at 18 Years of Age - Girls (measured with: Kg; Better indicated by higher values) [2 mg prednisone]												
1 (Lai 2000)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	23	23	-	MD 1.7 higher (3.37 lower to 6.77 higher)	VERY LOW	CRITICAL
Height at 18 Years of Age - Boys (measured with: cm; Better indicated by higher values) [1 mg prednisone]												
1 (Lai 2000)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	34	21	-	MD 3.9 lower (7.77 to 0.03 lower)	VERY LOW	CRITICAL
Height at 18 Years of Age - Boys (measured with: cm; Better indicated by higher values) [2 mg prednisone]												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prednisone/ Prednisolone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1 (Lai 2000)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	31	21	-	MD 4.1 lower (7.82 to 0.38 lower)	VERY LOW	CRITICAL
Height at 18 Years of Age - Girls (measured with: cm; Better indicated by higher values) [1 mg prednisone]												
1 (Lai 2000)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	20	23	-	MD 1 lower (4.54 lower to 2.54 higher)	VERY LOW	CRITICAL
Height at 18 Years of Age - Girls (measured with: cm; Better indicated by higher values) [2 mg prednisone]												
1 (Lai 2000)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	23	23	-	MD 0.5 lower (4.43 lower to 3.43 higher)	VERY LOW	CRITICAL
Adverse effects - Cataracts (follow-up 4 years) [1 mg prednisone]												
1 (Eigen	randomised trials	serious[1]	no serious inconsistency	no serious	very serious[2]	none	3/95 (3.2%)	7/95 (7.4 %)	RR 0.43 (0.11	42 fewer per	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prednisone/ Prednisolone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1995)				indirectness					to 1.61)	1000 (from 66 fewer to 45 more)		
Adverse effects - Cataracts (follow-up 3 years) [2 mg prednisone]												
1 (Eigen 1995)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/95 (11.6%)	7/95 (7.4%)	RR 1.57 (0.64 to 3.88)	42 more per 1000 (from 27 fewer to 212 more)	VERY LOW	CRITICAL
Adverse effects - Diabetes mellitus (follow-up 4 years) [1 mg prednisone]												
1 (Eigen 1995)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/95 (3.2%)	1/95 (1.1%)	RR 3 (0.32 to 28.33)	21 more per 1000 (from 7 fewer to 288 more)	VERY LOW	CRITICAL
Adverse effects - Diabetes mellitus (follow-up 3 years) [2 mg prednisone]												
1 (Eigen	randomised trials	serious[1]	no serious inconsistency	no serious	very serious[2]	none	6/95 (6.3%)	1/95 (1.1%)	RR 6.00 (0.74 to	53 more per 1000	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prednisone/ Prednisolone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1995)				indirectness					48.89)	(from 3 fewer to 504 more)		
Adverse effects - Glycosuria (follow-up 4 years) [1 mg prednisone]												
1 (Eigen 1995)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/95 (6.3%)	4/95 (4.2%)	RR 1.5 (0.44 to 5.15)	21 more per 1000 (from 24 fewer to 175 more)	VERY LOW	CRITICAL
Adverse events - Glycosuria (follow-up 3 years) [2 mg prednisone]												
1 (Eigen 1995)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	10/95 (10.5%)	4/95 (4.2%)	RR 2.5 (0.81 to 7.69)	63 more per 1000 (from 8 fewer to 282 more)	LOW	CRITICAL
Adverse effects - Hyperglycaemia (follow-up 4 years) [1 mg prednisone]												
1 (Eigen	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/95 (3.2%)	2/95 (2.1%)	RR 1.5 (0.26	11 more per 1000 (from	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prednisone/ Prednisolone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1995)									to 8.78)	16 fewer to 164 more)		
Adverse effects - Hyperglycaemia (follow-up 3 years) [2 mg prednisone]												
1 (Eigen 1995)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	10/95 (10.5%)	2/95 (2.1%)	RR 5 (1.13 to 22.21)	84 more per 1000 (from 3 more to 447 more)	LOW	CRITICAL
Mortality (follow-up 4 years)												
1 (Auberch 1985)	randomised trials	no serious risk of bias[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	0/21 (0%)	1/24 (4.2%)	RR 0.38 (0.02 to 8.83)	26 fewer per 1000 (from 41 fewer to 326 more)	LOW	IMPORTANT

Abbreviations: CI: confidence interval; kg: kilogrammes; MD: mean difference; mg: milligrams; RR: risk ratio
1 The quality of the evidence was downgraded by 1, as allocation concealment and blinding were unclear.
2 The quality of the evidence downgraded by 2 as 95% CI crossed 2 default MIDs.
3 The quality of the evidence downgraded by 1 as 95% CI crossed 1 default MID.
4 The quality of the evidence was upgraded by 1 as there is evidence of dose-response within study
5 Allocation concealment and blinding were unclear, but the quality of the evidence was not downgraded for this outcome
6 The quality of the evidence was downgraded by 2 as 95%CI crossed the null effect line, and it is very wide.

Table 52: Clinical evidence profile: Comparison 3. Azithromycin *versus* placebo

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Azithromycin *versus* placebo**		**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Time to next exacerbation (follow-up mean 6 months; assessed with: time free of exacerbation)												
2 (Saiman 2003, Saiman 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	104/218 (47.7%)1	79/227 (34.8%)	HR 0.59 (0.44 to 0.79)	125 fewer per 1000 (from 61 fewer to 176 fewer)	HIGH	CRITICAL
								34.83%		125 fewer per 1000 (from 61 fewer to 177 fewer)		
Time to next exacerbation (follow-up 12 months)												
1 (Clement 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/40 (35%)1	2/42 (4.8%)	HR 0.37 (0.217 to 0.6299)[1]	30 fewer per 1000 (from 17 fewer to 37 fewer)	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin *versus* placebo		Relative (95% CI)	Absolute		
								3.6%		23 fewer per 1000 (from 13 fewer to 28 fewer)		
Mild adverse effects of antibiotic treatment - Hearing impairment (follow-up: 6 months)												
1 (Saiman 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/87 (1.1%)	1/98 (1%)	RR 1.13 (0.07 to 17.74)	1 more per 1000 (from 9 fewer to 171 more)	LOW	CRITICAL
Mild adverse effects of antibiotic treatment – Tinnitus (follow-up: 6 months)												
1 (Saiman 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/87 (1.1%)	1/98 (1%)	RR 1.13 (0.07 to 17.74)	1 more per 1000 (from 9 fewer to 171 more)	LOW	CRITICAL
Change in BMI z score (follow-up 12 months; Better indicated by higher values)												
1 (Clement	randomised trials	no serious risk	no serious inconsistency	no serious indirectness	serious[3]	none	40	42	-	MD 0.15 higher (0.03	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Azithromycin *versus* placebo**		**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
2006)		of bias								lower to 0.33 higher)		
Change in weight (kg) (Follow-up: 6 months; Better indicated by higher values)												
2 (Saiman 2003, Saiman 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	216	224	-	MD 0.62 higher (0.26 to 0.98 higher)	MODERATE	IMPORTANT
Quality of life: change in CFQ-R total (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Saiman 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	85	92	-	MD 1.6 higher (0.61 lower to 3.81 higher)	HIGH	IMPORTANT
Quality of life: change in CFQ-R physical domain score (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Saiman 2003	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	85	92	-	MD 2.7 higher (0.09 to 5.31 higher)	HIGH	IMPORTANT
Quality of life: change in CFQ-R psychosocial domain score (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Sai	randomised trials	no serious	no serious inconsistency	no serious indirectness	no serious	none	85	92	-	MD 0.4 higher (3	HIGH	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin *versus* placebo		Relative (95% CI)	Absolute		
man 2003		risk of bias			imprecision					lower to 3.8 higher)		
Quality of life: change in CFQ-R body image domain score (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Saiman 2003	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	85	92	-	MD 3.2 higher (0.24 lower to 6.64 higher)	HIGH	IMPORTANT

Abbreviations: BMI: body mass index; CFQ-R: cystic fibrosis questionnaire revised; CI: confidence interval; MD: mean difference; RR: risk ratio
1 Calculated by the NGA technical team from probability of remaining free from exacerbation.
2 The quality of the evidence downgraded by 2 as 95% CI crossed 2 default MIDs.
3 The quality of the evidence downgraded by 1 as 95% CI crossed 1 default MID.

Table 53: Clinical evidence profile: Comparison 4. Ibuprofen *versus* placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen	Placebo	Relative (95% CI)	Absolute		
Adverse effects: increase in abdominal pain (follow-up 2 years)												
1 (Lands 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/70 (1.4%)	4/72 (5.6%)	RR 0.26 (0.03 to 2.24)	41 fewer per 1000 (from 54 fewer to 69 more)	LOW	CRITICAL
Adverse effects: increase in abdominal pain (follow-up 4 years)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1 (Konstan 1995)	randomised trials	serious [2]	no serious inconsistency	no serious indirectness	very serious[1]	none	5/41 (12.2%)	7/43 (16.3 %)	RR 0.75 (0.26 to 2.17)	41 fewer per 1000 (from 120 fewer to 190 more)	VERY LOW	CRITICAL
Adverse effects: gastrointestinal bleeding (follow-up 2 years)												
1 (Lands 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/70 (1.4%)	0/72 (0%)	RR 3.08 (0.13 to 74.46)	Not calculable [2]	LOW	CRITICAL
Annual rate of change in % ideal body weight (follow-up 4 years; Better indicated by higher values)												
1 (Konstan 1995)	randomised trials	serious [3]	no serious inconsistency	no serious indirectness	serious[4]	none	41	43	-	MD 0.99 higher (0.17 to 1.81 higher)	LOW	IMPORTANT
Annual rate of change in % ideal body weight (by age) - Under 13 years at randomisation (follow-up 4 years; Better indicated by higher values)												
1 (Konstan 1995)	randomised trials	serious [3]	no serious inconsistency	no serious indirectness	serious[4]	none	24	25	-	MD 1.45 higher (0.33 to 2.57 higher)	LOW	IMPORTANT
Annual rate of change in % ideal body weight (by age) - 13 years or older at randomisation (follow-up 4 years; Better indicated by higher values)												
1 (Konstan 1995)	randomised trials	serious [3]	no serious inconsistency	no serious indirectness	very serious[1]	none	17	18	-	MD 0.34 higher (0.61 lower to	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen	Placebo	Relative (95% CI)	Absolute		
										1.29 higher)		

Abbreviations: CI: confidence interval; MD: mean difference; RR: risk ratio
1 The quality of the evidence downgraded by 2 due to serious imprecision as 95% CI crossed 2 default MIDs.
2 Absolute effect not calculable as there are 0 events in control (placebo) arm.
3 The quality of the evidence was downgraded by 1 due to reporting bias.
4 The quality of the evidence downgraded by 1 due to serious imprecision as 95% CI crossed 1 default MID.

J.13 Nutrition

J.13.1 Oral calorie supplementation

Table 54: Clinical evidence profile: Comparison 1.1. Oral calorie supplementation versus usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral calorie supplementation	Usual care	Relative (95% CI)	Absolute		
Change in weight (kg) (Follow-up: 3 months; Better indicated by higher values)												
1 (Poustie 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	48	51	-	MD 0.34 higher (0.07 lower to 0.75 higher)	MODERATE	CRITICAL
Change in weight (kg) (Follow-up: 6 months; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral calorie supplementation	Usual care	Relative (95% CI)	Absolute		
2 (Hanning 1993, Poustie 2006)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness[3]	serious[1]	none	59	58	-	MD 0.47 higher (0.07 lower to 1.02 higher)	LOW	CRITICAL
Change in weight (kg) (Follow-up: 1 year; Better indicated by higher values)												
1 (Poustie 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	52	-	MD 0.16 higher (0.68 lower to 1 higher)	MODERATE	CRITICAL
Change in height (cm) (Follow-up: 3 months; Better indicated by higher values)												
1 (Poustie 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	48	51	-	MD 0.03 lower (0.36 lower to 0.3 higher)	HIGH	CRITICAL
Change in height (cm) (Follow-up: 6 months; Better indicated by higher values)												
1 (Poustie 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	51	-	MD 0.47 lower (1.32 lower to 0.38 higher)	HIGH	CRITICAL
Change in height (cm) (Follow-up: 1 year; Better indicated by higher values)												
1 (Poustie 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious	none	50	52	-	MD 0.06 higher (0.5 lower	HIGH	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral calorie supplementation	Usual care	Relative (95% CI)	Absolute	**Quality**	**Importance**
					imprecision					to 0.62 higher)		
Change in weight as % expected for age and height (Follow-up: 6 months; Better indicated by higher values)												
1 (Hanning 1993)	randomised trials	serious[2]	no serious inconsistency	serious[4]	very serious[5]	none	9	7	-	MD 3.3 higher (6.27 lower to 12.87 higher)	VERY LOW	CRITICAL
Change in BMI (kg/m2) (Follow-up: 3 months; Better indicated by higher values)												
1 (Poustie 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	48	51	-	MD 0.14 higher (0.08 lower to 0.36 higher)	MODERATE	CRITICAL
Change in BMI (kg/m2) (Follow-up: 6 months; Better indicated by higher values)												
1 (Poustie 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	51	-	MD 0.24 higher (0.06 lower to 0.54 higher)	MODERATE	CRITICAL
Change in BMI (kg/m2) (Follow-up: 1 year; Better indicated by higher values)												
1 (Poustie 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	52	-	MD 0.08 higher (0.28 lower to 0.44 higher)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral calorie supplementation	Usual care	Relative (95% CI)	Absolute		
Change in BMI (centile) (Follow-up: 3 months; Better indicated by higher values)												
1 (Poustie 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	48	51	-	MD 3.28 higher (0.7 lower to 7.26 higher)	MODERATE	CRITICAL
Change in BMI (centile) (Follow-up: 6 months; Better indicated by higher values)												
1 (Poustie 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	51	-	MD 5.75 higher (0.22 to 11.28 higher)	MODERATE	CRITICAL
Change in BMI (centile) (Follow-up: 1 year; Better indicated by higher values)												
1 (Poustie 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	52	-	MD 2.99 higher (2.69 lower to 8.67 higher)	MODERATE	CRITICAL
Change in weight (centile) (Follow-up: 3 months; Better indicated by higher values)												
1 (Poustie 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	48	51	-	MD 1.72 higher (0.59 lower to 4.03 higher)	MODERATE	CRITICAL
Change in weight (centile) (Follow-up: 6 months; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral calorie supplementation	Usual care	Relative (95% CI)	Absolute		
1 (Poustie 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	51	-	MD 2.12 higher (0.94 lower to 5.18 higher)	MODERATE	CRITICAL
Change in weight (centile) (Follow-up: 1 year; Better indicated by higher values)												
1 (Poustie 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	52	-	MD 1.83 higher (1.77 lower to 5.43 higher)	MODERATE	CRITICAL
Change in height (centile) (Follow-up: 3 months; Better indicated by higher values)												
1 (Poustie 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	48	51	-	MD 0.56 lower (2.04 lower to 0.92 higher)	MODERATE	CRITICAL
Change in height (centile) (Follow-up: 6 months; Better indicated by higher values)												
1 (Poustie 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	51	-	MD 1.74 lower (4.4 lower to 0.92 higher)	HIGH	CRITICAL
Change in height (centile) (Follow-up: 1 year; Better indicated by higher values)												
1(Poustie 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	52	-	MD 0.65 lower (3.11	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral calorie supplementation	Usual care	Relative (95% CI)	Absolute	Quality	Importance
										lower to 1.81 higher)		
Change in height as % of expected for age (Follow-up: 6 months; Better indicated by higher values)												
1 (Hanning 1993)	randomised trials	serious[2]	no serious inconsistency	serious[4]	very serious[5]	none	9	7	-	MD 1.6 lower (21.54 lower to 18.34 higher)	VERY LOW	CRITICAL
Change in FEV_1 % predicted (Follow-up: 3 months; Better indicated by higher values)												
1 (Poustie 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	31	38	-	MD 7.92 lower (13.89 to 1.95 lower)	MODERATE	CRITICAL
Change in FEV_1 % predicted (Follow-up: 6 months; Better indicated by higher values)												
2 (Hanning 1993, Poustie 2006)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness[3]	serious[6]	none	41	45	-	MD 3.84 lower (9.63 lower to 1.94 higher)	LOW	CRITICAL
Change in FEV_1 % predicted (Follow-up: 1 year; Better indicated by higher values)												
1 (Poustie 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	32	38	-	MD 1.91 lower (8.57 lower to 4.75 higher)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral calorie supplementation	Usual care	Relative (95% CI)	Absolute	**Quality**	**Importance**
Quality of life												
No evidence available												
Adverse effects												
No evidence available												
Pulmonary exacerbations												
No evidence available												
Patient or carer satisfaction												
No evidence available												

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; cm: centimetres; FEV_1: forced expiratory volume in 1 second; kg: kilogrammes; kg/m2: kilogrammes per metre square; MD: mean difference
1 The quality of the evidence was downgraded by 1 because the CI crossed 1 default MID
2 The quality of the evidence was downgraded by 1 because of high risk of bias in relation to the randomisation (the treated group appeared to be in better clinical condition at baseline in 1 study).
3 The inclusion criteria in the paper by Hanning et al. did not mention underweight therefore the population in the study is unlikely to be representative of people who would usually receive oral supplements; however the quality of the evidence was not downgraded because the inclusion criteria in the paper by Poustie et al. are likely to be representative of people who receive oral supplements in clinical practice
4 The quality of the evidence was downgraded by 1 because the inclusion criteria did not mention underweight therefore the population in the study is unlikely to be representative of people who would receive oral supplements in clinical practice
5 The quality of the evidence was downgraded by 2 because the CI crossed 2 defaults MIDs
6 The quality of the evidence was downgraded by 1 because the CI crossed 1 clinical MID

Table 55: Clinical evidence profile: Comparison 1.2. Oral calorie supplementation versus nutritional advice

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral calorie supplementation	Nutritional advice	Relative (95% CI)	Absolute		
Change in weight (kg) (Follow-up: 3 months; Better indicated by higher values)												
1 (Kalnins 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7	6	-	MD 0.69 lower (3.3 lower to 1.92 higher)	VERY LOW	CRITICAL
Change in weight for height (%) (Follow-up: 3 months; Better indicated by higher values)												
1 (Kalnins 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7	12	-	MD 0.96 lower (5.23 lower to 3.31 higher)	VERY LOW	CRITICAL
Change in weight z score (Follow-up: 3 months; Better indicated by higher values)												
1 (Kalnins 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7	6	-	MD 0 higher (0.59 lower to 0.59 higher)	VERY LOW	CRITICAL
Change in weight z score (Follow-up: 6 months; Better indicated by higher values)												
1 (Kalnins 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7	6	-	MD 0.3 lower (0.98 lower to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral calorie supplementation	Nutritional advice	Relative (95% CI)	Absolute	Quality	Importance
										0.38 higher)		
Change in % ideal body weight (Follow-up: 3 months; Better indicated by higher values)												
1 (Kalnins 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7	6	-	MD 2 lower (10.59 lower to 6.59 higher)	VERY LOW	CRITICAL
Change in % ideal body weight (Follow-up: 6 months; Better indicated by higher values)												
1 (Kalnins 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7	6	-	MD 3 lower (11.59 lower to 5.59 higher)	VERY LOW	CRITICAL
Change in height (cm) (Follow-up: 3 months; Better indicated by higher values)												
1 (Kalnins 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7	6	-	MD 0.38 lower (3.05 lower to 2.29 higher)	VERY LOW	CRITICAL
Change in height z score (Follow-up: 3 months; Better indicated by higher values)												
1 (Kalnins 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7	6	-	MD 0 higher (0.96	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral calorie supplementation	Nutritional advice	Relative (95% CI)	Absolute	Quality	Importance
										lower to 0.96 higher)		
Change in height z score (Follow-up: 6 months; Better indicated by higher values)												
1 (Kalnins 2005)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7	6	-	MD 0.1 lower (1.07 lower to 0.87 higher)	VERY LOW	CRITICAL
Change in FEV_1 % predicted (Follow-up: 3 months; Better indicated by higher values)												
1 (Kalnins 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	7	6	-	MD 8.2 lower (23.37 lower to 6.97 higher)	VERY LOW	CRITICAL
Change in FEV_1 % predicted (Follow-up: 6 months; Better indicated by higher values)												
1 (Kalnins 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	7	6	-	MD 8 lower (26.96 lower to 10.96 higher)	VERY LOW	CRITICAL
Quality of life												
No evidence available												
Pulmonary exacerbations												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral calorie supplementation	Nutritional advice	Relative (95% CI)	Absolute		
No evidence available												
Adverse effects												
No evidence available												
Patient or carer satisfaction												
No evidence available												

Abbreviations: confidence interval; CF: cystic fibrosis; cm: centimetres; FEV_1: forced expiratory volume in 1 second; kg: kilogrammes; MD: mean difference
1 The quality of the evidence was downgraded by 2 because of unclear risk of bias in relation to randomisation, high risk of bias in relation to allocation concealment, and inability to make judgment in relation to other bias.
2 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
3 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 clinical MIDs

