National Institute for Health and Care Excellence

Final

Cystic Fibrosis: diagnosis and management

Appendix J

Main appendix document GRADE tables 25 October 2017

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 All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

Contents

Appendix J: GRADE Tables	6
J.1 Diagnosis of cystic fibrosis	6
J.2 Information and support	6
J.3 Service delivery	6
J.3.1 Service configuration	6
J.3.2 Multidisciplinary teams	. 28
J.4 Transition	28
J.5 Complications of cystic fibrosis	. 28
J.6 Pulmonary monitoring	. 28
J.6.1 Review 1. Monitoring for pulmonary disease onset in people with CF without clinical signs or symptoms of lung disease	. 28
J.6.2 Review 2. Monitoring for evolving pulmonary disease in people with CF with established lung disease	. 30
J.6.3 Review 3. Monitoring for evolving pulmonary disease in people with CF following an acute pulmonary exacerbation	. 31
J.7 Airway clearance techniques	. 33
J.8 Mucoactive agents	. 47
J.8.1 Mannitol	. 47
J.8.2 Dornase alfa	63
J.8.3 Nebulised sodium chloride	69
J.8.4 Acetylcysteine	. 77
J.9 Pulmonary infection – prophylaxis	.79
J.10Pulmonary infection – acute	90
J.10.1 Pseudomonas aeruginosa	90
J.10.2 Staphylococcus aureus	105
J.10.3 <i>Burkholderia cepacia</i> complex	105
J.10.4 Non-tuberculous <i>mycobacteria</i>	106
J.10.5Non-identified pathogen	106
J.11Pulmonary infection – chronic	106
J.11.1 <i>P Aeruginosa</i>	106
J.11.2S Aureus	143
J.11.3 <i>B Cepacia</i> Complex	143
J.11.4 Aspergillus Fumigatus	144
J.12Immunomodulatory agents	149
J.13Nutrition	162
J.13.1 Oral calorie supplementation	162
J.13.2 Enteral tube feeding	172
J.13.3Appetite stimulants	177
J.13.4 Nutritional education/ dietary advice	183

J 14Exocrine pancreatic insufficiency 197
J.14.1 Comparison 1. Acid suppressing agents as adjuvant therapy to PERT
J.14.2 Comparison 2. High-dose PERT versus low-dose of PERT 201
J.15Distal intestinal obstruction syndrome
J.16Liver 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? 205
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
nypertension with (out) oesophageal varices)?
J.17 Ursodeoxycholic acid
J.18Cystic fibrosis related diabetes
J.19Bone mineral density
J.20Exercise
J.20.1 Aerobic exercise programmes
J.20.2 Strength resistance training/ anaerobic training
J.20.3 High intensity interval training
J.20.4 Inspiratory muscle training
J.20.5 Combined programmes
J.20.6 Habitual physical activity
J.21Psychological assessment
J.22Cross infection
J.22.1 Outpatient care
J.22.1 Outpatient care

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: C	omparisor	n 1.1. Home versus hospital care for the administration of IV antibiotics in people with
	CF experiencing an acute	pulmonary	/ exacerbation

Quality	y assessment				No of treatments		Effect					
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Other consideration s	Home care for the admin istrati on of IV antibi otics	Hospital care for the administratio n of IV antibiotics	Relati ve (95% CI)	Absolut e	Qual ity	Importance	
Lung f	unction: chan	ge in FEV	1% predicted	(follow-up 21	days; range	of scores: 0-1	00; Bette	r indicated by I	higher va	lues)		