J.13.2 Enteral tube feeding

Table 56: Clinical evidence profile: Comparison 2. Enteral tube feeding *versus* usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enteral tube feeding	Usual care	Relative (95% CI)	Absolute		
Change in weight (kg) (Follow-up: 1 year; Better indicated by higher values)												
1 (White 2013)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15	6	-	MD 7.60 higher (4.74 to 10.46 higher)	VERY LOW	CRITICAL
Change in weight (kg) (Follow-up: 2 years; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enteral tube feeding	Usual care	Relative (95% CI)	Absolute	**Quality**	**Importance**
1 (White 2013)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15	6	-	MD 9.10 higher (5.43 to 12.77 higher)	VERY LOW	CRITICAL
Change in weight (kg) (Follow-up: 3 years; Better indicated by higher values)												
1 (White 2013)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15	6	-	MD 9.00 higher (5.21 to 12.79 higher)	VERY LOW	CRITICAL
Change in weight z score (Follow-up: 6 months; range of scores: -4-4; Better indicated by higher values)												
1 (Bradley 2012)	observational studies	serious [2]	no serious inconsistency	no serious indirectness	serious[3]	none	20	20	-	MD 0.62 higher (0.27 to 0.97 higher)	VERY LOW	CRITICAL
Change in weight z score (Follow-up: 1 year; range of scores: -4-4; Better indicated by higher values)												
1 (Bradley 2012)	observational studies	serious [2]	no serious inconsistency	no serious indirectness	serious[3]	none	20	20	-	MD 0.44 higher (0.11 to 0.77 higher)	VERY LOW	CRITICAL
Change in height z-score (Follow-up: 6 months; range of scores: -4-4; Better indicated by higher values)												
1 (Bradley 2012)	observational studies	serious [2]	no serious inconsistency	no serious indirectness	serious[3]	none	20	20	-	MD 0.2 higher (0.19 lower to 0.59 higher)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enteral tube feeding	Usual care	Relative (95% CI)	Absolute	Quality	Importance
Change in height z-score (Follow-up: 1 year; range of scores: -4-4; Better indicated by higher values)												
1 (Bradley 2012)	observational studies	serious [2]	no serious inconsistency	no serious indirectness	serious[3]	none	20	20	-	MD 0.1 higher (0.29 lower to 0.49 higher)	VERY LOW	CRITICAL
Change in BMI z score (Follow-up: 6 months; range of scores: -4-4; Better indicated by higher values)												
1 (Bradley 2012)	observational studies	serious [2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	MD 0.82 higher (0.48 to 1.16 higher)	VERY LOW	CRITICAL
Change in BMI z score (Follow-up: 1 year; range of scores: -4-4; Better indicated by higher values)												
1 (Bradley 2012)	observational studies	serious [2]	no serious inconsistency	no serious indirectness	serious[3]	none	20	20	-	MD 0.39 higher (0.09 to 0.69 higher)	VERY LOW	CRITICAL
Change in BMI (kg/m2) (Follow-up: 1 year; Better indicated by higher values)												
1 (White 2013)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15	6	-	MD 2.90 higher (2.2 to 3.6 higher)	VERY LOW	CRITICAL
Change in BMI (kg/m2) (Follow-up: 2 years; Better indicated by higher values)												
1 (White 2013)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15	6	-	MD 3.20 higher (2.33 to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enteral tube feeding	Usual care	Relative (95% CI)	Absolute	Quality	Importance
										4.07 higher)		
Change in BMI (kg/m2) (Follow-up: 3 years; Better indicated by higher values)												
1 (White 2013)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15	6	-	MD 2.50 higher (1.55 to 3.45 higher)	VERY LOW	CRITICAL
Change in FEV_1 % predicted (Follow-up: 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Bradley 2012)	observational studies	serious [2]	no serious inconsistency	no serious indirectness	very serious [4]	none	14	13	-	MD 4.5 lower (16.18 lower to 7.18 higher)	VERY LOW	CRITICAL
Change in FEV_1 % predicted (Follow-up: 1 year; range of scores: 0-100; Better indicated by higher values)												
1 (Bradley 2012)	observational studies	serious [2]	no serious inconsistency	no serious indirectness	serious [5]	none	14	13	-	MD 8.2 lower (20.5 lower to 4.1 higher)	VERY LOW	CRITICAL
1 (White 2013)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	very serious [4]	none	15	6	-	MD 10.60 higher (10.34 lower to 31.54 higher)	VERY LOW	CRITICAL
Change in FEV_1 % predicted (Follow-up: 2 years; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enteral tube feeding	Usual care	Relative (95% CI)	Absolute	**Quality**	**Importance**
1 (White 2013)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	serious[5]	none	15	6	-	MD 12.20 higher (2.57 lower to 26.97 higher)	VERY LOW	CRITICAL
Change in FEV_1 % predicted (Follow-up: 3 years; Better indicated by higher values)												
1 (White 2013)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	serious[5]	none	15	6	-	MD 12.20 higher (1.84 lower to 26.24 higher)	VERY LOW	CRITICAL
Change in IV treatment days (Follow-up: 1 year; Better indicated by lower values)												
1 (White 2013)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	serious[3]	none	15	6	-	MD 17.90 higher (5.96 lower to 41.76 higher)	VERY LOW	IMPORTANT
Change in IV treatment days (Follow-up: 2 years; Better indicated by lower values)												
1 (White 2013)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	serious[3]	none	15	6	-	MD 36.00 higher (5.06 to 66.94 higher)	VERY LOW	IMPORTANT
Change in IV treatment days (Follow-up: 3 years; Better indicated by lower values)												
1 (Whit	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	serious[3]	none	15	6	-	MD 36.20 higher (6.29	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enteral tube feeding	Usual care	Relative (95% CI)	Absolute		
e 2013)										lower to 78.69 higher)		
Quality of life												
No evidence available												
Patient or carer satisfaction												
No evidence available												
Adverse events												
No evidence available												

Abbreviations: BMI: body mass index; confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; IV: intravenous; k/m2g: kilogrammes per square metre; MD: mean difference
1 The quality of the evidence was downgraded by 2 due to high risk of bias in relation to selection of the study population and comparability of the 2 groups
2 The quality of the evidence was downgraded by 1 because of high risk of bias in relation to comparability
3 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
4 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 clinical MIDs
5 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 clinical MID

J.13.3 Appetite stimulants

Table 57: Clinical evidence profile: Comparison 3. Appetite stimulants versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Appetite stimulants	Placebo	Relative (95% CI)	Absolute		
Change in weight in kg. (follow-up 3 months; range of scores: 3-120; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Appetite stimulants	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1 (Eubanks 2002, Homnick 2004)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18	15	-	MD 2.97 higher (0.94 to 4.99 higher)	LOW	CRITICAL
Change in weight in kg. (follow-up 6 months; range of scores: 1-120; Better indicated by higher values)												
1 (Eubanks 2002)	randomised trials	very serious [2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	7	-	MD 3.8 higher (1.27 to 6.33 higher)	LOW	CRITICAL
Change in weight z score (follow-up 3 months; range of scores: -4-4; Better indicated by higher values)												
3 (Eubanks 2002, Homnick 2004, Marchand 2000)	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	MD 0.61 higher (0.29 to 0.93 higher)	LOW	CRITICAL
Change in weight z score (follow-up 6 months; range of scores: -4-4; Better indicated by higher values)												
1 (Eubanks 2002)	randomised trials	very serious [2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	7	-	MD 0.74 higher (0.26 to 1.22 higher)	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Appetite stimulants	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Change in height (cm) (follow-up 3 months; Better indicated by higher values)												
1 (Homnick 2004)	randomised trials	serious [4]	no serious inconsistency	serious[5]	very serious[6]	none	8	8	-	MD 0.2 higher (11.88 lower to 12.28 higher)	VERY LOW	CRITICAL
Change in BMI (kg/m2) (follow-up 3 months; Better indicated by higher values)												
1 (Homnick 2004)	randomised trials	serious [4]	no serious inconsistency	serious[5]	serious[7]	none	8	8	-	MD 0.88 higher (0.76 lower to 2.52 higher)	VERY LOW	CRITICAL
Change in BMI centile (follow-up 3 months; Better indicated by higher values)												
1 (Homnick 2004)	randomised trials	serious [4]	no serious inconsistency	serious[5]	serious[7]	none	8	8	-	MD 11.1 higher (0.15 to 22.05 higher)	VERY LOW	CRITICAL
Change in % ideal body weight (follow-up 3 months; Better indicated by higher values)												
1 (Homnick 2004)	randomised trials	serious [4]	no serious inconsistency	serious[5]	serious7	none	8	8	-	MD 5.14 higher (0.2 to 10.08 higher)	VERY LOW	CRITICAL
Change in FEV_1 % predicted (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Appetite stimulants	Placebo	Relative (95% CI)	Absolute		
1 (Eubanks 2002)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[8]	none	10	7	-	MD 13.55 higher (1.88 lower to 28.98 higher)	VERY LOW	CRITICAL
Change in FEV_1 % predicted (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Eubanks 2002)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[8]	none	10	7	-	MD 5.64 higher (4.43 lower to 15.71 higher)	VERY LOW	CRITICAL
Quality of life												
No evidence available												
Number of pulmonary exacerbations (follow-up: 3 months; Better indicated by lower values)												
1 (Marchand 2000)	randomised trials	very serious[9]	no serious inconsistency	no serious indirectness	very serious[6]	none	5/6 (83.3%)	3/6 (50%)	RR 1.67 (0.69 to 4)	335 more per 1000 (from 155 fewer to 1000 more)	VERY LOW	IMPORTANT
Adverse effects: constipation (follow-up: 6 months; Better indicated by lower values)												
1 (Eubanks 2002)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[6]	none	1/10 (10%)	0/7 (0%)	RR 2.18 (0.1 to 46.92)	-	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Appetite stimulants	Placebo	Relative (95% CI)	Absolute		
Adverse effects: high blood glucose levels (follow-up: 3 months; Better indicated by lower values)												
1 (Marchand 2000)	randomised trials	very serious [10]	no serious inconsistency	no serious indirectness	Not calculable	none	6 participants. Values not reported	6 participants. Values not reporter	Fasting blood glucose levels remained unchanged in both groups.		LOW	IMPORTANT
Adverse effects: decreased morning cortisol levels <0.6mcg/dl (follow-up: 3 months; Better indicated by higher values)												
1 (Marchand 2000)	randomised trials	very serious [10]	no serious inconsistency	no serious indirectness	Not calculable	none	4/6	Not reported	-	All participants in the intervention group had normal morning cortisol levels at baseline; at follow-up 4 out of the 6	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Appetite stimulants	Placebo	Relative (95% CI)	Absolute		
										participants in the intervention group had morning cortisol levels decreased to <0.6mcg/dl		
Adverse effects: decreased morning cortisol levels <30 nmol/L at 6 months												
1 (Eubanks 2002)	randomised trials	very serious [2]	no serious inconsistency	no serious indirectness	very serious[6]	none	7/10 (70%) [a] Baseline levels not reported	0/7 (0%) Baseline levels not reporter	RR 10.91 (0.72 to 164.61)	-	VERY LOW	IMPORTANT
Patient or carer satisfaction (Better indicated by higher values)												
No evidence available												

Abbreviations: BMI: body mass index; confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; IV: intravenous; kg: kilogrammes; kg/m2g: kilogrammes per square metre; MD: mean difference; nmol/L: nanomoles per litre; RR: risk ratio

1 The quality of the evidence was downgraded by 2 due to very serious risk of bias in relation to the evidence from the Eubanks 2002 paper and serious risk of bias in relation to the evidence from the Homnick 2004 paper

2 The quality of the evidence was downgraded by 2 due to unclear risk of bias in relation to allocation concealment, and high risk of bias in relation to incomplete outcome data and selective reporting.

3 The quality of the evidence was downgraded by 2 due to very serious risk of bias in relation to the evidence from the Eubanks 2002 paper, serious risk of bias in relation to the evidence from the Homnick 2004 paper, and very serious risk of bias in relation to the evidence from the Marchand 2000 paper.
4 The quality of the evidence was downgraded by 1 due to unclear risk of bias in relation to allocation concealment and high risk of bias in relation to selective reporting.
5 The evidence was downgraded by 1 because ideal body weight for height <100% was an inclusion criteria. However in clinical practice some people with ideal body weight for height under this cut-off may be considered with normal weight and therefore would not be the target population of appetite stimulants.
6 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
7 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
8 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 clinical MID
9 The quality of the evidence was downgraded by 2 due to unclear risk of bias in relation to random sequence generation and allocation concealment, and high risk of bias in relation to incomplete outcome data and selective reporting
10 The quality of the evidence was downgraded by 2 due to unclear risk of bias in relation to random sequence generation and allocation concealment, and high risk of bias in relation to incomplete outcome data, selective reporting, and bad reporting (relevant values not provided)
a Reversible decrease: 30+ days after treatment levels went back up to 270 +-6.9 nmol/L

J.13.4 Nutritional education/ dietary advice

Table 58: Clinical evidence profile: Comparison 4. Nutrition education *versus* usual care

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nutrition education	Standard treatment	Relative (95% CI)	Absolute	Quality	Importance
Change in weight (kg) (follow-up 6 months; range of scores: 1-120; Better indicated by higher values)												
1 (Watson 2008)	randomised trials	no serious risk of bias[1]	no serious inconsistency	serious indirectness[2]	very serious[3]	none	23	25	-	MD 0.4 lower (4.85 lower to 4.05 higher)	VERY LOW	CRITICAL
Change in weight (kg) (follow-up 1 years; range of scores: 1-120; Better indicated by higher values)												
1 (Watson 2008)	randomised trials	no serious risk of bias[1]	no serious inconsistency	serious indirectness[2]	serious[4]	none	23	25	-	MD 0.4 lower (4.87 lower to 4.07 higher)	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nutrition education	Standard treatment	Relative (95% CI)	Absolute		
Change in FEV_1 % predicted (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Watson 2008)	randomised trials	no serious risk of bias[1]	no serious inconsistency	serious indirectness[2]	very serious[5]	none	23	25	-	MD 1.49 higher (8.84 lower to 11.82 higher)	VERY LOW	CRITICAL
Change in FEV_1 % predicted (follow-up 1 years; range of scores: 0-100; Better indicated by higher values)												
1 (Watson 2008)	randomised trials	no serious risk of bias[1]	no serious inconsistency	serious indirectness[2]	very serious[5]	none	23	25	-	MD 0.99 higher (9.29 lower to 11.27 higher)	VERY LOW	CRITICAL
Quality of life: CFQOL, physical functioning (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Watson 2008)	randomised trials	serious[6]	no serious inconsistency	serious indirectness[2]	Not calculable	none	23	25	-	p-value: 0.05	LOW	CRITICAL
Quality of life: CFQOL, physical functioning (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1 (Watson 2008)	randomised trials	serious[6]	no serious inconsistency	serious indirectness[2]	Not calculable	none	23	25	-	p-value: 0.61	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nutrition education	Standard treatment	Relative (95% CI)	Absolute		
Quality of life: CFQOL, social functioning (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Watson 2008)	randomised trials	serious[6]	no serious inconsistency	serious indirectness[2]	Not calculable	none	23	25	-	p-value: 0.85	LOW	CRITICAL
Quality of life: CFQOL, social functioning at 12 months (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1 (Watson 2008)	randomised trials	serious[6]	no serious inconsistency	serious indirectness[2]	Not calculable	none	23	25	-	p-value: 0.54	LOW	CRITICAL
Quality of life: CFQOL, treatment issues (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Watson 2008)	randomised trials	serious[6]	no serious inconsistency	serious indirectness[2]	Not calculable	none	23	25	-	p-value: 0.74	LOW	CRITICAL
Quality of life: CFQOL, treatment issues (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1 (Watson 2008)	randomised trials	serious[6]	no serious inconsistency	serious indirectness[2]	Not calculable	none	23	25	-	p-value: 0.68	LOW	CRITICAL
Quality of life: CFQOL, chest symptoms (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Watson	randomised trials	serious[6]	no serious inconsistency	serious indirectness[2]	Not calculable	none	23	25	-	p-value: 0.59	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nutrition education	Standard treatment	Relative (95% CI)	Absolute		
2008)												
Quality of life: CFQOL, chest symptoms (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1 (Watson 2008)	randomised trials	serious[6]	no serious inconsistency	serious indirectness[2]	Not calculable	none	23	25	-	p-value: 0.62	LOW	CRITICAL
Quality of life: CFQOL, emotional responses (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Watson 2008)	randomised trials	serious[6]	no serious inconsistency	serious indirectness[2]	Not calculable	none	23	25	-	p-value: 0.45	LOW	CRITICAL
Quality of life: CFQOL, emotional responses (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1 (Watson 2008)	randomised trials	serious[6]	no serious inconsistency	serious indirectness[2]	Not calculable	none	23	25	-	p-value: 0.07	LOW	CRITICAL
Quality of life: CFQOL, concerns for the future (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Watson 2008)	randomised trials	serious[6]	no serious inconsistency	serious indirectness[2]	Not calculable	none	23	25	-	p-value: 0.46	LOW	CRITICAL
Quality of life: CFQOL, concerns for the future (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nutrition education	Standard treatment	Relative (95% CI)	Absolute	Quality	Importance
1 (Watson 2008)	randomised trials	serious[6]	no serious inconsistency	serious indirectness[2]	Not calculable	none	23	25	-	p-value 0.03:	LOW	CRITICAL
Quality of life: CFQOL, interpersonal relationship (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Watson 2008)	randomised trials	serious[6]	no serious inconsistency	serious indirectness[2]	Not calculable	none	23	25	-	p-value: 0.75	LOW	CRITICAL
Quality of life: CFQOL, interpersonal relationship (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1 (Watson 2008)	randomised trials	serious[6]	no serious inconsistency	serious indirectness[2]	Not calculable	none	23	25	-	p-value: 0.64	LOW	CRITICAL
Quality of life: CFQOL, body image (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Watson 2008)	randomised trials	serious[6]	no serious inconsistency	serious indirectness[2]	Not calculable	none	23	25	-	p-value: 0.24	LOW	CRITICAL
Quality of life: CFQOL, body image (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1 (Watson 2008)	randomised trials	serious[6]	no serious inconsistency	serious indirectness[2]	Not calculable	none	23	25	-	p-value: 0.59	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nutrition education	Standard treatment	Relative (95% CI)	Absolute		
Quality of life: CFQOL, career issues (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Watson 2008)	randomised trials	serious[6]	no serious inconsistency	serious indirectness[2]	Not calculable	none	23	25	-	p-value: 0.15	LOW	CRITICAL
Quality of life: CFQOL, career issues (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1 (Watson 2008)	randomised trials	serious[6]	no serious inconsistency	serious indirectness[2]	Not calculable	none	23	25	-	p-value: 0.28	LOW	CRITICAL
Pulmonary exacerbations												
No evidence available												
Adverse effects												
No evidence available												
Patient or carer satisfaction												
No evidence available												

Abbreviations: CI: confidence interval; CF: cystic fibrosis; CFQOL: cystic fibrosis quality of life questionnaire; FEV_1: forced expiratory volume in 1 second; kg: kilogrammes; MD: mean difference

1 The quality of the evidence was not downgraded despite unclear risk of bias in relation to blinding and selective reporting, because objective measures are unlikely to be influenced by the lack of blinding.