Quality No of studi es	y assessment Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	No of tr Home care for the admin istrati on of IV antibi otics	Hospital care for the administratio n of IV antibiotics	Effect Relati ve (95% CI)	Absolut e	Qual ity	Importance
1 (Wolt er 1997)	randomised trials ¹	seriou s ²	no serious inconsistenc y	no serious indirectnes s	very serious ³	none	13ª	18ª	-	MD 3 lower (13.61 lower to 7.61 higher)	VER Y LOW	CRITICAL
Lung f	unction: chan	ge in FEV	1 % predicted	(follow-up m	ean 18 days;	range of score	s: 0-100;	Better indicate	ed by hig	her value	s)	
1 (Don ati 1987)	observation al studies	no seriou s risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ⁴	none	31⁵	32 ^b	-	MD 5.60 lower (12.29 lower to 1.09 higher) c	VER Y LOW	CRITICAL
Lung f	unction: chan	ge in FEV	1 % predicted	(follow-up 15	days; range	e of scores: 0-1	00; Bette	r indicated by I	higher va	lues)		
1 (Esm ond 2006)	observation al studies	seriou S ⁵	no serious inconsistenc y	no serious indirectnes s	serious ⁴	none	15 ^d	15 ^d	-	MD 3.1 lower (6.93 lower to 0.73 higher)	VER Y LOW	CRITICAL
Patier exacer	nts starting nex bation) (follow	xt course v-up mea	of antibiotics n 18 days)	more than 12	e previou	is course (pro	xy outco	me for tin	ne to ne	xt		

Quality	/ assessment						No of treatments Effect					
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Home care for the admin istrati on of IV antibi otics	Hospital care for the administratio n of IV antibiotics	Relati ve (95% CI)	Absolut e	Qual ity	Importance
1 (Bos worth 1997)	observation al studies	no seriou s risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ⁶	none	13/27 (48.1 %) ^e	28/32 (87.5%) ^e	RR 0.55 (0.36 to 0.83)		VER Y LOW	CRITICAL
Weigh	t (change) kg ((follow-up	o 18 days; Bett	er indicated	by higher va	lues)						
1 (Don ati 1987)	observation al studies	no seriou s risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ⁶	none	37 ^b	37 ^b	-	MD 1.10 lower (4.29 lower to 2.09 higher) a	VER Y LOW	CRITICAL
Weigh	t change (kg)	(follow-u	p ≤10 days pos	st treatment;	Better indica	ated by higher	/alues)					
1 (Wolt er 1997)	observation al studies	seriou s ²	no serious inconsistenc y	no serious indirectnes s	very serious ⁷	none	13ª	18ª	-	MD 0.5 lower (8.06 lower to 7.06 higher)	VER Y LOW	IMPORTAN T
BMI (fo	ollow-up 15 da	ys; Bette	r indicated by	higher values	s)							
1 (Esm ond	observation al studies	seriou s ⁵	no serious inconsistenc y	no serious indirectnes s	serious ⁶	none	15 ^d	15 ^d	-	MD 0.2 lower (0.63	VER Y LOW	IMPORTAN T

Quality	/ assessment						No of t	reatments	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Home care for the admin istrati on of IV antibi otics	Hospital care for the administratio n of IV antibiotics	Relati ve (95% CI)	Absolut e	Qual	Importance
2006)										lower to 0.23 higher)		
Chang	e in quality of	life – CF-	QOL-Physical	(follow-up 15	5 days; range	e of scores: 0-1	00; Bette	er indicated by	higher va	alues)		
1 (Esm ond 2006)	observation al studies	seriou S ⁵	no serious inconsistenc y	no serious indirectnes s	very serious ^{3, f}	none	15 ^d	15 ^d	-	MD 2.2 lower (13.21 lower to 8.81 higher)	VER Y LOW	IMPORTAN T
Chang	e in quality of	life – CF-	QOL-Social (fo	ollow-up 15 d	ays; range o	f scores: 0-100	; Better i	ndicated by hig	gher valu	es)		
1 (Esm ond 2006)	observation al studies	seriou S ⁵	no serious inconsistenc y	no serious indirectnes s	very serious ^{3, f}	none	15 ^d	15 ^d	-	MD 3.4 lower (18.87 lower to 12.07 higher)	VER Y LOW	IMPORTAN T
Chang	e in quality of	life – CF-	QOL-Treatmer	nt (follow-up	15 days; ran	ge of scores: 0	-100; Bet	ter indicated b	y higher	values)		
1 (Esm ond 2006)	observation al studies	seriou S ⁵	no serious inconsistenc y	no serious indirectnes s	very serious ^{3, f}	none	15 ^d	15 ^d	-	MD 2 lower (17.15 lower to 13.15 higher)	VER Y LOW	IMPORTAN T