2 The quality of the evidence was downgraded by 1 because there was no inclusion criteria related to underweight, therefore the study population is unlikely to be representative of people who would receive this intervention in clinical practice

3 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs

4 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID

5 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 clinical MIDs

6 The quality of the evidence was downgraded by 1 because of unclear risk of bias in relation to selective reporting and high risk of bias due to bad reporting (only p values and U test statistic provided)

J.13.5 Psychological and behavioural interventions

Table 59: Clinical evidence profile: Comparison 5.1 Behavioural intervention *versus* usual care

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Behavioural intervention	Usual care	Relative (95% CI)	Absolute	Quality	Importance
Change in weight (kg) (follow-up 6 weeks; Better indicated by higher values)												
1 (Stark 1996)	randomised trials	serious [1]	no serious inconsistency	serious indirectness [2]	very serious[3]	none	5	4	-	MD 1.7 higher (4.02 lower to 7.42 higher)	VERY LOW	CRITICAL
Change in height (cm) (follow-up 6 weeks; Better indicated by higher values)												
1 (Stark 1996)	randomised trials	serious [1]	no serious inconsistency	serious indirectness [2]	very serious[3]	none	5	4	-	MD 0.1 lower (16.75 lower to 16.55 higher)	VERY LOW	CRITICAL
Change in weight z score (follow-up 6 weeks; Better indicated by higher values)												
1 (Stark 1996)	randomised trials	serious [1]	no serious inconsistency	serious indirectness [2]	serious[4]	none	5	4	-	MD 0.5 higher (0.19 lower to 1.19 higher)	VERY LOW	CRITICAL
Change in FEV_1 % predicted (follow-up 6 weeks; Better indicated by higher values)												
1 (Stark 1996)	randomised trials	serious [1]	no serious inconsistency	serious indirectness [2]	very serious[5]	none	5	4	-	MD 6.5 lower (28.09 lower to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Behavioural intervention	Usual care	Relative (95% CI)	Absolute	**Quality**	**Importance**
										15.09 higher)		
Quality of life												
No evidence available												
Pulmonary exacerbations												
No evidence available												
Adverse effects												
No evidence available												
Patient or carer satisfaction												
No evidence available												

Abbreviations: CI: confidence interval; CF: cystic fibrosis; cm: centimetres; FEV_1: forced expiratory volume in 1 second; MD: mean difference
1 The quality of the evidence was downgraded by 1 due to unclear risk of bias in relation to random sequence generation, allocation concealment and selective reporting. Cochrane rated the risk of bias for blinding as high however objective measures are unlikely to be influenced by the lack of blinding.
2. The quality of the evidence was downgraded by 1 because there were no inclusion criteria related to underweight or calorie intake therefore the study population is unlikely to be representative of people who would receive this intervention in clinical practice
3 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
4 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
5 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 clinical MIDs

Table 60: Clinical evidence profile: Comparison 5.2 Behavioural intervention *versus* education and attention control treatment

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Behavioural intervention	Educational intervention	Relative (95% CI)	Absolute	**Quality**	**Importance**
Change in weight z score (follow-up 6 months; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Behavioural intervention	Educational intervention	Relative (95% CI)	Absolute	Quality	Importance
1 (Powers 2015)	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36	42	-	MD 0.06 higher (0.1 lower to 0.22 higher)	MODERATE	CRITICAL
Change in weight z score (follow-up 18 months; Better indicated by higher values)												
1 (Powers 2015)	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36	42	-	MD 0.04 higher (0.2 lower to 0.28 higher)	HIGH	CRITICAL
Change in height z score (follow-up 18 months; Better indicated by higher values)												
1 (Powers 2015)	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36	42	-	MD 0.11 higher (0.02 lower to 0.24 higher)	MODERATE	CRITICAL
Quality of life												
No evidence available												
Pulmonary exacerbations												
No evidence available												
Adverse effects: digestive system (follow-up 6 months Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Behavioural intervention	Educational intervention	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29/36 (80.6%)	21/42 (50%) 50%	RR 1.61 (1.14 to 2.27)	305 more per 1000 (from 70 more to 635 more)	MODERATE	IMPORTANT
Patient or carer satisfaction												
No evidence available												

Abbreviations: CI: confidence interval; MD: mean difference
1 The quality of the evidence was not downgraded although there was unclear risk of bias in relation to allocation concealment and blinding, because objective measures are unlikely to be influenced by the lack of blinding.
2 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID

Table 61: Clinical evidence profile: Comparison 5.3 Behavioural management training + educational intervention *versus* educational intervention alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Behavioural management training + nutritional intervention	Educational intervention alone	Relative (95% CI)	Absolute		
Change in weight (kg) (follow-up: 2 months; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Behavioural management training + nutritional intervention	Educational intervention alone	Relative (95% CI)	Absolute	Quality	Importance
1 (Stark 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	33	34	-	MD 0.55 higher (0 to 1.1 higher)	MODERATE	CRITICAL
Change in weight (kg) (follow-up: 1 year; Better indicated by higher values)												
1 (Powers 2003)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	4	4	-	MD 0.43 lower (1.27 lower to 0.41 higher)	VERY LOW	CRITICAL
Change in weight (kg) (follow-up: 2 years; Better indicated by higher values)												
1 (Stark 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	28	31	-	MD 0.52 higher (1.34 lower to 2.38 higher)	MODERATE	CRITICAL
Change in BMI z score (follow-up: 2 months; Better indicated by higher values)												
1 (Stark 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	33	34	-	MD 0.2 higher (0.02 lower to 0.42 higher)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Behavioural management training + nutritional intervention	Educational intervention alone	Relative (95% CI)	Absolute	Quality	Importance
Change in BMI z score (follow-up: 2 years; Better indicated by higher values)												
1 (Stark 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	28	31	-	MD 0.35 higher (0 to 0.7 higher)	MODERATE	CRITICAL
Change in % ideal body weight (follow-up: 1 years; Better indicated by higher values)												
1 (Powers 2003)	randomised trials	serious2	no serious inconsistency	no serious indirectness	very serious[3]	none	4	3	-	MD 0.91 lower (37.52 lower to 35.7 higher)	VERY LOW	CRITICAL
Change in weight % for age (follow-up: 1 years; Better indicated by higher values)												
1 (Powers 2003)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	4	4	-	MD 0.6 lower (17.25 lower to 16.05 higher)	VERY LOW	CRITICAL
Change in height (cm) (follow-up: 1 years; Better indicated by higher values)												
1 (Powers 2003)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3	4	-	MD 2.03 lower (4.87 lower	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Behavioural management training + nutritional intervention	Educational intervention alone	Relative (95% CI)	Absolute	Quality	Importance
										to 0.81 higher)		
Change in height (cm) (follow-up: 2 years; Better indicated by higher values)												
1 (Stark 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	28	31	-	MD 0.2 lower (1.45 lower to 1.05 higher)	HIGH	CRITICAL
Change in height z score (follow-up: 2 years; Better indicated by higher values)												
1 (Stark 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	28	31	-	MD 0.01 lower (0.17 lower to 0.15 higher)	MODERATE	CRITICAL
Change in FEV_1 % predicted (follow-up: 2 years; Better indicated by higher values)												
1 (Stark 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	13	15	-	MD 5.16 higher (8.49 lower to 18.81 higher)	LOW	CRITICAL
Quality of life												
No evidence available												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Behavioural management training + nutritional intervention	Educational intervention alone	Relative (95% CI)	Absolute	Quality	Importance
Adverse effects												
No evidence available												
Time to next exacerbation												
No evidence available												
Patient or carer satisfaction (follow-up: 2 months; Better indicated by higher values)												
1 (Stark 2009)	randomised trials	serious risk of bias[5]	no serious inconsistency	no serious indirectness	Not calculable	none	33	34	Parents in both groups reported high ratings of satisfaction with treatment (>6 in a 7 point scale)		MODERATE	IMPORTANT

Abbreviations: BMI: body mass index; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; kg: kilogrammes; cm: centimetres; MD: mean difference
1 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
2 The quality of the evidence was downgraded by 1 because of unclear risk of bias in relation to random sequence generation, allocation concealment and incomplete outcome data. Cochrane rated the risk of bias in relation to blinding as high risk however objective measures are unlikely to be influenced by a lack of blinding.
3 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
4 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 clinical MIDs
5 The quality of the evidence was downgraded by 1 due to bad reporting (narrative reporting only)

J.14 Exocrine pancreatic insufficiency

J.14.1 Comparison 1. Acid suppressing agents as adjuvant therapy to PERT

Table 62: Clinical evidence profile: Comparison 1.1. PERT + Cimetidine versus. PERT alone in children

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PERT + Cimetidine	PERT alone	Relative (95% CI)	Absolute	Quality	Importance
Faecal fat excretion (FFE) (follow-up 14 days; measured as: % of intake, or consumed fat that is excreted ; Better indicated by lower values)												
1 (Durie 1980) [2]	randomised trials[1]	very serious [3]	no serious inconsistency	no serious indirectness	Not assessed[4]	none	21 Mean: 17.8±9.74	Mean: 27.6±13.3	-	-	LOW	CRITICAL
Faecal fat excretion (FFE) (follow-up 14 days; measured as: g/ 24hours*; Better indicated by lower values)												
1 (Durie 1980) [2]	randomised trials[1]	serious [5]	no serious inconsistency	very serious indirectness[6]	serious imprecision[7]	none	21		-	MD 11 lower (18.577 to 3.423 lower)	LOW	CRITICAL

Abbreviations: CI: confidence interval; FFE: faecal fat excretion; g: grams; MD: mean difference; PERT: pancreatic endocrine enzyme therapy
1 Cross-over trial
2 Treatment details: Cotazym 26 capsules/ day + Cimetadine 20 mg/kg/day or placebo
3 The quality of evidence was downgraded by 1 due to unclear randomization, concealment and single-blinding. The quality of the evidence was further downgraded by 1 due to the quality of the statistical analysis. Means are provided instead of medians, although it is not normally distributed.
4 Imprecision was not assessed, as it was considered not appropriate. See footnote 3.
5 The quality of evidence was downgraded by 1 due to unclear randomization, concealment and single-blinding.
6 The quality of the evidence was downgraded by 2 because method of measuring fat excreted is inaccurate, as it does not take into account fat intake.
7 The quality of the evidence was downgraded by 1 because the CI crossed 1 clinical MID

Table 63: Clinical evidence profile: Comparison 1.2. PERT + Ranitidine versus. PERT alone in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PERT + Ranitidine	PERT alone	Relative (95% CI)	Absolute		
Fat absorption (CFA) (follow-up 12 days; measured as: % of intake, or consumed fat that is absorbed; Better indicated by higher values) [PERT + low-dose ranitidine]												
1 (Francisco 2002)[2]	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	Not calculable[3]	none[4]	12 Median: 83.60 (74.10 to 89.67) *versus*. 80.37 (72.43 to 89.44)		-	p=0.87*	HIGH	CRITICAL
Fat absorption (CFA) (follow-up 12 days; measured as: % of intake, or consumed fat that is absorbed; Better indicated by higher values) [PERT + high-dose ranitidine]												
1 (Francisco 2002)[5]	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	Not calculable[3]	none[4]	12 Median 80.91 (74.15 to 88.21) *versus*. 80.37 (72.43 to 89.44)		-	p=1*	HIGH	CRITICAL

Abbreviations: CFA: coefficient of fat absorption; CI: confidence interval; MD: mean difference; PERT: pancreatic endocrine enzyme therapy
** The paper provided raw data. Medians and p-values were calculated by the NGA technical team*
1 Cross-over trial
2 Treatment details: low-dose Pancrease M10 or M16 + ranitidine or placebo. Children weighting ≤40 kg were given 5 mg/kg. Children weighting >40 kg received 150 mg. twice daily.
3 Imprecision cannot be calculated from medians.
4 Reporting bias not detected, but drugs were provided by the Pharmaceutical industry
5 Treatment details: high-dose Pancrease M10 or M16 + ranitidine or placebo. Children weighting ≤40 kg were given 10 mg/kg. Children weighting >40 kg received 300 mg. twice daily.

Table 64: Clinical evidence profile: Comparison 1.3. PERT + Omeprazole versus. PERT alone in adults

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PERT + Omeprazole	PERT alone	Relative (95% CI)	Absolute	Quality	Importance
Fat absorption (CFA) (follow-up 12 days; measured with: % of intake or consumed fat that is absorbed; Better indicated by higher values)												
1 (Francisco 2002)[2]	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	Not calculable[3]	Other[4]	9 Median: 87.40 (84.72 to 90.88) *versus*. 88.59 (79.01 to 93.46)		-	p≤0.05 *	MODERATE	CRITICAL
Faecal fat excretion (FFE) (follow-up 4 weeks; measured with: % of intake, or consumed fat that is excreted; Better indicated by lower values) [low-dose PERT + omeprazole or placebo]												
1 (Heijerman 1991)[5]	randomised trials[1]	serious[6]	no serious inconsistency	very serious[7]	Not calculable[8]	Other[9]	9 Median: 14 (6 to 32) *versus*. 20 (12 to 44)		-	p>0.05	VERY LOW	CRITICAL
Faecal fat excretion (FFE) (follow-up 4 weeks; measured with: % of intake, or consumed fat that is excreted; Better indicated by lower values) [high-dose PERT + omeprazole or placebo]												
1 (Heijerman 1991)[10]	randomised trials[1]	serious[6]	no serious inconsistency	very serious[7]	Not calculable[8]	Other[9]	9 Median: 9 (4 to 25) *versus*. 18 (10 to 34)		-	p<0.01	VERY LOW	CRITICAL
Faecal fat excretion (FFE) (follow-up 4 weeks; measured with: % of intake, or consumed fat that is excreted; Better indicated by lower values)												
1 (Heijerman 1993)[11]	randomised trials[1]	no serious risk of bias	no serious inconsistency	very serious[12]	Not calculable[13]	none	11 Median: 17 (4 to 45) *versus*. 20 (12 to 44)		-	p>0.05	LOW	CRITICAL

Abbreviations: CFA: coefficient of fat absorption; CI: confidence interval; FFE: faecal fat excretion; PERT: pancreatic endocrine enzyme therapy
** The paper provided raw data. Medians and p-values were calculated by the NGA technical team*
1 Cross-over trial
2 Treatment details: Pancrease M10 or M16 + omeprazole 20 mg/day or placebo
3 Imprecision cannot be calculated from medians
4 Reporting bias not detected, but drugs were provided by the Pharmaceutical industry. Quality of evidence was downgraded by 1 due to small population (n=9).

5 Treatment details: PERT 2 capsules x 3 times per day + Omeprazole 20mg/day or placebo. Constituent enzymes per capsule 5000u lipase, 2900u lipase, 330u protease. Fat intake was not standardized.
6 The quality of the evidence was downgraded by 1 due to unclear randomization and concealment
7 The quality of the evidence was of evidence downgraded by 2 as this dosage is not used in current practice
8 Imprecision cannot be calculated from medians.
9 Reporting bias not detected. Evidence downgraded by 1 due to small sample size (n=9).
10 Treatment details: PERT 4 capsules x 3 times per day + Omeprazole 20mg/day or placebo. Constituent enzymes per capsule 5000u lipase, 2900u lipase, 330u protease. Fat intake was not standardized.
11 Treatment details: PERT 2 capsules x 3 times per day + Omeprazole 20mg/day or placebo. Constituent enzymes per capsule 5000u lipase, 2900u lipase, 330u protease. Fat intake was not standardized.
12 The quality of the evidence was of evidence downgraded by 2 as this dosage is not used in current practice
13 Imprecision cannot be calculated from medians

Table 65: Clinical evidence profile: Comparison 1.4. PERT + Ranitidine versus. PERT alone in adults

Quality assessment							**No of patients**		**Effect**			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PERT + Ranitidine	PERT alone	Relative (95% CI)	Absolute	**Quality**	**Importance**
Fat absorption (CFA) (follow-up 12 days; measured with: % of intake or consumed fat that is absorbed; Better indicated by higher values) [PERT + low-dose ranitidine]												
1 (Francisco 2002)[2]	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	Not calculable[3]	none[4]	10 Median: 93.06 (84.90 to 96.11) *versus*. 89.20 (79.38 to 93.04)		-	p=0.01*	HIGH	CRITICAL
Fat absorption (CFA) (follow-up 12 days; measured with: % of intake or consumed fat that is absorbed; Better indicated by higher values) [PERT + high-dose ranitidine]												
1 (Francisco 2002)[5]	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	Not calculable[3]	Other[4,6]	9 Median: 88.92 (81.89 to 91.87) *versus*. 88.59 (79.01 to 93.76)		-	p≤0.05*	MODERATE	CRITICAL

Abbreviations: CFA: coefficient of fat absorption; CI: confidence interval; PERT: pancreatic endocrine enzyme therapy
** The paper provided raw data. Medians and p-values were calculated by the NGA technical team*
1 Cross-over study
2 Treatment details: Pancrease M10 or M16 + ranitidine 150 mg. twice daily or placebo

3 Imprecision cannot be calculated from medians.
4 Reporting bias not detected, but drugs were provided by the Pharmaceutical industry
5 Treatment details: Pancrease M10 or M16 + ranitidine 300 mg. twice daily or placebo
6 Reporting bias not detected. Evidence downgraded by 1 due to small sample size (n=9).

J.14.2 Comparison 2. High-dose PERT versus low-dose of PERT

Table 66: Clinical evidence profile: Comparison 2.1. High dose PERT versus low dose PERT in children

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose PERT	Low dose PERT	Relative (95% CI)	Absolute	Quality	Importance
Faecal fat excretion (FFE) (follow-up 14 days; measured with: g/kg/day; Better indicated by lower values)												
1 (Brady 1991)[1]	randomised trials[2]	serious[3]	no serious inconsistency	very serious[4,a]	not calculable[5]	Other[6]	9	-		MD 0.141 lower (0.253 to 0.029 lower)	VERY LOW	CRITICAL
Faecal fat excretion (FFE) (follow-up 14 days; measured with: % of intake , or consumed fat that is excreted; Better indicated by lower values)												
1 (Brady 1991)[1]	randomised trials[2]	serious[3]	no serious inconsistency	very serious[4]	not calculable[5]	Other[6]	9 Mean±SEM[5] 8.7±2.2 *versus* 13±3.06	-		-	VERY LOW	CRITICAL
Faecal fat excretion (FFE) (follow-up 9 days; measured with: g/day; Better indicated by lower values)												
2 (Brady 1991[1], Beker 1994[3])	randomised trials[2]	serious[7]	no serious inconsistency	very serious[4,a]	Not calculable[5]	none	30	-		MD 5 lower (8.877 to 1.123 lower)	VERY LOW	CRITICAL
Faecal fat excretion (FFE) (follow-up 4 weeks; measured with: g/day; Better indicated by lower values)												
1	randomised trials[2]	serious[9]	no serious inconsistency	very serious[4,a]	serious[10]	none[11]	12 Mean±SD[9]	-		ns	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose PERT	Low dose PERT	Relative (95% CI)	Absolute	Quality	Importance
(Mitchell 1982)[8]							8.7±4.1 *versus*. 11.5±6.9					
Fat absorption (CFA) (follow-up 4 weeks; measured with: % of intake or consumed fat that is absorbed; Better indicated by higher values)												
1 (Mitchel 1982)[8]	randomised trials[2]	serious[9]	no serious inconsistency	very serious[4]	very serious[12]	none[11]	12 Mean±SEM[11] 89.5±4.2 *versus*. 85.4±11.26		-	-	VERY LOW	CRITICAL
Fat absorption (CFA) (follow-up 9 days; measured with: % of intake; Better indicated by higher values)												
1 (Beker 1984)[3]	randomised trials[2]	serious[13]	no serious inconsistency	very serious[4]	very serious[12]	none[14]	21 Mean±SEM[11] 91.2±1.6 *versus*. 86.2±3.2		-		VERY LOW	CRITICAL
Stool frequency (follow-up 4 weeks; measured with: bowel movements/ day, self-report; Better indicated by lower values)												
1 (Mitchel 1982)[8]	randomised trials[2]	serious[9]	no serious inconsistency	very serious[4]	no serious imprecision	none[11]	12			MD 0.1 lower (0.189 lower to 0.011 higher)	VERY LOW	CRITICAL
Abdominal pain (follow-up 4 weeks; assessed with: self-report; Better indicated by lower values)												
1 (Mitchell 1982)[8]	randomised trials[2]	serious[9]	no serious inconsistency	very serious[4]	Not calculable[15]	none[11]	12		-	The study reports that there were no differences between the groups[15]	VERY LOW	CRITICAL
							-	-				

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose PERT	Low dose PERT	Relative (95% CI)	Absolute	Quality	Importance
Adverse events (constipation, elevation in serum uric acid levels) (follow-up 9 days; assessed with: self-report; Better indicated by lower values)												
1 (Beker 1994)[3]	randomised trials[2]	serious[1] [3]	no serious inconsistency	very serious[4]	Not calculable[15]	none[14]	0/21 (0%)	0/21 (0%)	-	No episodes were observed[15]	VERY LOW	CRITICAL

Abbreviations: CFA: coefficient of fat absorption; CI: confidence interval; FFE: faecal fat excretion; g: grams; kg: kilogrammes; MD: mean difference; ns: not significant; PERT: pancreatic endocrine enzyme therapy; SEM: standard error of measurement
a. The method of measuring fat excreted is inaccurate, as it does not take into account fat intake. The evidence could not be downgraded further for indirectness.
1 Cross-over trial
2 Treatment details: high-dose 12 (8 to 18) & low-dose 3 (2 to 5) capsules per meal. Constituent enzymes per capsule: 7.020u of lipase. Daily fat intake (g) 94±6 in both groups.
3 Treatment details: high-dose: 1500u lipase per kg/body for meals & 750u lipase per kg/body for snacks. Low-dose: 500u lipase per kg/body for meals & 250u lipase per kg/body for snacks. Daily fat intake (g): 100g in both groups.
4 The quality of the evidence was downgraded by 2 as these doses are not used in current practice. Low-dose is in fact very low dose, and high-dose is just low-dose
5 Imprecision could not be calculated, as SD was not available for the control group
6 Reporting bias not detected, although funding not reported. Evidence downgraded by 1 due to small sample (n=9)
7 The quality of the evidence was downgraded by 1 due to unclear randomization and concealment in both studies.
8 Treatment details: high-dose 22 capsules/day & low-dose 11 capsules/ day Pancrease®. Constituent enzymes per capsule 4,000 USNF lipase units; 25,000 USNF protease units; 20,000 amylase units.
9 The quality of the evidence was downgraded by 1 due to unclear randomization and concealment. It is unclear if blinding was done, but given the outcome this may not have an impact.
10 The quality of the evidence was downgraded by 1 as the results are poorly reported: authors do not report p-value and MD cannot be calculated
11 Reporting bias not detected, although Pancrealipase capsules were provided by Ethnor Pty Ltd.
12 The quality of the evidence was downgraded by 2 due to the quality of the statistical analysis. Means are provided instead of medians, although it is not normally distributed, therefore differences cannot be calculated as it is not appropriate.
13 The quality of the evidence was downgraded by 1 because it is an open-label study.
14 Reporting bias not detected, although the study is partly funded by a grant from Johnson Pharmaceutical.
15 Imprecision cannot be calculated.

Table 67: Clinical evidence profile: Comparison 2.2. High dose PERT versus low dose PERT in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose PERT	Low dose PERT	Relative (95% CI)	Absolute		
Faecal fat excretion (FFE) (follow-up 14 days; measured with: % of intake, or consumed fat that is excreted; Better indicated by lower values)												
1 (Heijerman 1991)[2]	randomised trials[1]	serious[3]	no serious inconsistency	very serious[4]	Not calculable[5]	other[6]	9 Median: 18 (10 to 34) *versus*. 20 (12 to 44)		-	p>0.05	VERY LOW	CRITICAL

Abbreviations: CI: confidence interval; FFE: faecal fat excretion;; PERT: pancreatic endocrine enzyme therapy
1 Cross-over trial
2 Treatment details: high-dose 4 capsules x 3 times per day & low-dose 2 capsules x 3 times per day. Constituent enzymes per capsule 5000u lipase, 2900u lipase, 330u protease. Fat intake was not standardized.
3 The quality of the evidence was downgraded by 1 due to unclear randomization and concealment.
4 The quality of the evidence was downgraded by 2 as these doses are not used in current practice. Low-dose is in fact very low dose, and high-dose is just low-dose
5 Imprecision cannot be calculated from medians
6 Reporting bias not detected. Evidence downgraded by 1 due to small sample size (n=9).

J.15 Distal intestinal obstruction syndrome

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

J.16 Liver disease

J.16.1 Review question 1. What is the diagnostic accuracy of tests to detect/ strategies to detect early and late CF liver disease?

J.16.1.1 Target condition: cystic fibrosis liver disease (CFLD) (including cirrhosis)

Table 68: Test 16. Index test (Transient elastography) versus practice guideline CFLD definition† to detect CFLD

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
Test 16. Transient elastography using Fibroscan 5.5kPa cut off in a population of adults and children												
1 (Rath 2012)	Cohort study	136	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	52.7 (95% CI: 44.9-58.9)*	82.3 (95% CI: 72.9-89.7)*	2.97 (95% CI: 1.65-5.70)*	0.58 (95% CI: 0.46-0.76)*	0.68 (95% CI: 0.59-0.77)	HIGH
Test 16. Subgroup analysis: Transient elastography using Fibroscan @ 5.5kPa cut off in a population of adults												
1 (Rath 2012)	Cohort study	61	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	55.2 (95% CI: 40.7-66.8)*	78.1 (95% CI: 65.0-88.7)*	2.52 (95% CI: 1.16-5.89)*	0.57 (95% CI: 0.38-0.91)*	0.69 (95% CI: 0.56-0.81)	HIGH
Test 16. Subgroup analysis:Transient elastography using Fibroscan @ 5.5kPa cut off in a population of children												
1 (Rath 2012)	Cohort study	75	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	53.3 (95% CI: 43.2-61.2)*	76.7 (95% CI: 61.4-88.4)*	2.29 (95% CI: 1.12-5.28)*	0.61 (95% CI: 0.44-0.93)*	0.68 (95% CI: 0.56-0.81)	HIGH

Abbreviations: AST: aminotransferase; ALT: alanine aminotransferase; AUROC: area under the curve; CFLD: cystic fibrosis liver disease; CI: confidence interval; kPA: kilopascal
†Diagnosis of CFLD was established according to published guidelines (Debray 2011) if least 2 of the following conditions on at least 2 consecutive examinations spanning a 1-year period were present: (i) Hepatomegaly (liver span >2 cm below the costal margin on the medioclavicular line) confirmed by ultrasound, (ii) 2 abnormal serum liver enzyme levels (ALT, AST, γGT > ULN), (iii) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins).
** Calculated by the NGA technical team from data available in the study report*

Table 69: Tests 8 & 13. Index tests (Ultrasound and Transient elastography) versus Clinical CFLD definition† to detect CFLD

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
Test 8. Ultrasound (cut off value Williams score ≥ 4) in a population of adults and children												
1 (Witters 2009)	Cohort study	66	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious imprecision [a]	66.7 (95% CI: 25.0-93.9)*	66.7 (95% CI: 62.5-69.4)*	2.0 (95% CI: 0.67-3.07)*	0.50 (95% CI: 0.09-1.2)*	0.77 (95% CI: 0.51-1.02)	LOW
Test 13. Transient elastography using Fibroscan (Age-specific cut-off values at 5.63kPa for <12 years and 6.50kPa for ≥12 years) in a population of adults and children												
1 (Witters 2009)	Cohort study	66	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious imprecision [a]	83.3 (95% CI: 38.7-99.1)*	85.0 (95% CI: 80.5-86.6)*	5.6 (95% CI: 2.0-7.4)*	0.20 (95% CI: 0.01-0.76)*	0.93 (95% CI: 0.85-1.01)	LOW

Abbreviations: AUROC: area under the curve; CFLD: cystic fibrosis liver disease; CI: confidence interval; kPA: kilopascal
†Diagnosis of CFLD according to the presence or absence of hepatomegaly or splenomegaly determined by clinical examination
** Calculated by the NGA technical team from data available in the study report*
a. 95% confidence interval for sensitivity was very wide (width ≥30%)

Table 70: Tests 9 & 14. Index tests (Ultrasound and Transient elastography) versus Biochemical CFLD† definition to detect CFLD

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
Test 9. Ultrasound (cut off of Williams score ≥ 4) in a population of adults and children												
1 (Witters 2009)	Cohort study	66	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious imprecision[a]	50.0 (95% CI: 14.3-85.6)*	66.7 (95% CI: 63.1-70.2)*	1.5 (95% CI: 0.39-2.88)*	0.75 (95% CI: 0.21-1.36)*	0.62 (95% CI: 0.40-0.84)	LOW
Test 14. Transient elastography using Fibroscan (Age-specific cut-off values at 5.63kPa for <12 years and 6.50kPa for ≥12 years) in a population of adults and children												
1 (Witters 2009)	Cohort study	66	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious imprecision[a]	50.0 (95% CI: 14.5-85.3)*	83.3 (95% CI: 79.8-86.9)	3.0 (95% CI: 0.72-6.5)*	0.60 (95% CI: 0.17-1.07)*	0.78 (95% CI: 0.61-0.95)	LOW

Abbreviations: AUROC: area under the curve; CFLD: cystic fibrosis liver disease; CI: confidence interval; kPA: kilopascal
†Diagnosis of CFLD was defined as persistently elevated results (3–6 months, 1.5 times age-dependent upper limit of normal) for 2 of these liver tests: AST, ALT, alkaline phosphatase, bilirubin and gamma-GT.
** Calculated by the NGA from data available in the study report*
a. 95% confidence interval for sensitivity was very wide (width ≥30 percentage points)

Table 71: Tests 10 & 15. Index test (Ultrasound) versus Clinical and/or biochemical definition† to detect CFLD

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % 95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
Test 10. Ultrasound (cut off of Williams score ≥ 4) in a population of adults and children												

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % 95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
1 (Fagundes 2004)[a]	Cohort study	70	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[b]	50.0 (95% CI: 22.0-75.1)*	91.7 (95% CI: 87.0-95.8)*	6.0 (95% CI: 1.70-18.07)*	0.55 (95% CI: 0.26-0.90	Not reported	MODERATE
1(Witters 2009)[c]	Cohort study	66	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[b]	63.6 (95% CI: 33.6-87.0)*	70.9 (95% CI: 64.9-75.6)*	2.19 (95% CI: 0.96-3.56)*	0.51 (95% CI: 0.17-1.02)*	0.70 (95% CI: 0.51-0.89)	MODERATE
Test 15. Transient elastography using Fibroscan (Age-specific cut-off values at 5.63kPa for <12 years and 6.50kPa for ≥12 years in a population of adults and children												
1 (Witters 2009)[c]	Cohort study	66	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[b]	63.6 (95% CI: 34.4-86.0)*	87.3 (95% CI: 81.4-91.8)*	5.0 (95% CI: 1.86-10.43)*	0.42 (95% CI: 0.15-0.81)*	0.86 (95% CI: 0.74-0.98)	MODERATE

Abbreviations: AUROC: area under the curve; CFLD: cystic fibrosis liver disease; CI: confidence interval; kPA: kilopascal
†Diagnosis of CFLD was defined using clinical and biochemical criteria.
** Calculated by the NGA technical team from data available in the study report*
a. Diagnosis of CFLD: Abnormal clinical examination: the presence of a palpable spleen and/or hepatomegaly (presence of a palpable liver more than 2.5 cm below the right costal margin of firm consistency). Abnormal biochemistry: a significant and persistent increase, of at least 1.5 times the upper limit of the reference range, of at least 2 of the enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP) or gamma-glutamyl transpeptidase (GGT), for a period of more than 6 months
b. 95% confidence interval for sensitivity was wide (width 20-30 percentage points)
c. The North-American cystic fibrosis foundation (CFF) consensus workgroup definition of CFLD: the presence of either clinical or biochemical liver disease. Clinical liver disease was defined as the presence of hepatomegaly or splenomegaly. Biochemical liver disease was defined as persistently elevated results (3–6 months, 1.5 times age-dependent upper limit of normal) for 2 of these liver tests: AST, ALT, alkaline phosphatase, bilirubin and gamma-GT

Table 72: Test 2. Index tests (ALT, AST, GGT) versus Ultrasound definition† to detect CFLD

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % 95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
Test 2. ALT using an unspecified cutoff in a population of children												
1 (Patriquin 1999)	Cohort study	195	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	63.2 (95% CI: 48.0-76.3)*	79.0 (95% CI: 75.3-82.2)*	3.0 (95% CI: 1.95-4.28)*	0.47 (95% CI: 0.29-0.69)*	Not reported	HIGH
Test 2. AST using an unspecified cutoff in a population of children												
1 (Patriquin 1999)	Cohort study	195	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	47.4 (95% CI: 33.4-60.6)*	87.9 (95% CI: 84.5-91.1)*	3.91 (95% CI: 2.16-6.80)*	0.60 (95% CI: 0.43-0.79)*	Not reported	HIGH
Test 2. GGT using an unspecified cutoff in a population of children												
1 (Patriquin 1999)	Cohort study	195	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	50.0 (95% CI: 36.2-62.4)*	90.4 (95% CI: 87.1-93.4)*	5.23 (95% CI: 2.80-9.53)*	0.55 (95% CI: 0.40-0.73)*	Not reported	HIGH

Abbreviations: AST: aminotransferase, ALT: alanine aminotransferase, AUROC: area under the ROC curve; CFLD: cystic fibrosis liver disease; CI: confidence interval; GGT: gamma glutamyltransferase

** Calculated by the NGA from data available in the study report*

†Diagnosis of CFLD: Ultrasound signs were interpreted as follows: hypoechogenicity with prominent portal tracts as oedema, hyperechogenicity as steatosis, hyperechogenicity with increased attenuation and nodules within or at the edge of the liver as cirrhosis. Signs of portal hypertension also were sought and Doppler US used to assess presence and direction of blood flow and detection of oesophageal varices.

Table 73: Tests 5-7 & 17. Index tests (ALP, APRI, Forns score and Transient Elastography) versus practice guideline CFLD definitions† to detect CFLD

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
Test 5. ALP using laboratory determined age and gender specific cutoffs in a population of children and adults												
1 (Rath 2013)[a]	Cohort study	45	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[b]	70.6 (95% CI: 49.5-85.5)*	82.1 (95% CI: 69.3-91.2)*	3.95 (95% CI: 1.61-9.74)*	0.36 (95% CI: 0.16-0.73)*	0.61 (95% CI: 0.44-0.79)	MODERATE
Test 6. APRI using a cut off of 0.133 in a population of children and adults												
1 (Rath 2013)[a]	Cohort study	45	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	47.1 (95% CI: 28.2-56.7)*	93.1 (95% CI: 82.0-98.7)*	6.82 (95% CI: 1.57-44.7)*	0.57 (95% CI: 0.44-0.88)*	0.75 (95% CI: 0.58-0.91)	HIGH
Test 6. APRI using a cut off of 0.231 in a population of adults												
1 (Karlas 2012)[c]	Cohort study	55	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[b]	85.7 (95% CI: 60-97.4)*	70.7 (95% CI: 62.0-74.7)*	2.93 (95% CI: 1.58-3.86)*	0.20 (95% CI: 0.04-0.65)*	0.82 (95% CI: 0.69-0.91)	MODERATE
Test 6. APRI using a cut off of 0.4 in a population of adults												
1(Sadler 2015)[d]	Cohort study	122	serious[e]	no serious inconsistency	no serious indirectness	serious imprecision[b]	50 (95% CI: 29-69)*	92 (95% CI: 88-95)*	6.06 (95% CI:	0.55 (95% CI:	0.70 (95% CI:	LOW

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
									2.48-13.50)*	0.33-0.80)*	0.54-0.86)	
Test 6. APRI using a cut off of 0.5 in a population of adults												
1(Sadler 2015)[d]	Cohort study	122	serious[e]	no serious inconsistency	no serious indirectness	serious imprecision[b]	50 (95% CI: 29-68)*	94 (95% CI: 90-97)*	7.79 (95% CI: 2.99-19.44)*	0.53 (95% CI: 0.33-0.78)*	Not reported	LOW
Test 7. Forns score using a cut off of >2.154 in a population of adults												
1 (Karlas 2012)[c]	Cohort study	55	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[b]	92.9 (95% CI: 67.8-99.6)*	61.0 (95% CI: 52.4-63.3)*	2.38 (95% CI: 1.43-2.71)*	0.12 (95% CI: 0.006-0.61)*	0.79 (95% CI: 0.65-0.89)	MODERATE
Test 17. Transient elastography using Fibroscan at a cut off of 3.7kPa in a population of adults												
1(Sadler 2015)[d]	Cohort study	127	serious[e]	no serious inconsistency	no serious indirectness	serious imprecision[b]	89 (95% CI: 66-98)*	37 (95% CI: 33-38)*	1.40 (95% CI: 0.98-1.59)*	0.30 (95% CI: 0.05-1.04)*	Not reported	LOW
Test 17. Transient elastography using Fibroscan at a cutoff of 5.3kPa in a population of adults												
1(Sadler 2015)[d]	Cohort study	127	serious[e]	no serious inconsistency	no serious indirectness	serious imprecision[b]	67 (95% CI: 43-85)*	83 (95% CI: 79-86)*	3.83 (95% CI:	0.40 (95% CI: 0.18-0.72)*	0.78 (95% CI: 0.65-0.92)	LOW

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
									2.04-5.87)*			
Test 17. Transient elastography using Fibroscan at a cutoff of 5.9kPa in a population of adults												
1 (Karlas 2012)[c]	Cohort study	49	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[b]	42.9 (95% CI: 22.6-49.6)*	97.1 (95% CI: 89.0-99.8)*	15.0 (95% CI: 2.06-328.3)*	0.59 (95% CI: 0.51-0.87)*	0.68 (95% CI: 0.53-0.80)	MODERATE
Test 17. Transient elastography using Fibroscan at a cutoff of 6.0kPa in a population of adults												
1(Sadler 2015)[d]	Cohort study	127	serious[e]	no serious inconsistency	no serious indirectness	serious imprecision[b]	56 (95% CI: 34-75)*	91 (95% CI: 87-94)*	6.06 (95% CI: 2.65-12.32)*	0.49 (95% CI: 0.27-0.76)*	Not reported	LOW
Test 17. Transient elastography using Fibroscan at a cutoff of 6.3kPa in a population of children and adults												
1 (Rath 2013)[a]	Cohort study	45	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	82.4 (95% CI: 64.2-85.3)*	98.2 (95% CI: 87.4-100)*	46.9 (95% CI: 5.1-25489647)*	0.18 (95% CI: 0.15-0.41)*	0.91 (95% CI: 0.78-1.00)	HIGH
Test 17. Transient elastography using Fibroscan at a cutoff of 6.8kPa in a population of adults												
1 (Kitson 2013)[f]	Case Control study	50	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	76 (95% CI: 61.6-82.5)*	92 (95% CI: 77.6-98.5)*	9.5 (95% CI:	0.26 (95% CI: 0.18-0.50)*	0.87 (95% CI: 0.77-0.98)	LOW

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
									2.75-55.6)*			

Abbreviations: ALP: Alkaline phosphatase; APRI: Aspartate aminotransferase to Platelets-Ratio-Index; AUROC: area under the ROC curve; CFLD: cystic fibrosis liver disease; CI: confidence interval; kPA: kilopascal

†Practice guideline definitions included criteria for clinical, biochemical and ultrasound testing.

** Calculated by the NGA technical team from data available in the study report*

a. Rath 2013 Diagnosis of CFLD (Flume 2007, Kerem 2005) if least 2 of the following conditions on at least 2 consecutive examinations spanning a 1-year period were present: (i) Hepatomegaly (liver span >2 cm below the costal margin on the medioclavicular line) confirmed by ultrasound, (ii) 2 abnormal serum liver enzyme levels (ALT, AST, γGT > ULN), (iii) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins).

b. 95% confidence interval for sensitivity was wide (width 20-30 percentage points)

c. Karlas 2012 Diagnosis of CFLD (Sokol 1999, Colombo 2002) if at least 2 of the following conditions present on at least 2 consecutive examinations spanning a 1-year period: (1) Ultrasound confirmed hepatomegaly;(2) elevated serum liver enzyme levels of ALT, AST, AP, or GGT;(3) ultrasound abnormalities other than hepatomegaly (i.e., increased, heterogeneous echogenicity, nodularity, irregular margins, splenomegaly).

d. Sadler 2015 Diagnosis of CFLD (Colombo 2002, Debray 2011) if least 2 of the following conditions were present: (i) Hepatomegaly and/or splenomegaly confirmed by ultrasonography, (ii) abnormal liver biochemistry consisting of elevated levels of any 2 of ALT, AST, or GGT, (iii) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins, splenomegaly presence).

e. High risk of bias being introduced from the patient flow

f. Kitson 2013 Diagnosis of CFLD (Colombo 2002, Debray 2011) if least 2 of the following conditions on consecutive examinations spanning a 1-year period were present:(i) Hepatomegaly and/or splenomegaly confirmed by ultrasound;(ii) abnormal serum liver enzyme levels, consisting of elevation above the upper limit of normal of 2 of the following: ALT, AST, GGT;(iii) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins; splenomegaly; presence of porto-systemic collateral veins; ascites).