Quality No of studi es	y assessment Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	No of tr Home care for the admin istrati on of IV antibi	Preatments Hospital care for the administratio n of IV antibiotics	Effect Relati ve (95% CI)	Absolut e	Qual	
Chang	o in quality of	life CE	OOL Sympton	ne (follow up	15 days: ror	an of scores: 0	Otics	ttor indicated b	v higher	values)	ity	Importance
1 (Esm ond 2006)	observation al studies	seriou s ⁵	no serious inconsistenc y	no serious indirectnes s	serious ^{4, f}	none	- 100; Be 15₫	15 ^d	-	MD 17.1 lower (31.25 to 2.95 lower)	VER Y LOW	IMPORTAN T
Chang	e in quality of	life – CF-	QOL-Emotiona	al (follow-up	15 days; ran	ge of scores: 0-	100; Bet	ter indicated b	y higher	values)		
1 (Esm ond 2006)	observation al studies	seriou s ⁵	no serious inconsistenc y	no serious indirectnes s	very serious ^{3, f}	none	15 ^d	15 ^d	-	MD 4.2 higher (8.67 lower to 17.07 higher)	VER Y LOW	IMPORTAN T
Chang	e in quality of	life – CF-	QOL-Future (f	ollow-up 15 d	lays; range o	of scores: 0-100	; Better	indicated by hi	gher valu	ies)		
1 (Esm ond 2006)	observation al studies	seriou S ⁵	no serious inconsistenc y	no serious indirectnes s	very serious ^{3, f}	none	15 ^d	15 ^d	-	MD 5.5 lower (17.96 lower to 6.96 higher)	VER Y LOW	IMPORTAN T
Chang	e in quality of	life – CF-	QOL-Relations	ships (follow-	up 15 days;	range of scores	s: 0-100;	Better indicate	d by hig	her values	S)	

Quality	v assassmant					No of t	reatments	Effect				
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Home care for the admin istrati on of IV antibi otics	Hospital care for the administratio n of IV antibiotics	Relati ve (95% CI)	Absolut e	Qual	Importance
1 (Esm ond 2006)	observation al studies	seriou S ⁵	no serious inconsistenc y	no serious indirectnes s	very serious ^{3, f}	none	15 ^d	15 ^d	-	MD 7.4 higher (5.6 lower to 20.4 higher)	VER Y LOW	IMPORTAN T
Chang	e in quality of	life – CF	QOL-Body ima	age (follow-u	p 15 days; ra	ange of scores:	0-100; B	etter indicated	by highe	r values)		
1 (Esm ond 2006)	observation al studies	seriou S ⁵	no serious inconsistenc y	no serious indirectnes s	very serious ^{3, f}	none	15 ^d	15 ^d	-	MD 0.9 higher (13.92 lower to 15.72 higher)	VER Y LOW	IMPORTAN T
Chang	le in quality of	life – CF	QOL-Career (f	ollow-up 15 c	days; range	of scores: 0-100); Better	indicated by hi	gher valu	ues)		
1 (Esm ond 2006)	observation al studies	seriou S ⁵	no serious inconsistenc y	no serious indirectnes s	very serious ^{3, f}	none	15 ^d	15 ^d	-	MD 8.3 higher (5.76 lower to 22.36 higher)	VER Y LOW	IMPORTAN T

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; CF-QOL: cystic fibrosis quality of life questionnaire; FEV1: 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*

							N		E 11			
Quality No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	No of me care for the adm inist ratio n of IV anti bioti cs	Hospital care for the administratio n of IV AB	Relati ve (95% CI)	Absolut e	Quali	Importance
Lung f	unction: Chan	ge in FEV	1 % predicted	(follow-up 14	days; range	of scores: 0-10	0; Bett	ter indicated by	higher v	alues)		
1 (Riet hmue Iler 2002)	observation al studies	serious 1	no serious inconsistenc y	no serious indirectnes s	very serious ²	none	29ª	27 ^a	-	MD 2 higher (9.81 lower to 13.81 higher)	VER Y LOW	CRITICAL
Nutriti	onal status: ch	ange in v	veight (kg) (fol	low-up 14 day	ys; Better in	dicated by high	er valu	es)				