Table 74: Tests 1, 3, 4, 11, 19 & 20. Index tests (Clinical examination, biochemical testing and/or ultrasound) versus Biopsy CLFD definitions† to detect CFLD

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
Test 1. Clinical examination[a] to detect F1-F4 fibrosis in a population of children												

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
1 (Lewindon 2011)	Cohort study	40	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	68 (95% CI: 61-77)*	33 (95% CI: 10-65)*	1.02 (95% CI: 0.67-2.23)*	0.97 (95% CI: 0.35-4.11)*	0.51 (95% CI: not reported)	HIGH
Test 4. ALT[b] to detect F1-F4 fibrosis in a population of children												
1 (Lewindon 2011)	Cohort study	40	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[c]	30 (95% CI: 0-0.60)*	98 (95% CI: 96-100)*	1.34 (95% CI: 0-1408086.43)*	0.99 (95% CI: 0.94-1.04)*	0.59 (95% CI: not reported)	MODERATE
Test 3. Liver function tests[d] to detect moderate or severe fibrosis and cirrhosis and/or moderate to severe steatosis in a population of children and adults												
1 (Lindblad 1999)	Cohort study	41	serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	83 (95% CI: 68-94)*	44 (95% CI: 26-58)*	1.49 (95% CI: 0.92-2.25)*	0.39 (95% CI: 0.11-1.22)*	not reported	MODERATE
Test 3. Liver function tests[d] to detect moderate or severe fibrosis and cirrhosis in a population of children and adults												
1 (Lindblad 1999)	Cohort study	41	serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[c]	100 (95% CI: 78-100)*	44 (95% CI: 33-44)*	1.8 (95% CI: 1.17-1.8)*	0 (95% CI: 0-0.67)*	not reported	LOW
Test 11. Ultrasound[e] to detect F1-F4 fibrosis in a population of children												
1 (Lewindon 2011)	Cohort study	40	no serious	no serious inconsistency	no serious indirectness	no serious imprecision	81 (95% CI: 73-89)*	44 (95% CI: 17-73)*	1.45 (95% CI:	0.44 (95% CI:	0.63 (95% CI: not	HIGH

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
			risk of bias						0.87-3.3)*	0.15-1.64)*	reported)	
Test 11. Ultrasound[f] to detect F1-F4 fibrosis in a population of children												
1 (Mueller Abt 2008)	Cohort study	30	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	65 (95% CI: 55-74)*	57 (95% CI: 22-87)*	1.52 (95% CI: 0.7-5.78)*	0.61 (95% CI: 0.29-2.06)*	not reported	HIGH
Test 11. Ultrasound[g] to detect moderate or severe fibrosis and cirrhosis and/or moderate to severe steatosis in a population of children and adults												
1 (Lindblad 1999)	Cohort study	41	serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	70 (95% CI: 54-80)*	78 (95% CI: 58-92)*	3.13 (95% CI: 1.3-9.5)*	0.39 (95% CI: 0.22-0.8)*	not reported	MODERATE
Test 11. Ultrasound[g] t detect moderate or severe fibrosis and cirrhosis in a population of children and adults												
1 (Lindblad 1999)	Cohort study	41	serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[c]	86 (95% CI: 61-97)*	70 (95% CI: 58-76)*	2.9 (95% CI: 1.45-4.13)*	0.2 (95% CI: 0.03-0.67)*	not reported	LOW
Test 19. Liver function tests[d] and ultrasound[f] to detect moderate or severe fibrosis and cirrhosis and/or moderate to severe steatosis in a population of children and adults												
1 (Lindblad 1999)	Cohort study	41	serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	65 (95% CI: 50-76)*	78 (95% CI: 58-92)*	2.94 (95% CI:	0.45 (95% CI:	not reported	MODERATE

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
									1.18-9.1)*	0.26-0.87)*		
Test 19. Liver function tests[d] and ultrasound[f] to detect moderate or severe fibrosis and cirrhosis in a population of children and adults												
1 (Lindblad 1999)	Cohort study	41	serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[c]	86 (95% CI: 62-97)*	74 (95% CI: 62-80)*	3.31 (95% CI: 1.6-4.9)*	0.19 (95% CI: 0.03-0.63)*	not reported	LOW
Test 20. Clinical examination[a], liver function tests[b] and ultrasound[e] to detect F1-F4 fibrosis in a population of children												
1 (Lewindon 2011)	Cohort study	40	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	97 (95% CI: 85-100)*	13 (95% CI: 4-15)*	1.12 (95% CI: 0.89-1.18)*	0.22 (95% CI: 0-3.6)*	0.69 (95% CI: not reported)	HIGH
Test 20. Clinical examination[a], liver function tests[b] and ultrasound[e] to detect F2-F4 significant fibrosis in a population of children												
1 (Lewindon 2011)	Cohort study	40	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[c]	82 (95% CI: 62-95)*	48 (95% CI: 33-57)*	1.58 (95% CI: 0.93-2.22)*	0.37 (95% CI: 0.09-1.15)*	0.68 (95% CI: not reported)	MODERATE

Abbreviations: ALT: alanine transferase; AUROC: area under the ROC curve; CFLD: cystic fibrosis liver disease; CI: confidence interval
† Biopsy sampling was interpreted using Scheuer Scores in Lewindon 2011 and Mueller-Abt 2008. In Lindblad 1999 biospy samples were evaluated regarding fibrosis (normal; slight, enlarged portal zones; moderate, tendency towards septa formation; severe, bridging fibrosis; and cirrhosis, complete septa with regenerative noduli). Steatosis, bile duct proliferation, and inflammation were classified as absent, slight, moderate, or severe. A minimum of 4 portal zones were evaluated in each biopsy..
** Calculated by the NGA technical team from data available in the study report*
a. Clinical liver examination was to identify hepatomegaly with or without splenomegaly
b. Serum ALT levels were performed at enrolment. An abnormal result occurred at >1.5 upper limit of normal
c. 95% confidence interval for sensitivity was wide (width 20-30 percentage points)
d. Liver function tests included ALT, AST and GGT which had upper reference levels of 0.8, 0.8 and 0.5 µkata/ respectively.

e. Ultrasound liver images were recorded as nodular edge, nodular, heterogeneous, or normal echogenicity with or without splenomegaly. A normal ultrasound was defined as normal echogenicity with no splenomegaly. Ultrasound evidence of PHT included a nodular liver with splenomegaly.
f. Ultrasound images were categorised as normal, indeterminate (suggestion of liver disease but no definite signs of cirrhosis) and cirrhosis. Increased hepatic echogenicity, heterogeneity and/or increased attenuation in the absence of nodularity of the liver surface were classified as indeterminate. Splenomegaly as an isolated finding was also regarded as indeterminate. All patients with nodularity of the liver surface were classified as cirrhosis.
g. Ultrasonography was characterized as normal or pathological (increased and/or irregular echogenicity).

Table 75: Tests 12 & 18. Index tests (Transient Elastography or MRI) versus liver function tests or ultrasound abnormalities† to detect CFLD

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
Test 12. Transient elastography to detect F2-F4[a] in a population of adults												
1 (Lemaitre 2016)	Cohort study	23	serious risk of bias[b]	no serious inconsistency	no serious indirectness	very serious imprecision[c]	75 (95% CI: 24.2-98.6)*	84.2 (95% CI: 73.5-89.2)*	4.75 (95% CI: 0.91-9.12)*	0.30 (95% CI: 0.02-1.03)*	Not reported	VERY LOW
Test 18. MRI to detect at least 1 abnormal sign[d] in a population of adults												
1 (Lemaitre 2016)	Cohort study	23	serious risk of bias[b]	no serious inconsistency	no serious indirectness	very serious imprecision[c]	36.4 (95% CI: 14.7-51.1)*	83.3 (95% CI: 63.5-96.8)*	2.18 (95% CI: 0.40-16.06)*	0.76 (95% CI: 0.50-1.34)*	Not reported	MODERATE

Abbreviations: AUROC: area under the ROC curve; CFLD: cystic fibrosis liver disease; CI: confidence interval; MRI: magnetic resonance
† Details not reported
** Calculated by the NGA technical team from data available in the study report*
a. Results were expressed in kilopascal (kPa) using the Metavir scoring system based on previous study of transient elastography in chronic biliary disease (Corpechot 2006): Metavir F0-F1 score corresponded to LSM of ≥7.2 kPa, and F2, F3, and F4 corresponded to ≥7.3 kPa, 9.8 kPa, and 17.3 kPa, respectively
b. It is unclear how the reference standard was conducted and interpreted; it is also unclear whether index and reference tests were conducted at the same time
c. 95% confidence interval for sensitivity was very wide (width ≥30 percentage points)
d. The following items were studied for each patient using a standardized scale: atrophy of either right or left hepatic lobe and/or hypertrophy of the caudate lobe, marked lobulations of liver surface, first-segment hypertrophy, splenomegaly (long axis superior to 12 cm), portal vein dilatation (diameter superior to 12 mm), splenic vein dilatation, intrahepatic or extrahepatic biliary duct irregularity (segmental strictures and dilatations), ascites, and steatosis.

J.16.1.2 Target condition: Cirrhosis

Table 76: Tests 1, 2 and 4. Index tests (APRI, Forn's score and Transient Elastography) versus clinical and ultrasound cirrhosis definition to detect cirrhosis in a population with CFLD (practice guideline defined) †

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
Test 1. APRI using a cut off of 0.344 in a population of adults with CFLD												
1 (Karlas 2012)	Cohort study	14	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious imprecision[a]	83.3 (95% CI: 45.0-98.5)*	87.5 (95% CI: 58.8-98.9)*	6.67 (95% CI: 1.09-88.5)*	0.19 (95% CI: 0.02-0.94)*	0.88 (95% CI: 0.59-0.99)	LOW
Test 2. Forn's score using a cut off of 4.059 in a population of adults with CFLD												
1 (Karlas 2012)	Cohort study	14	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious imprecision[a]	66.7 (95% CI: 30.1-75.0)*	94.1 (95% CI: 68.3-100)*	11.3 (95% CI: 0.95-6684670)*	0.35 (95% CI: 0.25-1.02)*	0.85 (95% CI: 0.57-0.98)	LOW
Test 4. Transient elastography using a cut off of 4.4kPa in a population of adults with CFLD												
1 (Karlas 2012)	Cohort study	14	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious imprecision[a]	92.3 (95% CI: 56.2-100)*	75 (95% CI: 45.7-81.2)*	3.69 (95% CI: 1.04-5.33)*	0.10 (95% CI: 0-0.96)*	0.88 (95% CI: 0.59-0.99)	LOW

Abbreviations: AUROC: area under the ROC curve; APRI: Aspartate aminotransferase to Platelets-Ratio-Index; CFLD: cystic fibrosis related disease; CI: confidence interval
†Diagnosis of CFLD (Sokol 1999, Colombo 2002) if at least 2 of the following conditions present on at least 2 consecutive examinations spanning a 1-year period: (1) Ultrasound confirmed hepatomegaly;(2) elevated serum liver enzyme levels of ALT, AST, AP, or GGT;(3) ultrasound abnormalities other than hepatomegaly (i.e., increased, heterogeneous echogenicity, nodularity, irregular margins, splenomegaly). Liver cirrhosis: distinct ultrasonographic signs (i.e. coarse nodularity, presence of portal hypertension and rarefication of peripheral portal veins) and clinical signs (e.g. esophageal varices, splenomegaly)
** Calculated by the NGA technical team from data available in the study report*
a. 95% confidence interval for sensitivity was very wide (width ≥30 percentage points)

Table 77: Test 3. Index test (Ultrasound) versus biopsy definition to detect cirrhosis

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
Test 3. Ultrasound[a] to detect F1-F4 fibrosis in a population of children												
1 (Mueller-Abt 2008)	Cohort study	30	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[b]	0.57 (95% CI: 0.36-0.64)*	0.94 (95% CI: 0.75-1.00)*	9.14 (95% CI: 1.47-192.8)*	0.46 (95% CI: 0.36-0.85)*	Not reported	MODERATE

Abbreviations: AUROC: area under the ROC curve; CFLD: cystic fibrosis liver disease; CI: confidence interval
** Calculated by the NGA technical team from data available in the study report*
a. Ultrasound images were categorised as normal, indeterminate (suggestion of liver disease but no definite signs of cirrhosis) and cirrhosis. Increased hepatic echogenicity, heterogeneity and/or increased attenuation in the absence of nodularity of the liver surface were classified as indeterminate. Splenomegaly as an isolated finding was also regarded as indeterminate. All patients with nodularity of the liver surface were classified as cirrhosis.
b. 95% confidence interval for sensitivity was wide (width 20-30 percentage points)

J.16.1.3 Target condition: portal hypertension

Table 78: Tests 1 to 3. Index tests (APRI, Forn's score, transient elatography) versus clinical definition to detect portal hypertension†

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
Test 1. APRI at a cut off of ≥ 0.49 in a population of adults												
1(Kitson 2013)	Case control study	50	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	87.5 (95% CI: 52.0-99.3)*	92.9 (95% CI: 86.1-95.1)*	12.3 (95% CI: 3.74-20.3)*	0.14 (95% CI: 0.01-0.56)*	0.97 (95% CI: 0.93-1.00)	LOW

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
Test 1. Subgroup analysis: APRI at a cut off of ≥ 0.49 in a population of adults with CFLD												
1(Kitson 2013)	Case control study	25	no serious risk of bias of bias	no serious inconsistency	no serious indirectness	no serious imprecision	87.5 (95% CI: 54.8-98.9)*	94.1 (95% CI: 78.7-99.5)*	14.9 (95% CI: 2.6-189.4)*	0.13 (95% CI: 0.01-0.58)*	0.98 (95% CI: 0.93-1.00)	LOW
Test 2. Forn's at a cut off of ≥ 0.68 in a population of adults												
1(Kitson 2013)	Case control study	50	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	87.5 (95% CI: 50.7-99.3)*	85.7 (95% CI: 78.7-88.0)*	6.13 (95% CI: 2.38-8.26)*	0.15 (95% CI: 0.01-0.63)*	0.93 (95% CI: 0.85-1.00)	LOW
Test 2. Subgroup analysis: Forn's score at a cut off of ≥ 0.68 in a population of adults with CFLD												
1(Kitson 2013)	Case control study	25	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	87.5 (95% CI: 53.2-99.3)*	82.4 (95% CI: 66.2-87.9)*	5.0 (95% CI: 1.6-8.2)*	0.15 (95% CI: 0.01-0.71)*	0.93 (95% CI: 0.82-1.00)	LOW
Test 3. Transient elastography at a cut off of ≥ 8.9 kPa in a population of adults												
1(Kitson 2013)	Case control study	50	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	87.5 (95% CI: 51.4-99.3)*	90.5 (95% CI: 83.6-92.7)*	9.19 (95% CI: 3.14-13.66)*	0.14 (95% CI: 0.01-0.58)*	0.96 (95% CI: 0.92-1.00)	LOW
Test 3. Subgroup analysis: Transient elastography at a cut off of ≥ 8.9 kPa in a population of adults with CFLD												

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
1(Kitson 2013)	Case control study	25	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	87.5 (95% CI: 52.9-99.3)*	76.5 (95% CI: 60.2-82.0)*	3.7 (95% CI: 1.33-5.53)*	0.16 (95% CI: 0.01-0.78)*	0.91 (95% CI: 0.79-1.00)	LOW

Abbreviations: APRI Aspartate aminotransferase to Platelets-Ratio-Index; AUROC: area under the ROC curve; CFLD: cystic fibrosis liver disease; CI: confidence interval; kPa: kilopascal
†Diagnosis of CFLD (Sokol 1999, Colombo 2002) if at least 2 of the following conditions present on at least 2 consecutive examinations spanning a 1-year period: (1) Ultrasound confirmed hepatomegaly;(2) elevated serum liver enzyme levels of ALT, AST, AP, or GGT;(3) ultrasound abnormalities other than hepatomegaly (i.e., increased, heterogeneous echogenicity, nodularity, irregular margins, splenomegaly). Liver cirrhosis: distinct ultrasonographic signs (i.e. coarse nodularity, presence of portal hypertension and rarefication of peripheral portal veins) and clinical signs (e.g. esophageal varices, splenomegaly). Portal hypertension: platelet count <140x109/L, splenomegaly, presence of porto-systemic collateral veins, portal diameter >13mm, or ascites
** Calculated by the NGA technical team from data available in the study report*

Table 79: Test 4. Index test (Transient elastography) versus biochemical and imaging defined portal hypertension †

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
Transient elastography at a cut off of 11.5 kPA in an adult population												
1(Rath 2012)	Cohort study	70	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	66.7 (95% CI: 36.2-77.2)*	98.4 (95% CI: 93.9-99.9)*	40.67 (95% CI: 5.91-877.4)*	0.34 (95% CI: 0.23-0.68)*	0.86 (95% CI: 0.66-1.00)	HIGH

Abbreviations: AUROC: area under the ROC curve; CFLD: cystic fibrosis liver disease; CI: confidence interval; kPa: kilopascal
†Diagnosis of CFLD was established according to published guidelines (Debray 2011) if least 2 of the following conditions on at least 2 consecutive examinations spanning a 1-year period were present: (i) Hepatomegaly (liver span >2 cm below the costal margin on the mediolavicular line) confirmed by ultrasound, (ii) 2 abnormal serum liver enzyme levels (ALT, AST, γGT > ULN), (iii) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins). Diagnosis of portal hypertension was based on clinical and lab data combined with sonographic or endoscopic signs of PHT (defined splenomegaly, increased portal vein pressure in duplex Doppler sonography, platelet count 150,000/mm3, oesophageal varices or other signs of portal hypertension on oesophagogastroduodenoscopy

** Calculated by the NGA technical team from data available in the study report*

J.16.1.4 Target condition: Oesophageal varices

Table 80: Tests 1 to 3. Index tests (APRI, Forn's score, Transient elastography) versus published definition of oesophageal varices †

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
Test 1. APRI using a cut off of ≥ 0.49 in a population of adults												
1(Kitson 2013)	Case control study	23	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	100 (95% CI: 60.0-100)*	94.1(95% CI: 80.0-94.1)*	17.0 (95% CI: 3.0-17.0)*	0 (95% CI: 0-0.50)*	0.99 (95% CI: 0.96-1.00)	LOW
Test 1. Subgroup analysis: APRI using a cut off of ≥ 0.49 in a population of adults with CFLD												
1(Kitson 2013)	Case control study	13	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[a]	100 (95% CI: 62.9-100)*	93.3(95% CI: 63.7-93.3)*	15.0 (95% CI: 1.73-15.0)*	0 (95% CI: 0-0.58)*	1.00 (95% CI: 1.00-1.00)	VERY LOW
Test 2. Forn's score using a cut off of ≥ 0.68 in a population of adults												
1(Kitson 2013)	Case control study	23	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	100 (95% CI: 58.9-100)*	88.2 (95% CI: 73.7-88.2)*	8.5 (95% CI: 2.2-8.5)*	0 (95% CI: 0-0.56)*	0.98 (95% CI: 0.93-1.00)	LOW
Test 2. Subgroup analysis: Forn's score using a cut off of ≥ 0.68 in a population of adults with CFLD												
1(Kitson 2013)	Case control study	13	no serious	no serious inconsistency	no serious	very serious	100 (95% CI: 62.9-100)*	85.7 (95% CI:	7.0 (95% CI: 1.37-7.0)*	0 (95% CI: 0-0.69)*	0.98 (95% CI:	VERY LOW

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
			risk of bias		indirectness	imprecision[a]		53.9-85.7)*			0.91-1.00)	
Test 3. Transient elastography using a cut off of ≥ 8.9 kPa in a population of adults												
1(Kitson 2013)	Case control study	23	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[a]	100 (95% CI: 57.8-100)*	76.5 (95% CI: 61.6-76.5)*	4.25 (95% CI: 1.51-4.25)*	0 (95% CI: 0-0.69)*	0.91 (95% CI: 0.78-1.00)	LOW

Abbreviations: APRI Aspartate aminotransferase to Platelets-Ratio-Index; AUROC: area under the ROC curve; CFLD: cystic fibrosis liver disease; CI: confidence interval; kPa: kilopascal

†Diagnosis of CFLD (Sokol 1999, Colombo 2002) if at least 2 of the following conditions present on at least 2 consecutive examinations spanning a 1-year period: (1) Ultrasound confirmed hepatomegaly;(2) elevated serum liver enzyme levels of ALT, AST, AP, or GGT;(3) ultrasound abnormalities other than hepatomegaly (i.e., increased, heterogeneous echogenicity, nodularity, irregular margins, splenomegaly). Liver cirrhosis: distinct ultrasonographic signs (i.e. coarse nodularity, presence of portal hypertension and rarefication of peripheral portal veins) and clinical signs (e.g. oesophageal varices, splenomegaly). Portal hypertension: platelet count <140x109/L, splenomegaly, presence of porto-systemic collateral veins, portal diameter >13mm, or ascites. Patients with evidence of portal hypertension underwent upper gastrointestinal endoscopy for variceal screening.

a. 95% confidence interval for sensitivity was wide (width 20-30 percentage points)

b. 95% confidence interval for sensitivity was very wide (width ≥30 percentage points)

J.16.2 Review question 2. What is the diagnostic and prognostic value of different strategies to detect CF liver disease and predict progression (including progression to cirrhosis and portal hypertension with (out) oesophageal varices)?

Table 13 Index tests (transient elastography and biopsy) for prognosis of CFLD and portal hypertension

Index Prognostic factors	Included studies	Study design	Setting	N	Adjusted OR/HRs	Quality	Notes
CFLD (includes cirrhosis)							
Liver stiffness measurement (kPa)	1 study (Kitson 2013)	Case control study	CF referral centre for adults	50	adjOR: 2.74 (95% CI 1.53-4.89, p=0.001)	LOW	Multiple logistic regression model of variables with p<0.05 on univariate analysis was performed to identify independent predictors of CFLD presence
Liver enzymes: AST ≥ 1.5 ULN	1 study (Woodruff 2017)	Prospective cohort	CF clinic in a children's hospital	278	aHR: 6.53 (2.02–21.1)	HIGH	Hazards Ratios for the presence of clinically diagnosed liver disease, adjusted for sex, CFTR

Index Prognostic factors	Included studies	Study design	Setting	N	Adjusted OR/HRs	Quality	Notes
					Follow-up median: 7.23 years		mutation severity, and the presence of meconium ileus.
Liver enzymes: AST ≥ 2 ULN	1 study (Woodruff 2017)	Prospective cohort	CF clinic in a children's hospital	278	adjHR: 6.52 (0.72–138.5) Follow-up median: 7.23 years	HIGH	Hazards Ratios for the presence of clinically diagnosed liver disease, adjusted for sex, CFTR mutation severity, and the presence of meconium ileus.
Liver enzymes: ALT ≥ 1.5 ULN	1 study (Woodruff 2017)	Prospective cohort	CF clinic in a children's hospital	278	adjHR: 1.95 (0.81–4.27) Follow-up median: 7.23 years	HIGH	Hazards Ratios for the presence of clinically diagnosed liver disease, adjusted for sex, CFTR mutation severity, and the presence of meconium ileus.
Liver enzymes: ALT ≥ 2 ULN	1 study (Woodruff 2017)	Prospective cohort	CF clinic in a children's hospital	278	adjHR: 1.88 (0.82–3.91) Follow-up median: 7.23 years	HIGH	Hazards Ratios for the presence of clinically diagnosed liver disease, adjusted for sex, CFTR mutation severity, and the presence of meconium ileus.
Liver enzymes: GGTP ≥ 1.5 ULN	1 study (Woodruff 2017)	Prospective cohort	CF clinic in a children's hospital	278	adjHR: 4.03 (1.15–13.45) Follow-up median: 7.23 years	HIGH	Hazards Ratios for the presence of clinically diagnosed liver disease, adjusted for sex, CFTR mutation severity, and the presence of meconium ileus.
Liver enzymes GGTP ≥ 2 ULN	1 study (Woodruff 2017)	Prospective cohort	CF clinic in a children's hospital	278	adjHR: 2.44 (0.86-6.13) Follow-up median: 7.23 years	HIGH	Hazards Ratios for the presence of clinically diagnosed liver disease, adjusted for sex, CFTR mutation severity, and the presence of meconium ileus.
Portal Hypertension							
Increasing fibrosis detected by biopsy	1 study (Lewindon 2011)	Cohort study	CF clinic in a city hospital	40	From birth adjHR: 3.9 (p<0.001, no 95% CI given)	HIGH	Fibrosis stages (Scheuer 2002): F0 no fibrosis; F1 mild fibrosis; F2 moderate fibrosis; F3 advanced fibrosis; F4 cirrhosis Multivariate analysis was adjusted for age, FEV at enrolment, URSO treatment, steatosis presence,

Index Prognostic factors	Included studies	Study design	Setting	N	Adjusted OR/HRs	Quality	Notes
							diabetes mellitus presence. A Cox proportional hazards model was used to determine factors independently associated with time to PHT development
Increasing fibrosis detected by biopsy	1 Lewindon 2011	Cohort study	CF clinic in a city hospital	40	From time of biopsy adjHR: 3.4 (p<0.002, no 95% CI given)	HIGH	Fibrosis stages (Scheuer 2002): F0 no fibrosis; F1 mild fibrosis; F2 moderate fibrosis; F3 advanced fibrosis; F4 cirrhosis Multivariate analysis was adjusted for age, FEV at enrolment, URSO treatment, steatosis presence, diabetes mellitus presence. A Cox proportional hazards model was used to determine factors independently associated with time to PHT development

Abbreviations: adjOR: adjusted odds ratio; CFLD: cystic fibrosis liver disease; CI: confidence interval; ALT: alanine aminotransferase; AST: aminotransferase; GGT: gamma glutamyltransferase

J.17 Ursodeoxycholic acid

Table 81: Clinical evidence profile: Comparison 1. UDCA versus placebo or control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UDCA	Placebo/control	Relative (95% CI)	Absolute		
Lack of normalisation of AST (follow-up 6 months)												
2 (Merli 1994, O'Brien	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	6/6 (100 %)	5/8 (62.5%)	RR 1.51 (0.83 to 2.78)	319 more per 1000 (from 106 fewer to	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UDCA	Placebo/control	Relative (95% CI)	Absolute		
1992)										1000 more)		
								75%		382 more per 1000 (from 128 fewer to 1000 more)		
Lack of normalisation of ALT (follow-up 6 months)												
2 (Merli 1994, O'Brien 1992)	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	4/8 (50%)	3/4 (75%)	RR 0.69 (0.27 to 1.74)	233 fewer per 1000 (from 548 fewer to 555 more)	MODERATE	CRITICAL
								83.3%		258 fewer per 1000 (from 608 fewer to 616 more)		

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UDCA	Placebo/control	Relative (95% CI)	Absolute		
Lack of normalisation of GGT (follow-up 6 months)												
2 (Merli 1994, O'Brien 1992)	randomised trials1	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	2/6 (33.3 %)	2/4 (50%)	RR 0.6 (0.16 to 2.29)	200 fewer per 1000 (from 420 fewer to 645 more)	LOW	CRITICAL
								33.3%		133 fewer per 1000 (from 280 fewer to 430 more)		
Final bilirubin value (umol/l) (follow-up 6 months; Better indicated by lower values)												
1 (O'Brien 1992)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	6	6	-	MD 4 higher (3.72 lower to 11.72 higher)	LOW	CRITICAL
Percentage change in AST (follow-up 12 months; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UDCA	Placebo/control	Relative (95% CI)	Absolute		
1 (Colombo 1996)	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[2]	none	15	12	-	MD -14 (-39.93 to 11.93)	LOW	CRITICAL
Percentage change in ALT (follow-up 12 months; Better indicated by lower values)												
1 (Colombo 1996)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	none	15	12	-	MD -13 (-29.35 to 3.35)	LOW	CRITICAL
Percentage change in GGT (follow-up 12 months; Better indicated by lower values)												
1 (Colombo 1996)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	none	15	12	-	MD -11.00 (-36.74 to 14.74)	LOW	
No development of liver disease (follow-up 6 months)												
1 (Merli 1994)	randomised trials1	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/11 (100%)	11/11 (100%)	Not calculable[5]	-	HIGH	CRITICAL
Liver failure (jaundice) (follow-up 12 months)												
1 (Colombo 1996)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/15	0/13	RR 2.62 (0.12 to 59.40)	Not calculable[6]	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UDCA	Placebo/control	Relative (95% CI)	Absolute		
Liver transplantation (follow-up 12 months)												
1 (Colombo 1996)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	Not applicable		15 1 patient in the treatment group was withdrawn to receive transplantation	13	Not applicable	Not applicable	MODERATE	CRITICAL

Abbreviations: CFLD: ALT: alanine aminotransferase; AST: aminotransferase; cystic fibrosis liver disease; CI: confidence interval; GGT: gamma glutamyltransferase; MD: mean difference; RR: risk ratio
1 Merli (1994) used a cross-over study design
2 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID.
3 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs.
4 The quality of the evidence was downgraded by 1 due to lack of allocation concealment reporting.
5 RR not calculable - no development of liver disease in 11/11 participants who did not have CF related liver disease at entry in this cross-over trial.
6 Not calculable - 0 events in placebo arm.

J.18 Cystic fibrosis related diabetes

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

J.19 Bone mineral density

Not applicable to this review.

J.20 Exercise

J.20.1 Aerobic exercise programmes

Table 82: Clinical evidence profile: Comparison 1. Aerobic exercise training programme versus no exercise programme

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise training programme	No exercise programme	Relative (95% CI)	Absolute	Quality	Importance
Change in FEV_1 % predicted at hospital discharge - *Supervised programme* (follow-up mean 18.7 days; range of scores: 0-100; Better indicated by higher values)												
1 (Selvaduraai 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22	22	-	MD 2.03 higher (2.31 lower to 6.37 higher)	LOW	CRITICAL
Change in FEV_1 % predicted - *Unsupervised programme* (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
2 (Hommerding 2015, Krie	randomised trials	very serious[3]	very serious[4]	no serious indirectness	very serious[5]	none	31	27	-	MD 5.23 higher (10.06 lower to 20.52	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise training programme	No exercise programme	Relative (95% CI)	Absolute	Quality	Importance
mler 2013)										higher)		
Change in FEV_1 % predicted - *Unsupervised programme* (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Kriemler 2013)	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15	10	-	MD 17.17 higher (8.59 to 25.75 higher)	LOW	CRITICAL
Change in FEV_1 % predicted - *Unsupervised programme* (follow-up 3 years; range of scores: 0-100; Better indicated by higher values)												
1 (Schneiderman-Walker 2000)	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	35	-	MD 2.01 higher (0.06 lower to 4.08 higher)	MODERATE	CRITICAL
Change in FVC % predicted at hospital discharge - *Supervised programme* (follow-up mean 18.7 days; range of scores: 0-100; Better indicated by higher values)												
1 (Selvadurai	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	22	22	-	MD 0.06 higher (2.55 lower to	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise training programme	No exercise programme	Relative (95% CI)	Absolute	Quality	Importance
2002)										2.67 higher)		
Change in FVC % predicted - *Unsupervised programme* (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
2 (Hommerding 2015, Kriemler 2013)	randomised trials	very serious[3]	very serious[9]	no serious indirectness	very serious[8]	none	31	27	-	MD 3.99 higher (6.62 lower to 14.61 higher)	VERY LOW	IMPORTANT
Change in FVC % predicted - *Unsupervised programme* (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Kriemler 2013)	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15	10	-	MD 12.51 higher (5.9 to 19.12 higher)	LOW	IMPORTANT
Change in FVC % predicted - *Unsupervised programme* (follow-up 3 years; range of scores: 0-100; Better indicated by higher values)												
1 (Schneiderman-Walker	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[10]	none	30	35	-	MD 2.17 higher (0.47 to 3.87	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise training programme	No exercise programme	Relative (95% CI)	Absolute	Quality	Importance
2000)										higher)		
Change in FEV_1 peak - *Unsupervised programme* (follow-up 3 months; measured with: ml/min per kg body weight; Better indicated by higher values)												
2 (Hommerding 2015, Kriemler 2013)	randomised trials	very serious[11]	very serious[12]	no serious indirectness	very serious[8]	none	32	27	-	MD 3.76 higher (6.89 lower to 14.41 higher)	VERY LOW	IMPORTANT
Change in FEV_1 peak - *Unsupervised programme* (follow-up 6 months; measured with: ml/min per kg body weight; Better indicated by higher values)												
1 (Kriemler 2013)	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15	10	-	MD 18.33 higher (8.95 to 27.71 higher)	LOW	IMPORTANT
Change in FEV_1 peak at hospital discharge - *Supervised programme* (follow-up mean 18.7 days; measured with: ml/min per kg body weight; Better indicated by higher values)												
1 (Selvadurai	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious	none	22	22	-	MD 8.53 higher (4.85	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise training programme	No exercise programme	Relative (95% CI)	Absolute		
2002)					imprecision					to 12.21 higher)		
Time to next exacerbation												
No evidence available												
Change in BMI - *Unsupervised programme* (follow-up 3 months; measured with: kg/m2; Better indicated by higher values)												
1 (Kriemler 2013)	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	serious[10]	none	15	10	-	MD 0.3 higher (0.13 lower to 0.73 higher)	VERY LOW	IMPORTANT
Change in BMI - *Unsupervised programme* (follow-up 6 months; Better indicated by higher values)												
1 (Kriemler 2013)	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	serious[10]	none	15	10	-	MD 0.4 higher (0 to 0.8 higher)	VERY LOW	IMPORTANT
Change in BMI - *Supervised programme*												
No evidence available												
Quality of life												
No evidence available												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise training programme	No exercise programme	Relative (95% CI)	Absolute	Quality	Importance
Preference for training programme												
No evidence available												
Adverse events												
No evidence available												

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; kg: kilogrammes MD: mean difference; min: minute; ml: millilitres; FEV_1 max/ peak: maximal oxygen consumption

1 The quality of the evidence was downgraded by 1 because of unclear risk of bias in relation to random sequence generation, blinding of participants and personnel and blinding of outcome assessment.

2 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 clinical MID

3 The quality of the evidence was downgraded by 2 because of unclear risk of bias in relation to allocation concealment, blinding of participants and personnel and blinding of outcome assessment in 1 study; high risk of bias in relation to random sequence generation and allocation concealment, unclear risk of blinding of personnel, unclear risk of other bias (due to the deterioration of physical health in the control group) in the other study

4 The quality of the evidence was downgraded by 2 due to very serious heterogeneity (chi-squared p<0.1, I-squared inconsistency statistic of 90%) and no plausible explanation was found with sensitivity or subgroup analysis.

5 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 clinical MIDs

6 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to random sequence generation and allocation concealment, unclear risk of bias in relation to blinding of participants and personnel, and unclear risk of other bias (due to the deterioration of physical health in the control group)

7 The quality of the evidence was downgraded by 1 because of unclear risk of bias in relation to allocation concealment, blinding of participants and personnel, incomplete outcome data and other bias (exclusion criteria were not stated)

8 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs

9 The quality of the evidence was downgraded by 2 due to very serious heterogeneity (chi-squared p<0.1, I-squared inconsistency statistic of 84%) and no plausible explanation was found with sensitivity or subgroup analysis.

10 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID

11 The quality of the evidence was downgraded by 2 because of unclear risk of bias in relation to allocation concealment, blinding of participants and personnel, blinding of outcome assessment and other bias (the mean peak heart rate reached during the exercise test is indicative of submaximal effort, which is likely to underestimate the true FEV_1 peak of the study participants) in 1 study; high risk of bias in relation to random sequence generation and allocation concealment, unclear risk of blinding of personnel, unclear risk of other bias (due to the deterioration of physical health in the control group) in the other study

12 The quality of the evidence was downgraded by 2 due to very serious heterogeneity (chi-squared p<0.1, I-squared inconsistency statistic of 75%) and no plausible explanation was found with sensitivity or subgroup analysis.

J.20.2 Strength resistance training/ anaerobic training

Table 83: Clinical evidence profile: Comparison 2.1. Strength resistance/ anaerobic training programme versus no exercise programme

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Strength resistance/ anaerobic training programme	No exercise programme	Relative (95% CI)	Absolute	**Quality**	**Importance**
Change in FEV_1 % predicted at hospital discharge - *Supervised programme* (follow-up mean 18.7 days; range of scores: 0-100; Better indicated by higher values)												
1 (Selvadurai 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22	22	-	MD 5.58 higher (1.34 to 9.82 higher)	LOW	CRITICAL
Change in FEV_1 % predicted - *Unsupervised programme* (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Kriemler 2013)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11	10	-	MD 11.11 higher (5.16 to 17.06 higher)	LOW	CRITICAL
Change in FEV_1 % predicted - *Unsupervised programme* (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Kriemler 2013)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11	10	-	MD 19.51 higher (10.57 to 28.45 higher)	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Strength resistance/ anaerobic training programme	No exercise programme	Relative (95% CI)	Absolute	Quality	Importance
Change in FVC % predicted at hospital discharge - *Supervised programme* (follow-up mean 18.7 days; range of scores: 0-100; Better indicated by higher values)												
1 (Selvaduraai 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	22	22	-	MD 0.17 higher (2.31 lower to 2.65 higher)	VERY LOW	IMPORTANT
Change in FVC % predicted - *Unsupervised programme* (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Kriemler 2013)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	11	10	-	MD 7.37 higher (1.89 to 12.85 higher)	VERY LOW	IMPORTANT
Change in FVC % predicted - *Unsupervised programme* (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Kriemler 2013)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11	10	-	MD 14.05 higher (7.16 to 20.94 higher)	LOW	IMPORTANT
Change in FEV_1 peak at hospital discharge - *Supervised programme* (follow-up mean 18.7 days; measured with: ml/min per kg body weight; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Strength resistance/ anaerobic training programme	No exercise programme	Relative (95% CI)	Absolute	Quality	Importance
1 (Selvaduraai 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	22	22	-	MD 1.95 higher (1.61 lower to 5.51 higher)	LOW	IMPORTANT
Change in FEV_1 peak – *Pooled results from both supervised and unsupervised programmes* (follow-up 3 months; measured with: ml/min per kg body weight; Better indicated by higher values)												
2 (Kriemler 2013, Klijn 2004)	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	serious[5]	none	22	19	-	MD 6.36 higher (1.22 to 11.49 higher)	VERY LOW	IMPORTANT
Change in FEV_1 peak - *Unsupervised programme* (follow-up 3 months; measured with: ml/min per kg body weight; Better indicated by higher values)												
1 (Kriemler 2013)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	11	10	-	MD 9.34 higher (1.66 to 17.02 higher)	VERY LOW	IMPORTANT
Change in FEV_1 peak - *Supervised programme* (follow-up 3 months; measured with: ml/min per kg body weight; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Strength resistance/ anaerobic training programme	No exercise programme	Relative (95% CI)	Absolute		
1 (Klijn 2004)	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[5]	none	11	9	-	MD 3.95 higher (2.95 lower to 10.85 higher)	LOW	IMPORTANT
Change in FEV_1 peak - *Unsupervised programme* (follow-up 6 months; measured with: ml/min per kg body weight; Better indicated by higher values)												
1 (Kriemler 2013)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	8	10	-	MD 17.7 higher (5.98 to 29.42 higher)	VERY LOW	IMPORTANT
Time to next exacerbation												
No evidence available												
Change in BMI - *Unsupervised programme* (follow-up 3 months; Better indicated by higher values)												
1 (Kriemler 2013)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	15	10	-	MD 0.5 higher (0.07 to 0.93 higher)	VERY LOW	IMPORTANT
Change in BMI - *Unsupervised programme* (follow-up 6 months; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Strength resistance/ anaerobic training programme	No exercise programme	Relative (95% CI)	Absolute		
1 (Kriemler 2013)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15	10	-	MD 0.7 higher (0.27 to 1.13 higher)	LOW	IMPORTANT
Change in BMI - *Supervised programme*												
No evidence available												
Change in quality of life - *Unsupervised programme*												
No evidence available												
Change in quality of life - *Supervised programme* (follow-up 3 months; measured with: CFQ - physical function domain; range of scores: 0-100; Better indicated by higher values)												
1 (Klijn 2004)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[8]	none	11	9	-	MD 1.3 higher (11.55 lower to 14.15 higher)	VERY LOW	CRITICAL
Preference for training programme												
No evidence available												
Adverse events												
No evidence available												

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; kg: kilogrammes MD: mean difference; min: minute; ml: millilitres; FEV_1 max/ peak: maximal oxygen consumption

1 The quality of the evidence was downgraded by 1 because of unclear risk of bias in relation to random sequence generation, blinding of participants and personnel and blinding of outcome assessment.

2 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 clinical MID

3 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to random sequence generation and allocation concealment, unclear risk of bias in relation to blinding of participants and personnel, and unclear risk of other bias (due to the deterioration of physical health in the control group)
4 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
5 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
6 The quality of the evidence was downgraded by 2 because of: high risk of bias in relation to random sequence generation and allocation concealment, unclear risk of bias in relation to blinding of participants and personnel, and unclear risk of other bias (due to the deterioration of physical health in the control group) in 1 study; unclear risk of bias in relation to random sequence generation, blinding of participants and personnel, blinding of outcome assessment, other bias (exclusion criteria were not reported) in the other study.
7 The quality of the evidence was downgraded by 1 because of unclear risk of bias in relation to random sequence generation (described as randomised but no details given), blinding of participants and personnel, blinding of outcome assessment (the primary researcher was blinded but their role in the study is unclear), other bias (exclusion criteria were not reported)
8 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 clinical MIDs

Table 84: Clinical evidence profile: Comparison 2.2. Strength/ anaerobic training programme versus aerobic training programme