Quality	y assessment					No of treatments Effe			Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Ho me care for the adm inist ratio n of IV anti bioti cs	Hospital care for the administratio n of IV AB	Relati ve (95% CI)	Absolut e	Quali ty	Importance
1 (Riet hmue Iler 2002)	observation al studies	serious 1	no serious inconsistenc y	no serious indirectnes s	very serious ³	none	29ª	28ª	-	MD 0 higher (4.38 lower to 4.38 higher)	VER Y LOW	IMPORTAN T
Nutriti	onal status: ch	nange in v	veight for heig	ht (%) (follow	-up 14 days;	Better indicate	d by h	igher values)				
1 (Riet hmue Iler 2002)	observation al studies	serious 1	no serious inconsistenc y	no serious indirectnes s	serious ⁴	none	29ª	28ª	-	MD 1 lower (4.64 lower to 2.64 higher)	VER Y LOW	IMPORTAN T

Abbreviations: CI: confidence interval; CF: cystic fibrosis; FEV₁: 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			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	CF centr e care	Shared care (UK equivalent)	Relati ve (95% CI)	Absolut e	Quali ty	Importance
Chang	e in FEV ₁ (% p	redicted)	(follow-up 1 ye	ar; range of s	scores: 0-100	; Better indicate	ed by hi	gher values)				
1 (Van Kool wijk 2002)	observationa I studies	very serious 1	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	41	41	-	MD 0.5 lower (3.05 lower to 2.05 higher)	VER Y LOW	CRITICAL
First to	last FEV ₁ (%	per year)	(follow-up 3 ye	ears; range of	f scores: 0-1	00; Better indica	ated by I	higher value	s)			
1 (Tho mas 2008)	observationa I studies	very serious 2	no serious inconsistenc y	no serious indirectnes s	serious ³	none	67	30	-	MD 2.4 lower (5.72 lower to 0.92 higher)	VER Y LOW	CRITICAL
Slope I	FEV₁ (% per ye	ar) (follo	w-up 3 years; r	ange of score	es: 0-100; Bet	tter indicated by	y higher	values)				
1 (Tho mas 2008)	observationa I studies	very serious 2	no serious inconsistenc y	no serious indirectnes s	serious3	none	67	30	-	MD 2.2 lower (5.37 lower to 0.97 higher)	VER Y LOW	CRITICAL
BMI (fo	ollow-up 1 year	; Better i	ndicated by hig	jher values)								
1 (Van Kool wijk 2002)	observationa I studies	very serious	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	41	41	-	MD 0.12 lower (0.44 lower to	VER Y LOW	IMPORTAN T

Quality No of studi es	r assessment Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	No of CF centr e care	Shared Care (UK equivalent)	Effect Relati ve (95% CI)	Absolut e	Quali ty	Importance
								,		0.2 higher)		
Quality	of life: CFQ-T	een - Phy	sical (range of	scores: 0-10	0; Better indi	cated by higher	values					
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	serious ^{3, a}	none	24	10	-	MD 17.8 lower (30.28 to 5.32 lower)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-T	een - Rol	e (range of sco	res: 0-100; B	etter indicate	d by higher val	ues)					
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	serious ^{3, a}	none	24	10	-	MD 10.4 lower (26.45 lower to 5.65 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-T	een - Vita	lity (range of s	cores: 0-100;	Better indica	ated by lower va	alues)					
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	serious ^{3, a}	none	24	10	-	MD 18.2 lower (32.5 to 3.9 lower)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-T	een - Em	otional (range o	of scores: 0-1	00; Better in	dicated by high	er value	s)				
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	serious ^{3, a}	none	24	10	-	MD 5.5 lower (18.35 lower to 7.35 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-T	een - Soc	ial (range of so	cores: 0-100;	Better indica	ted by higher va	alues)					

Quality	assessment						No of r	oatients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	CF centr e care	Shared care (UK equivalent)	Relati ve (95% CI)	Absolut e	Quali ty	Importance
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	serious ^{3, a}	none	24	10	-	MD 17.6 lower (26.71 to 8.49 lower)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-T	een - Bod	ly (range of sc	o <mark>res: 0-100;</mark> B	etter indicat	ed by higher va	lues)					
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	very serious ^{5, a}	none	24	10	-	MD 4.5 lower (21.56 lower to 12.56 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-T	een - Eati	ng (range of s	cores: 0-100;	Better indica	ted by higher v	alues)					
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	very serious ^{5, a}	none	24	10	-	MD 4.5 lower (21.56 lower to 12.56 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-T	een - TB	(range of score	es: 0-100; Bet	er indicated	by higher value	es)					
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	very serious ^{5, a}	none	24	10	-	MD 9.6 lower (28.01 lower to 8.81 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-T	een - Hea	Ith (range of so	cores: 0-100;	Better indica	ited by higher v	alues)					
1 (Tho	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	serious ^{3, a}	none	24	10	-	MD 14.8 lower (31.75	VER Y LOW	IMPORTAN T