Quality assessment							**No of patients**		**Effect**			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Strength/ anaerobic training	Aerobic training	Relative (95% CI)	Absolute	**Quality**	**Importance**
Change in FEV_1 % predicted at hospital discharge - *Supervised programme* (Follow-up: mean 18.7 days; range of scores: 0-100; Better indicated by higher values)												
1 (Selvaduraі 2002)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	22	22	-	MD 3.55 higher (0.94 lower to 8.04 higher)	LOW	CRITICAL
Change in FEV_1 % predicted - *Unsupervised programme* (Follow-up: 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Kriemler 2013)	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	serious[2]	none	11	14	-	MD 1.7 lower (7.67 lower to 4.27 higher)	VERY LOW	CRITICAL
Change in FEV_1 % predicted– *Unsupervised programme* (Follow-up: 6 months; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Strength/ anaerobic training	Aerobic training	Relative (95% CI)	Absolute		
1 (Kriemler 2013)	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	very serious[4]	none	11	15	-	MD 2.34 higher (6.33 lower to 11.01 higher)	VERY LOW	CRITICAL
Change in FEV_1 % predicted - *Supervised programme* (Follow-up: 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Orenstein 2004)	randomised trials	very serious [5]	no serious inconsistency	no serious indirectness	very serious[4]	none	30	26	-	MD 1.66 lower (11.24 lower to 7.92 higher)	VERY LOW	CRITICAL
Change in FEV_1 % predicted– *Pooled results for supervised and unsupervised* (Follow-up: 6 months; range of scores: 0-100; Better indicated by higher values)												
2 (Kriemler 2013, Orenstein 2004)	randomised trials	very serious [6]	no serious inconsistency	no serious indirectness	very serious[4]	none	41	41	-	MD 0.54 higher (5.89 lower to 6.97 higher)	VERY LOW	CRITICAL
Change in FEV_1 % predicted - *Supervised programme* (Follow-up: 12 months; range of scores: 0-100; Better indicated by higher values)												
1 (Orenstein 2004)	randomised trials	very serious [5]	no serious inconsistency	no serious indirectness	very serious[4]	none	28	25	-	MD 0.3 higher (9.21 lower to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Strength/ anaerobic training	Aerobic training	Relative (95% CI)	Absolute	Quality	Importance
										9.81 higher)		
Change in FVC % predicted - *Supervised programme* (Follow-up: at hospital discharge, mean 18.7 days; range of scores: 0-100; Better indicated by higher values)												
1 (Selvaduraj 2002)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[7]	none	22	22	-	MD 0.11 higher (2.49 lower to 2.71 higher)	VERY LOW	IMPORTANT
Change in FVC % predicted - *Unsupervised programme* (Follow-up: 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Kriemler 2013)	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	Serious[8]	none	11	14	-	MD 1.87 lower (7.33 lower to 3.59 higher)	VERY LOW	IMPORTANT
Change in FVC % predicted - *Unsupervised programme* (Follow-up: 6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Kriemler 2013)	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	very serious[7]	none	11	15	-	MD 1.54 higher (5.12 lower to 8.2 higher)	VERY LOW	IMPORTANT
Change in FEV_1 peak - Supervised programme (Follow-up: at hospital discharge, mean 18.7 days Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Strength/ anaerobic training	Aerobic training	Relative (95% CI)	Absolute		
1 (Selvaduraі 2002	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[8]	none	22	22	-	MD 6.58 lower (10.18 to 2.98 lower)	LOW	IMPORTANT
Change in FEV_1 peak - *Unsupervised programme* (Follow-up: 3 months; Better indicated by higher values)												
1 (Kriemler 2013)	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	very serious[7]	none	11	15	-	MD 0.24 higher (6.1 lower to 6.58 higher)	VERY LOW	IMPORTANT
Change in FEV_1 max - *Unsupervised programme* (Follow-up: 6 months; Better indicated by higher values)												
1 (Kriemler 2013)	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	very serious[7]	none	11	15	-	MD 0.63 lower (10.94 lower to 9.68 higher)	VERY LOW	IMPORTANT
Change in FEV_1 max - *Supervised programme* (Follow-up: 6 months; Better indicated by higher values)												
1 (Orenstein 2004)	randomised trials	very serious [5]	no serious inconsistency	no serious indirectness	serious[8]	none	30	26	-	MD 0.25 lower (3.35 lower to 2.85 higher)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Strength/ anaerobic training	Aerobic training	Relative (95% CI)	Absolute		
Change in FEV_1 max – *Pooled results for supervised and unsupervised programmes* (Follow-up: 6 months; Better indicated by higher values)												
2 (Kriemler 2013, Orenstein 2004)	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41	41		MD 0.28 lower (3.25 lower to 2.69 higher)	LOW	IMPORTANT
Change in FEV_1 max - *Supervised programme* (Follow-up: 12 months; Better indicated by higher values)												
1 (Orenstein 2004)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[8]	none	28	25	-	MD 0.82 lower (4.32 lower to 2.68 higher)	VERY LOW	IMPORTANT
Change in BMI - *Unsupervised programme* (Follow-up: 3 months; Better indicated by higher values)												
1 (Kriemler 2013)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[8]	none	15	15	-	MD 0.2 higher (0.23 lower to 0.63 higher)	VERY LOW	IMPORTANT
Change in BMI - *Unsupervised programme* (Follow-up: 6 months; Better indicated by higher values)												
1 (Kriemler 2013)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[8]	none	15	15	-	MD 0.3 higher (0.1 lower to 0.7 higher)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Strength/ anaerobic training	Aerobic training	Relative (95% CI)	Absolute	Quality	Importance
Change in BMI - Supervised programme												
No evidence available												
Quality of life												
No evidence available												
Preference for training programme												
No evidence available												
Adverse events												
No evidence available												

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; kg: kilogrammes MD: mean difference; min: minute; ml: millilitres; FEV_1 max/ peak: maximal oxygen consumption
1 The quality of the evidence was downgraded by 1 because of unclear risk of bias in relation to random sequence generation, blinding of participants and personnel and blinding of outcome assessment.
2 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 clinical MID
3 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to random sequence generation and allocation concealment, unclear risk of bias in relation to blinding of participants and personnel, and unclear risk of other bias (due to the deterioration of physical health in the control group)
4 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 clinical MIDs
5 The quality of the evidence was downgraded by 2 due to high risk of bias in relation to blinding of participants and personnel and unclear risk of bias in relation to random sequence generation and allocation concealment.
6 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to random sequence generation and allocation concealment in 1 study, and unclear risk of bias in relation to the same domains in the other study; high risk of bias in relation to blinding of participants and personnel in 1 study and unclear risk of bias in relation to the same domains in the other study; and unclear risk of other bias in 1 study (due to the deterioration of physical health in the control group).
7 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
8 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID

J.20.3 High intensity interval training

Table 85: Clinical evidence profile: Comparison 3. High-intensity interval training versus standard aerobic and anaerobic exercise programme

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High intensity interval training programme	Standard combined aerobic and anaerobic exercise programme	Relative (95% CI)	Absolute	Quality	Importance
Change in FEV_1 - *Unsupervised programme*												
No evidence available												
Change in FEV_1% predicted - *Supervised programme* (follow-up 6 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (Gruber 2014)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	23	-	MD 3.9 lower (7.61 to 0.19 lower) 5	VERY LOW	CRITICAL
Change in vital capacity (VC) % predicted - *Unsupervised programme*												
No evidence available												
Change in vital capacity (VC) % predicted - *Supervised programme* (follow-up 6 weeks; range of scores 0-100; Better indicated by higher values)												
1 (Gruber 2014)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	20	23	-	MD 5.1 lower (11.05 lower to 0.85 higher) 5	VERY LOW	IMPORTANT
Change in FEV_1 peak												
No evidence available												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High intensity interval training programme	Standard combined aerobic and anaerobic exercise programme	Relative (95% CI)	Absolute	Quality	Importance
Change in FEV_1 peak - *Supervised programme* (follow-up 6 weeks; Better indicated by higher values)												
1 (Gruber 2014)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	20	23	-	MD 0.8 lower (4.59 lower to 2.99 higher)[5]	VERY LOW	IMPORTANT
Time to next exacerbation												
No evidence available												
Change in BMI - *Unsupervised programme*												
No evidence available												
Change in BMI - *Supervised programme* (follow-up 6 weeks; Better indicated by higher values)												
1 (Gruber 2014)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	21	23	-	MD 0 higher (1.34 lower to 1.34 higher)[5]	VERY LOW	IMPORTANT
Quality of life												
No evidence available												
Preference for training programme												
No evidence available												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High intensity interval training programme	Standard combined aerobic and anaerobic exercise programme	Relative (95% CI)	Absolute	Quality	Importance
Adverse events												
No evidence available												

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; VC: vital capacity; kg: kilogrammes MD: mean difference; min: minute; ml: millilitres; FEV_1 max/ peak: maximal oxygen consumption
1 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to the selection of the participants for each group and the comparability of the groups
2 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 clinical MID
3 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
4 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
5 Calculated by the NGA technical team

J.20.4 Inspiratory muscle training

Table 86: Clinical evidence profile: Comparison 4. Inspiratory muscle training (80% of maximal effort) versus usual care

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inspiratory muscle training (80% of maximal effort) programme	Usual care	Relative (95% CI)	Absolute	Quality	Importance
Change in FEV_1 (litres) (Follow up: 2-6 months; Better indicated by higher values)												
1 (Enrig	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9	10	-	MD 0 higher (0.9 lower to	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inspiratory muscle training (80% of maximal effort) programme	Usual care	Relative (95% CI)	Absolute	Quality	Importance
htt 2004)										0.9 higher)		
Change in FVC (litres) (Follow up: 2-6 months; Better indicated by higher values)												
1 (Enright 2004)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9	10	-	MD 0.1 higher (0.9 lower to 1.1 higher)	VERY LOW	CRITICAL
FEV_1 peak												
No evidence available												
Time to next exacerbation												
No evidence available												
Body composition												
No evidence available												
Quality of life												
No evidence available												
Preference for training programme												
No evidence available												
Adverse events												
No evidence available												

Abbreviations: CI: confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; MD: mean difference
1 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to blinding (performance bias and detection bias), and unclear risk of bias in relation to random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other bias.
2 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs

J.20.5 Combined programmes

Table 87: Clinical evidence profile: Comparison 5. Combined aerobic and anaerobic training programme versus no exercise programme

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined aerobic and anaerobic training programme	No exercise programme	Relative (95% CI)	Absolute	Quality	Importance
Change in FEV_1 % predicted - *Unsupervised programme* (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
3 (Beaudoin 2016, Rovedder 2014, Schindel 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	44	45	-	MD 4.27 lower (9.63 lower to 1.09 higher)	LOW	CRITICAL
Change in FEV_1 % predicted - *Unsupervised programme* (follow-up 3-6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Hebestreit 2010)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	22	13	-	MD 2 higher (5.31 lower to 9.31 higher)	VERY LOW	CRITICAL
Change in FEV_1 % predicted - *Supervised programme*												
No evidence available												
Change in FVC % predicted - *Unsupervised programme* (follow-up 3 months; range of score: 0-100; Better indicated by higher values)												
3 (Beaudoin 2016.Rovedder	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	44	45	-	MD 1.47 lower (6.21	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined aerobic and anaerobic training programme	No exercise programme	Relative (95% CI)	Absolute	Quality	Importance
2014, Schindel 2015)										lower to 3.27 higher)		
Change in FVC % predicted at 3-6 months - *Unsupervised programme* (follow-up 3-6 months; range of scores: 0-100; Better indicated by higher values)												
1 (Hebestreit 2010)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[6]	none	22	13	-	MD 0.5 higher (4.3 lower to 5.3 higher)	VERY LOW	IMPORTANT
Change in FVC % predicted - *Supervised programme*												
No evidence available												
Change in FEV_1 peak - *Unsupervised programme* (follow-up 3 months; Better indicated by higher values)												
1 (Beaudoin 2016)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	very serious[6]	none	8	6	-	MD 2.13 lower (7.06 lower to 2.80 higher)	VERY LOW	IMPORTANT
Change in FEV_1 peak - *Unsupervised programme* (follow-up 3-6 months; Better indicated by higher values)												
1 (Hebestreit 2010)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23	15	-	MD 2.04 higher (0.08	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined aerobic and anaerobic training programme	No exercise programme	Relative (95% CI)	Absolute	Quality	Importance
										to 4 higher)		
Change in FEV_1 peak - *Supervised programme*												
No evidence available												
Time to next exacerbation												
No evidence available												
Change in weight (kg) - *Unsupervised programme* (follow-up 3 months; Better indicated by higher values)												
1 (Beaudoin 2016)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	8	6	-	MD 0.27 lower (12.95 lower to 12.41 higher)	VERY LOW	IMPORTANT
Change in BMI - *Unsupervised programme* (follow-up 3 months; Better indicated by higher values)												
1 (Beaudoin 2016)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	very serious[6]	none	8	6	-	MD 0.06 higher (2.68 lower to 2.80 higher)	VERY LOW	IMPORTANT
Change in BMI - *Unsupervised programme* (follow-up 3-6 months; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined aerobic and anaerobic training programme	No exercise programme	Relative (95% CI)	Absolute	**Quality**	**Importance**
1 (Hebestreit 2010)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	22	13	-	MD 0.4 higher (0.17 lower to 0.97 higher)	VERY LOW	IMPORTANT
Change in BMI - *Unsupervised programme* (follow-up 12 months; Better indicated by higher values)												
1 (Moorcroft 2004)	randomised trials	very serious[8]	no serious inconsistency	no serious indirectness	serious[5]	none	30	18	-	MD 0.54 higher (0.09 lower to 1.17 higher)	VERY LOW	IMPORTANT
Change in BMI - *Supervised programme*												
No evidence available												
Change in quality of life: CFQ-R physical - *Unsupervised programme* (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Beaudoin 2016)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	very serious[4]	none	8	6	-	MD 0.60 higher (17.56 lower to 18.76 higher)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined aerobic and anaerobic training programme	No exercise programme	Relative (95% CI)	Absolute		
1 (Rovedder 2014)	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	Not calculable [10]	none	19 Median (IQR): 6.1 (-4 to 8)	22 Median (IQR): 2.4 (--1.0 to 13)	P=0.742	Not calculable	MODERATE	CRITICAL
Change in quality of life: CFQ-R body image - *Unsupervised programme* (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Beaudoin 2016)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious[2]	none	8	6	-	MD 6.03 lower (18.89 lower to 6.83 higher)	VERY LOW	CRITICAL
1 (Rovedder 2014)	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	Not calculable [10]	none	19 Median (IQR): 3.3 (-11 to 22)	22 Median (IQR): 3.0 (-2 to 11)	P=0.915	Not calculable	MODERATE	CRITICAL
Change in quality of life: CFQ-R digestive - *Unsupervised programme* (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Beaudoin 2016)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious[2]	none	8	6	-	MD 14.80 higher (0.43 to 29.17 higher)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined aerobic and anaerobic training programme	No exercise programme	Relative (95% CI)	Absolute		
1 (Rovedder 2014)	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	Not calculable [10]	none	19 Median (IQR): -1.0 (-4 to 0)	22 Median (IQR): -0.5 (0 to 0)	P=0.953	Not calculable	MODERATE	CRITICAL
Change in quality of life: CFQ-R respiratory - *Unsupervised programme* (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Beaudoin 2016)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious[2]	none	8	6	-	MD 4.63 lower (16.88 lower to 7.62 higher)	VERY LOW	CRITICAL
1 (Rovedder 2014)	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	Not calculable [10]	none	19 Median (IQR): 3.8 (0 to 11)	22 Median (IQR): -4.7 (-1 to 7)	P=0.925	Not calculable	MODERATE	CRITICAL
Change in quality of life: CFQ-R emotional - *Unsupervised programme* (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Beaudoin 2016)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious[2]	none	8	6	-	MD 7.78 lower (18.65 lower	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined aerobic and anaerobic training programme	No exercise programme	Relative (95% CI)	Absolute	Quality	Importance
										to 3.09 higher)		
1 (Rovedder 2014)	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	Not calculable [10]	none	19 Median (IQR): 1.2 (-6 to 6)	22 Median (IQR): -4.3 (-13 to 6)	P=0.458	Not calculable	MODERATE	CRITICAL
Change in quality of life: CFQ-R social - *Unsupervised programme* (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Beaudoin 2016)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious[2]	none	8	6	-	MD 5.29 lower (18.10 lower to 7.52 higher)	VERY LOW	CRITICAL
1 (Rovedder 2014)	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	Not calculable [10]	none	19 Median (IQR): -1.1 (-11 to 5)	22 Median (IQR): -1.7 (5 to 11)	P=0.953	Not calculable	MODERATE	CRITICAL
Change in quality of life: CFQ-R eating disturbances- *Unsupervised programme* (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Beaudoin 2016)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8	6		MD -1.39 (4.91 lower	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined aerobic and anaerobic training programme	No exercise programme	Relative (95% CI)	Absolute	Quality	Importance
										to 2.13 higher)		
1 (Rovedder 2014)	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	Not calculable [10]	none	19 Median (IQR): -0.3 (-11 to 6)	22 Median (IQR): -2.0 (-11 to 0)	P=0.913	Not calculable	MODERATE	CRITICAL
Change in quality of life: CFQ-R treatment - *Unsupervised programme* (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Beaudoin 2016)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	very serious[4]	none	8	6	-	MD 5.56 lower (26.03 lower to 14.91 higher)	VERY LOW	CRITICAL
1 (Rovedder 2014)	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	Not calculable [10]	none	19 Median (IQR): -2.0 (-11 to 0)	22 Median (IQR): -2.5 (-11 to11)	P=0.850	Not calculable	MODERATE	CRITICAL
Change in quality of life: CFQ-R vitality - *Unsupervised programme* (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Beaudoin 2016)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	very serious[4]	none	8	6	-	MD 3.13 higher	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined aerobic and anaerobic training programme	No exercise programme	Relative (95% CI)	Absolute		
										(13.45 lower to 19.71 higher)		
1 (Rovedder 2014)	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	Not calculable [10]	none	19 Median (IQR): -1.2 (-16 to 8)	22 Median (IQR): 2.6 (-8 to 10)	P=0.579	Not calculable	MODERATE	CRITICAL
Change in quality of life: CFQ-R health - *Unsupervised programme* (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Beaudoin 2016)	randomised trials	very serious 7	no serious inconsistency	no serious indirectness	very serious4	none	8	6	-	MD 5.57 lower (21.75 lower to 10.61 higher)	VERY LOW	CRITICAL
1 (Rovedder 2014)	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	Not calculable [10]	none	19 Median (IQR): 1.7 (-11 to 16)	22 Median (IQR): -3.0 (-11 to 0)	P=0.382	Not calculable	MODERATE	CRITICAL
Change in quality of life: CFQ-R weight - *Unsupervised programme* (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined aerobic and anaerobic training programme	No exercise programme	Relative (95% CI)	Absolute	**Quality**	**Importance**
1 (Beaudoin 2016)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	very serious[4]	none	8	6	-	MD 8.34 lower (36.73 lower to 20.05 higher)	VERY LOW	CRITICAL
1 (Rovedder 2014)	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	Not calculable [10]	none	19 Median (IQR): 4.6 (0 to 33)	22 Median (IQR): 12.1 (0 to 11)	P=0.410	Not calculable	MODERATE	CRITICAL
Change in quality of life: CFQ-R social limitations - *Unsupervised programme* (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Beaudoin 2016)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious2	none	8	6	-	MD 5.29 lower (18.10 lower to 7.52 higher)	VERY LOW	CRITICAL
1 (Rovedder 2014)	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	Not calculable [10]	none	19 Median (IQR): 0.8 (-8 to 8)	22 Median (IQR): 1.8 (-2 to 0)	P=0.935	Not calculable	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined aerobic and anaerobic training programme	No exercise programme	Relative (95% CI)	Absolute	Quality	Importance
Change in quality of life: CFQ-R role limitations - *Unsupervised programme* (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1 (Beaudoin 2016)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	very serious[4]	none	8	6	-	MD 4.52 higher (13.37 lower to 22.41 higher)	VERY LOW	CRITICAL
Change in quality of life- *Supervised programme* (follow-up 2 months; measured with: CFQ-R children's; range of scores: 0-100; Better indicated by higher values)												
1 (Santana-Sosa 2012)	randomised trials	very serious[11]	no serious inconsistency	no serious indirectness	Not calculable[10]	none	11 Median pre-intervention: 696 (495 to 741) Median post-intervention: 719 (550 to 734)	11 Median pre-intervention: 649 (578 to 768) Median post-intervention: 638 (461 to 791)	p=0.257	Not calculable	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined aerobic and anaerobic training programme	No exercise programme	Relative (95% CI)	Absolute		
Change in quality of life- *Supervised programme* (follow-up 2 months; measured with: CFQ-R parents'; range of scores: 0-100; Better indicated by higher values)												
1 (Santana-Sosa 2012)	randomised trials	very serious[11]	no serious inconsistency	no serious indirectness	Not calculable[10]	none	11 Median pre-intervention: 896 (688 to 1011) Median post-intervention: 889 (811 to 973)	11 Median pre-intervention: 911 (842 to 1028) Median post-intervention: 978 (684 to 1059);	p=0.143	Not calculable	LOW	CRITICAL
Preference for training programme												
No evidence available												
Adverse events - *Unsupervised programme*												
No evidence available												
Adverse events - *Supervised programme* (follow-up 2 months)												
1 (Santana-Sosa 2012)	randomised trials	very serious[11]	no serious inconsistency	no serious indirectness	Not calculable[10]	none	11 No adverse events occurred during	11 No data reported	-	Not calculable	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined aerobic and anaerobic training programme	No exercise programme	Relative (95% CI)	Absolute	**Quality**	**Importance**
							exercise training					

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; CFQ-R: cystic fibrosis questionnaire revised; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; kg: kilogrammes MD: mean difference; min: minute; ml: millilitres; FEV_1 max/ peak: maximal oxygen consumption
1 The quality of the evidence was downgraded by 1 because of unclear risk of bias in relation to the allocation concealment and blinding of participants and personnel across the three studies; high risk of bias in relation to incomplete outcome data and unclear risk of bias in relation to blinding of outcome assessors and selective reporting in 1 study
2 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 clinical MID
3 The quality of the evidence was downgraded by 2 because of high risk of bias for the random sequence generation and allocation concealment domains and unclear risk of bias for the blinding, outcome assessment and reporting domains
4 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 clinical MIDs
5 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
6 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
7 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to incomplete outcome data, unclear risk of bias in relation to allocation concealment, selective reporting, blinding of participants and personnel and outcome assessors
8 The quality of the evidence was downgraded by 2 due to unclear risk of bias for the random sequence generation, allocation concealment, blinding and incomplete outcome data domains
9 The quality of the evidence was downgraded by 1 because of unclear risk of bias for the domains allocation concealment and blinding.
10 Imprecision cannot be calculated, as results are provided as medians
11 The quality of the evidence was downgraded by 2 because of high risk of bias for incomplete outcome data, and unclear risk of bias for random sequence generation, allocation concealment and blinding

Table 88: Clinical evidence profile: Comparison 6. Combined inspiratory muscle training, resistance and aerobic training

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined inspiratory muscle training resistance and aerobic training	No exercise programme	Relative (95% CI)	Absolute	**Quality**	**Importance**
Change in FEV_1 (litres) - *Unsupervised programme*												
No evidence available												
Change in FEV_1 (litres) - *Supervised programme* (follow-up 2 months; Better indicated by higher values)												
1 (Santana-Sosa 2014)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	10	-	MD 0.07 higher (0.54 lower to 0.68 higher)	LOW	CRITICAL
Change in FVC (litres) - *Unsupervised programme*												
No evidence available												
Change in FVC (litres) - *Supervised programme* (follow-up 2 months; Better indicated by higher values)												
1 (Santana-Sosa 2014)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 0.16 higher (0.68 lower to 1 higher)	VERY LOW	CRITICAL
Change in FEV_1 peak												
No evidence available												
Time to next exacerbation												
No evidence available												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined inspiratory muscle training resistance and aerobic training	No exercise programme	Relative (95% CI)	Absolute	**Quality**	**Importance**
Change in weight - *Unsupervised programme*												
No evidence available												
Change in weight (kg) - *Supervised programme* (follow-up 2 months; Better indicated by higher values)												
1 (Santana-Sosa 2014)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 0.50 higher (10.51 lower to 11.51 higher)	VERY LOW	CRITICAL
Change in QOL (CFQ-R) - *Unsupervised programme*												
No evidence available												
Change in QOL (CFQ-R) - *Supervised programme* (follow-up 2 months; range of scores: 0-100; Better indicated by higher values)												
1 (Santana-Sosa 2014)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	Not calculable [3]	none	10 Median pre-intervention: 629 (505 to 701) Median post-intervention: 688	10 Median pre-intervention: 636 (626 to 745) Median post-intervention: 638	p=0.071	Not calculable	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined inspiratory muscle training resistance and aerobic training	No exercise programme	Relative (95% CI)	Absolute	**Quality**	**Importance**
							(609 to 791)	(626 to 737)				
Preference for training programme												
No evidence available												
Adverse events - *Unsupervised programme*												
No evidence available												
Adverse events - *Supervised programme* (follow-up 2 months)												
1 (Santana-Sosa 2014)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	Not calculable [3]	none	10 No adverse events occurred during exercise training	10 No data reported	-	Not calculable	LOW	CRITICAL

Abbreviations: CI: confidence interval; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; kg: kilogrammes MD: mean difference; FEV_1 max/ peak: maximal oxygen consumption
1 The quality of the evidence was downgraded by 2 due to high risk of bias for outcome reporting, and unclear risk of bias for randomization, allocation concealment and blinding
2 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs
3 Imprecision could not be calculated, as data was reported narratively only

J.20.6 Habitual physical activity

Table 89: Clinical evidence profile: Comparison 7. Physical activity for higher amount or longer duration versus lower amount or shorter duration

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physical activity for higher amount or longer duration	Physical activity for lower amount or shorter duration	Relative (95% CI)	Absolute	**Quality**	**Importance**
Lung function: FEV_1% predicted												
No evidence available												
Lung function: FVC% predicted												
No evidence available												
FEV_1 **peak**												
No evidence available												
Body composition												
No evidence available												
Quality of life												
No evidence available												
Preference for training programme												
No evidence available												
Adverse events												
No evidence available												
Need for hospitalization (follow-up: 12 months; better indicated by lower values) [≥30 minutes daily *versus* < 30 minutes]												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physical activity for higher amount or longer duration	Physical activity for lower amount or shorter duration	Relative (95% CI)	Absolute	**Quality**	**Importance**
1 (Cox 2016)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	16/33 (48.5%)	19/28 (67.9%)	RR 0.71 (0.46 to 1.1)	197 fewer per 1000 (from 366 fewer to 68 more)	VERY LOW	CRITICAL
Need for hospitalization (follow-up: 12 months; better indicated by lower values) [≥ 30 minutes for ≥ 10 minutes bouts daily *versus* lower amount or shorter duration]												
1 (Cox 2016)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/21 (38.1%)	26/40 (65%)	RR 0.59 (0.32 to 1.06)	266 fewer per 1000 (from 442 fewer to 39 more)	VERY LOW	CRITICAL

Abbreviations: CI: confidence interval; RR: risk ratio
1 The quality of the evidence was downgraded by 2 due to high risk of bias in relation to the selection of the study population and the comparability of the 2 groups
2 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID.

J.21 Psychological assessment

Not applicable to this review.

J.22 Cross infection

J.22.1 Outpatient care

Table 90: Clinical evidence profile: Comparison 1. Cohort segregation by clinic times versus no cohort segregation

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cohort segregation into different pathogens by clinic times	No cohort segregation	Relative (95% CI)	Absolute	**Quality**	**Importance**
10-year incidence of *P aeruginosa* infections (Follow-up 10 years)												
1 (Hayes 2010)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	13/21 (61.9%)	14/18 (77.8%)	RR 0.8 (0.52 to 1.21)	156 fewer per 1000 (from 373 fewer to 163 more)	LOW	CRITICAL
4-year prevalence of MRSA (percentages) (follow-up 4 years)												
1 (McKay 2009)	observational studies	very serious [3]	no serious inconsistency	no serious indirectness	Not calculable [2]	none	1.3%[4]	1%[4]	ns	-	VERY LOW	CRITICAL
4-year prevalence of non-mucoid *P aeruginosa* (percentages) (follow-up 4 years)												
1 (McKay 2009)	observational studies	very serious [3]	no serious inconsistency	no serious indirectness	Not calculable [2]	none	22.7%[4]	22.3%[4]	ns	-	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cohort segregation into different pathogens by clinic times	No cohort segregation	Relative (95% CI)	Absolute	Quality	Importance
4-year prevalence of mucoid *P aeruginosa* (percentages) (follow-up 4 years)												
1 (McKay 2009)	observational studies	very serious [3]	no serious inconsistency	no serious indirectness	Not calculable [2]	none	1.0%[4]	5.9%[4]	P=0.001	-	VERY LOW	CRITICAL
Staff compliance (percentages) (follow-up 4 years)												
1 (McKay 2009)	observational studies	very serious [3]	no serious inconsistency	no serious indirectness	Not calculable [2]	none	Adherence to the "coloured" clinic booking scheme: % of children attending the red clinic who were 5 and under: 2004: 96.8%; 2005: 97.5%; 2006: 94.4%; 2007: 95.9%.[4] N of patients	N of patients not reported	-	-	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cohort segregation into different pathogens by clinic times	No cohort segregation	Relative (95% CI)	Absolute		
							not reported					

Abbreviations: CI: confidence interval; MRSA: methicillin-resistant staphylococcus aureus; ns: not significant; RR: risk ratio
1 The quality of the evidence was downgraded by 1 due to unclear randomization, allocation concealment, blinding, incomplete data outcome and selective reporting
2 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
3 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to sample selection, comparability between groups and outcome reporting
4 Intervention group: data for the period 2004 to 2007; comparison group: data for the period 1999 to 2002. Intervention introduced in 2003.

Table 91: Clinical evidence profile: Comparison 2. Cohort segregation by location versus no cohort segregation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cohort segregation into different pathogens by location	No cohort segregation	Relative (95% CI)	Absolute		
Annual incidence of new growths of *P aeruginosa* (follow-up 9 years)												
1 (Lee 2004)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	Not calculable [2]	none	The annual incidence of new growths of *P aeruginosa* , while fluctuating, showed no downward trend, despite segregation.[3] N of patients unclear.		ns	-	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cohort segregation into different pathogens by location	No cohort segregation	Relative (95% CI)	Absolute		
Yearly prevalence of chronic *P aeruginosa* infection (follow-up 9 years)												
1 (Lee 2004)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	serious[4]	none	326/1803 patient months (18.1%)[3]	237/966 patient months (24.5%)[3]	OR 0.68 (0.56 to 0.82)	64 fewer per 1000 (from 35 fewer to 91 fewer)	VERY LOW	CRITICAL
Yearly prevalence of intermittent *P aeruginosa* infection (follow-up 9 years)												
1 (Lee 2004)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	622/1083 patient months (57.4%)[3]	253/966 patient months (26.2%)[3]	OR 3.8 (3.15 to 4.59)	312 more per 1000 (from 266 more to 358 more)	VERY LOW	CRITICAL

Abbreviations: CI: confidence interval; ns: not significant; OR: odds ratio
1 The quality of the evidence was downgraded by 2 because high risk of bias in relation to sample selection, comparability between groups, and outcome assessment and reporting
2 Imprecision cannot be calculated with the data provided
3 Intervention group: data from 2000; comparison group: data from 1990. Intervention implemented in 1991.
4 The quality of the evidence was downgraded by 1 as the CI crossed 1 default MID

Table 92: Clinical evidence profile: Comparison 3. Combination of protective equipment + individual segregation versus incomplete protective equipment + incomplete individual segregation

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Protective equipment + individual segregation	Incomplete protective equipment + incomplete individual segregation	Relative (95% CI)	Absolute	**Quality**	**Importance**
4-month prevalence of *P aeruginosa* infections (percentages) (follow-up 5 years)												
1 (Savant 2014)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	Not calculable [2]	none	21.78% (range: 31.09 to 12.95)[3]	29.79% (range: 38.74 to 12.95)[3]	p<0.0001	-	VERY LOW	CRITICAL
4-month prevalence of MRSA infections (percentages) (follow-up 5 years)												
1 (Savant 2014)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	Not calculable [2]	none	8.68% (range 12.78 to 5.38)[3]	10.76% (12.5 to 7.34)[3]	p=0.008	-	VERY LOW	CRITICAL

Abbreviations: CI: confidence interval; MRSA: methicillin-resistant staphylococcus aureus
1 The quality of the evidence was downgraded by 2 because of high risk bias in relation to sample selection, comparability between groups and outcome assessment.
2 Imprecision cannot be assessed with the reported data.
3 Intervention group: mean data for the period 2008 to 2012; comparison group: mean data for the period 2005 to 2007. Intervention implemented in 2007.

J.22.2 Inpatient care

Table 93: Clinical evidence profile: Comparison 4. Cohort segregation by location versus no cohort segregation

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cohort segregation into different pathogens by location	No cohort segregation	Relative (95% CI)	Absolute	Quality	Importance
Annual incidence of *B cepacia complex* (percentages) (follow-up 1 year)												
1 (Chen 2001)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	Not calculable [2]	none	3.7%[3]	5.8%[3]	-	-		CRITICAL
5-month incidence of hospital-associated colonisation of *B cepacia* (follow-up 5 months)												
1 (Thomassen 1986)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/235 (2.6%)[5]	24/308 (7.8%)[5]	OR 0.31 (0.12 to 0.77)	52 fewer per 1000 (from 17 fewer to 68 fewer)	VERY LOW	CRITICAL

Abbreviations: CI: confidence interval; OR: odds ratio
1 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to sample selection, comparability between groups and outcome assessment
2 Imprecision cannot be calculated with the data reported
3 Intervention group: data from 1991; comparison group: data from 1989. Intervention implemented in early 1990.
4 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to the comparability between groups and outcome assessment
5 Intervention group: data for the period 1 Aug 1983 to 31 Dec 1984; comparison group: data for the period 1 Mar 1982 to 31 Jul 1983. Intervention introduced in August 1983.

Table 94: Clinical evidence profile: Comparison 5. Individual segregation by location versus usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Individual segregation	Usual care	Relative (95% CI)	Absolute		
Patient's satisfaction												
1 (Russo 2006)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	Not calculable [2]	none	92% of children supported segregated treatment	-	-	-	VERY LOW	CRITICAL
Parents' satisfaction												
1 (Russo 2006)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	Not calculable [2]	none	91% of parents supported segregated treatment	-	-	-	VERY LOW	CRITICAL

Abbreviations: CI: confidence interval
1 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to sample selection, the comparability between groups and outcome assessment.
2 The imprecision cannot be calculated with the data reported

J.22.3 Combined inpatient and outpatient care

Table 95: Clinical evidence profile: Comparison 6. Cohort segregation versus no cohort segregation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cohort segregation into pathogens	Control	Relative (95% CI)	Absolute		
Monthly incidence of multiply resistant *P aeruginosa* strain (follow-up 1 month)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cohort segregation into pathogens	Control	Relative (95% CI)	Absolute	Quality	Importance
1 (Hoiby & Pedersen 1989)	observational studies	serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/77 (6.5%)[2]	22/107 (20.6%)[2]	OR 0.27 (0.1 to 0.74)	140 fewer per 1000 (from 45 fewer to 180 fewer)	VERY LOW	CRITICAL
Annual incidence of intermittent *P aeruginosa* (follow-up 1 year)												
1 (Frederiksen 1999)	observational studies	serious [3]	no serious inconsistency	no serious indirectness	very serious[4]	none	9/40 (22.5%)[5]	15/45 (33.3%)[5]	OR 0.58 (0.22 to 1.53)	109 fewer per 1000 (from 234 fewer to 100 more)	VERY LOW	CRITICAL
Annual incidence of chronic *P aeruginosa* (follow-up 1 year)												
1 (Frederiksen 1999)	observational studies	serious [3]	no serious inconsistency	no serious indirectness	serious[6]	none	7/69 (10.1%)[5]	15/75 (20%)[5]	OR 0.45 (0.17 to 1.19)	99 fewer per 1000 (from 159 fewer to 29 more)	VERY LOW	CRITICAL
6-month incidence *B Cepacia* (follow-up 6 months)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cohort segregation into pathogens	Control	Relative (95% CI)	Absolute	Quality	Importance
1 (Whiteford 1995)	observational studies	very serious [7]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/93 (1.1%)[8]	5/109 (4.6%) [8]	OR 0.23 (0.03 to 1.97)	35 fewer per 1000 (from 44 fewer to 41 more)	VERY LOW	CRITICAL
Annual incidence of Burkholderia species infection (percentages) (follow-up 1 year)												
1 (France 2008)	observational studies	very serious [9]	no serious inconsistency	no serious indirectness	Not calculable [10]	none	16.3%[11]	3-5%[11]	-	-	VERY LOW	CRITICAL
Monthly prevalence of multiple resistant *P aeruginosa* strain (percentages) (follow-up 1 month)												
1 (Hoiby 1989)	observational studies	serious [1]	no serious inconsistency	no serious indirectness	very serious[4]	none	37% (44/119)[2]	33% (39/119)[2]	OR 1.02 (0.60 to 1.76)	4 more per 1000 (from 101 fewer to 134 more)	VERY LOW	CRITICAL
Prevalence of AES-1 *P aeruginosa* epidemic strain (follow-up: 2 years)												
1 (Griffiths 2005)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	-	-	adjRR 0.64 (0.47 to 0.87)[12]	-	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cohort segregation into pathogens	Control	Relative (95% CI)	Absolute		
Annual prevalence of chronic *P aeruginosa* infection (follow-up 1 year)												
1 (Jones 2005)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	184/228 (80.7%)[13]	156/216 (72.2 %)[13]	OR 1.61 (1.03 to 2.51)	85 more per 1000 (from 6 more to 145 more)	VERY LOW	CRITICAL
Annual prevalence of transmissible *P aeruginosa* infection (follow-up 1 year)												
1 (Jones 2005)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	35/228 (15.4%)[13]	28/216 (13%)[13]	OR 1.22 (0.71 to 2.08)	24 more per 1000 (from 34 fewer to 107 more)	VERY LOW	CRITICAL
Annual prevalence of chronic infection with transmissible *P aeruginosa* strain (percentages) (follow-up 1 year)												
1 (Jones 2005)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	Not calculable[10]	none	15.4%[13]	13.0%[13]	-	-	VERY LOW	CRITICAL

Abbreviations: adjRR: adjusted risk ratio; ASUSP-1: Australian epidemic strain, type 1; CI: confidence interval; MRSA: methicillin-resistant staphylococcus aureus; OR: odds ratio

1 The quality of the evidence was downgraded by 1 because of high risk of bias in relation to comparability of the groups, and outcome reporting

2 Intervention group: data from May 1983; comparison group: data from March 1983. Intervention implemented in April 1983.

3 The quality of the evidence was downgraded by 1 because of high risk of bias in relation to comparability between groups, and outcome assessment

4 The quality of the evidence was downgraded by 2 because the 95% CI crossed 2 default MIDs

5 Intervention group: data from 1982; comparison group: data from 1980. Intervention implemented in 1981

6 The quality of the evidence was downgraded by 1 because the 95% CI crossed 1 default MID
7 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to the comparability between groups, outcome assessment and unclear sample selection
8 Intervention group: data from December 1992; comparison group: data from May 1992. Intervention implemented in June 1992.
9 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to sample selection, comparability between groups and outcome assessment
10 Imprecision cannot be calculated with the data reported
11 Intervention group: data from 1992; comparison group: data from 1983-1990. Intervention implemented in November 1991.Intervention was incomplete cohort segregation.
12 Intervention group: data from 2002; comparison group: data from 1999. Intervention implemented in January 2000.
13 Intervention group: data from 2001; comparison group: data from 1999. Intervention implemented in 2000.

Table 96: Clinical evidence profile: Comparison 7. Complete cohort segregation versus incomplete cohort segregation

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Complete cohort segregation	Incomplete cohort segregation	Relative (95% CI)	Absolute		
Annual incidence of *Burkholderia* species (percentages) (follow-up 1 year)												
1 (France 2008)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	Not calculable [2]	none	< 3% (for all but 1 year) [3]	16.3%[3]	-	-	VERY LOW	CRITICAL

Abbreviations: CI: confidence interval
1 The quality of the evidence was downgraded by 2 because high risk of bias in relation to sample selection, the comparability between the groups and the outcome reporting and assessment.
2 Imprecision cannot be calculated with the data reported
3 Intervention group: data after 1993; comparison group: data from 1992. Intervention implemented in November 1993.

Table 97: Clinical evidence profile: Comparison 8. Individual segregation versus usual care

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Individual segregation	Usual care	Relative (95% CI)	Absolute		
Patient satisfaction												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Individual segregation	Usual care	Relative (95% CI)	Absolute		
1 (Waine 2007)	observational studies	very serious 1	no serious inconsistency	no serious indirectness	not calculable [2]	none	N=48 n=30 (62.5%) said that their quality of life did not suffer as a result.	N=43 n=10 (23.3%) said that their quality of life would suffer a 'significant amount' or 'a great deal' if they were to begin avoiding others	-	-	VERY LOW	CRITICAL

Abbreviations: CI: confidence interval
1 The quality of the evidence was downgraded by 2 because high risk of bias in relation to sample selection, the comparability between the groups and the outcome reporting and assessment.
2 Imprecision cannot be calculated with the data reported

Table 98: Clinical evidence profile: Comparison 9. Cohort segregation + individual segregation versus cohort segregation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cohort segregation + individual segregation	Cohort segregation	Relative (95% CI)	Absolute		
Yearly prevalence of *B cepacia* complex infection (percentages) (follow-up 1 year)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cohort segregation + individual segregation	Cohort segregation	Relative (95% CI)	Absolute		
1 (Chen 2001)	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	not calculable [2]	none	7%[3]	15%[3]	-	-	VERY LOW	CRITICAL
Yearly prevalence of *Burkholderia* species (percentages) (follow-up: 5 years)												
1 (France 2008)	observational studies	very serious [4]	no serious inconsistency	no serious indirectness	not calculable [2]	none	9.3%[5]	31.2%[5]	-	-	VERY LOW	CRITICAL

Abbreviations: CI: confidence interval
1 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to sample selection, comparability between groups and outcome assessment
2 Imprecision cannot be calculated with the data reported
3 Intervention group: data from 1999; comparison group: data from 1992. Intervention introduced in 1996.
4 The quality of the evidence was downgraded by 2 because high risk of bias in relation to sample selection, the comparability between the groups and the outcome reporting and assessment.
5 Intervention group: data from 2005; comparison group: data from 1994. Intervention implemented in 2000.

Table 99: Clinical evidence profile: Comparison 10. Cohort segregation + individual segregation + protective equipment versus usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cohort segregation + individual segregation + protective equipment	Usual care	Relative (95% CI)	Absolute		
Annual incidence of *B cepacia* complex infection (percentages) (follow-up 1 year)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cohort segregation + individual segregation + protective equipment	Usual care	Relative (95% CI)	Absolute		
1 (Chen 2001)	observational studies	very serious 1	no serious inconsistency	no serious indirectness	Not calculable [2]	none	< 1%[3]	8.8 %[3]	-	-	VERY LOW	CRITICAL

Abbreviations: CI: confidence interval
1 The quality of the evidence was downgraded by 2 because of high risk of bias in relation to sample selection, comparability between groups and outcome assessment
2 Imprecision cannot be calculated with the data reported
3 Intervention group: data post-implementation; comparison group: data from 1996. Intervention implemented in early 1997.

Table 100: Clinical evidence profile: Comparison 11. Cohort segregation + individual segregation versus usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cohort segregation into pathogens	Control	Relative (95% CI)	Absolute		
Patient satisfaction												
1 (Griffiths 2004)	observational studies	serious [1]	no serious inconsistency	no serious indirectness	Not calculable [2]	none	Positive: 63%: Negative: 12%: Unsure: 25% (p<0.001)	-	-	-	VERY LOW	IMPORTANT
Carer satisfaction												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cohort segregation into pathogens	Control	Relative (95% CI)	Absolute		
1 (Griffiths 2004)	observational studies	serious [1]	no serious inconsistency	no serious indirectness	Not calculable [2]	none	Positive: 85%: Negative: 4%: Unsure: 11% (p<0.001)	-	-	-	VERY LOW	IMPORTANT

Abbreviations: CI: confidence interval
1 The quality of the evidence was downgraded by 1 because of high risk of bias in relation to sample selection and outcome reporting
2 Imprecision cannot be calculated with the data reported