Quality	/ assessment						No of p	patients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	CF centr e care	Shared care (UK equivalent)	Relati ve (95% CI)	Absolut e	Quali ty	Importance
mas 2006)										lower to 2.15 higher)		
Quality	/ of life: CFQ-T	een - Wei	ght (range of s	cores: 0-100;	Better indica	ated by higher v	values)					
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	serious ^{3, a}	none	24	10	-	MD 12.5 lower (29.45 lower to 4.45 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-T	een - Res	piratory (range	e of scores: 0	-100; Better i	ndicated by hig	her valu	ies)				
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	serious ^{3, a}	none	24	10	-	MD 4.5 lower (15.25 lower to 6.25 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-T	een - Dig	estion (range o	of scores: 0-10	00; Better inc	licated by highe	er values	5)				
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	serious ^{3, a}	none	24	10	-	MD 7.9 lower (17.14 lower to 1.34 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-C	hild - Phy	sical (range of	f scores: 0-10	0; Better ind	icated by highe	r values)				
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	very serious ^{5, a}	none	46	37	-	MD 1.2 lower (10.97 lower to	VER Y LOW	IMPORTAN T

Quality No of studi	Quality assessmentNo of studiDesignRisk of biasInconsistenc yIndirectnes sImprecisio nOther conside 						No of I CF centr	oatients Shared care (UK equivalent	Effect Relati ve (95%	Absolut e	Quali	
							care)	CI)	8.57	ty	Importance
Quality	of life: CEO-C	hild - Em	otional (range	of scores: 0-1	Inn: Better in	dicated by high	or value			nigher)		
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n ª	none	46	37	-	MD 1.3 higher (5.13 lower to 7.73 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-C	hild - Soo	cial (range of s	cores: 0-100;	Better indica	ated by higher v	alues)					
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	serious ^{3, a}	none	46	37	-	MD 1.7 lower (9.46 lower to 6.06 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-C	hild - Bo	dy (range of sc	ores: 0-100; E	Better indicat	ted by higher va	lues)					
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	serious ^{3, a}	none	46	37	-	MD 2.8 lower (13.64 lower to 8.04 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-C	hild - Eat	ing (range of s	cores: 0-100;	Better indica	ated by higher v	alues)					
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	very serious5, a	none	46	37	-	MD 0.5 lower (11.94 lower to 10.94 higher)	VER Y LOW	IMPORTAN T

Quality No of studi es	<mark>assessment</mark> Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	No of p CF centr e care	Shared care (UK equivalent)	Effect Relati ve (95% CI)	Absolut e	Quali ty	Importance
Quality	of life: CFQ-C	hild - TB	(range of score	es: 0-100; Bet	ter indicated	by higher value	es)					
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	serious ^{3, a}	none	46	37	-	MD 4.7 higher (5.88 lower to 15.28 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-C	hild - Res	spiratory (range	e of scores: 0	-100; Better	indicated by hig	<mark>jher val</mark> i	ues)				
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	serious ^{3, a}	none	46	37	-	MD 3.9 higher (5.69 lower to 13.49 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-C	hild - Dig	estion (range o	of scores: 0-1	00; Better in	dicated by high	er value	s)				
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	serious ^{3, a}	none	46	37	-	MD 4 higher (8.38 lower to 16.38 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-P	arent - Pl	nysical (range o	of scores: 0-1	00; Better in	dicated by high	er value	s)				
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	serious ^{3, a}	none	45	35	-	MD 2.5 higher (6.96 lower to 11.96 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-P	arent - Vi	tality (range of	scores: 0-10	0; Better indi	cated by higher	values					

Quality No of studi es 1 (Tho mas 2006)	observationa I studies	Risk of bias very serious	Inconsistenc y no serious inconsistenc y	Indirectnes s no serious indirectnes s	Imprecisio n no serious imprecisio n ^a	Other consideration s none	No of p CF centr e care 45	Shared care (UK equivalent) 35	Effect Relati ve (95% CI) -	Absolut e MD 0.7 lower (7.78 lower to 6.38 higher)	Quali ty VER Y LOW	Importance IMPORTAN T
Quality	of life: CFQ-P	arent - Er	notional (range	e of scores: 0	-100; Better i	ndicated by hig	her valu	ies)				
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	serious ^{3, a}	none	45	35	-	MD 1.1 higher (7.52 lower to 9.72 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-P	arent - Bo	ody (range of s	cores: 0-100;	Better indica	ated by higher v	values)					
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	very serious ^{5, a}	none	45	35	-	MD 3 higher (9.12 lower to 15.12 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-P	arent - Ea	ating (range of	scores: 0-100	; Better indi	cated by higher	values)					
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	serious ^{3, a}	none	45	35	-	MD 7.5 lower (20.22 lower to 5.22 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-P	arent - TE	B (range of sco	res: 0-100; Be	etter indicate	d by higher value	ues)					

Quality No of studi es 1 (Tho mas 2006)	observationa I studies	Risk of bias very serious	Inconsistenc y no serious inconsistenc y	Indirectnes s no serious indirectnes s	Imprecisio n serious ^{3, a}	Other consideration s none	No of p CF centr e care 45	Shared care (UK equivalent) 35	Effect Relati ve (95% CI) -	Absolut e MD 6.2 lower (14.63 lower to 2.23 higher)	Quali ty VER Y LOW	Importance IMPORTAN T
Quality	of life: CFQ-P	arent - He	ealth (range of	scores: 0-100	; Better indi	cated by higher	values)					
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	very serious ^{5, a}	none	45	35	-	MD 1.1 higher (8.6 lower to 10.8 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-P	arent - W	eight (range of	scores: 0-10); Better indi	cated by higher	values					
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	very serious ^{5, a}	none	45	35	-	MD 0.8 lower (16.4 lower to 14.8 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-P	arent - Re	espiratory (ran	ge of scores:	0-100; Bette	r indicated by h	igher va	lues)				
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	very serious ^{5, a}	none	45	35	-	MD 0.5 lower (10.33 lower to 9.33 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-P	arent - Di	gestion (range	of scores: 0-	100; Better i	ndicated by hig	her valu	es)				

Quality No of studi es	/ assessment Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	No of p CF centr e care	Shared care (UK equivalent)	Effect Relati ve (95% CI)	Absolut e	Quali ty	Importance
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	serious ^{3, a}	none	45	35	-	MD 0.6 lower (8.76 lower to 7.56 higher)	VER Y LOW	IMPORTAN T
Quality	of life: CFQ-P	arent - So	chool function	(range of sco	res: 0-100; B	etter indicated	by highe	er values)				
1 (Tho mas 2006)	observationa I studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	very serious ^{5, a}	none	45	35	-	MD 0.60 lower (11.63 lower to 10.43 higher)	VER Y LOW	IMPORTAN T

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; CFQ: cystic fibrosis questionnaire; FEV₁: 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)

Quality	Quality assessment							oatients	Effect	Abachita		
studie s	Design	bias	y	s	n	consideration s	Centr e	care (below CF Trust	e (95% CI)	Absolute	Quali	
								recs)			ty	Importance
Change	e in lung funct	ion: FEV ₁	(% predicted) (follow-up 1 ye	ears; range o	f scores: 0-100;	Better in	ndicated	by highe	r values)		
1 (Van Koolw ijk 2002)	observationa I studies	very serious 1	no serious inconsistency	no serious indirectnes s	serious2	none	41	23	-	MD 2.7 higher (0.55 lower to 5.95 higher)	VER Y LOW	CRITICAL
Lung fu	unction: First t	o last FE	/ ₁ (% per year)	(follow-up 3 y	/ears; range (of scores: 0-100	; Better	indicated	l by high	er values)		
1 (Tho mas 2008)	observationa I studies	very serious 3	no serious inconsistency	no serious indirectnes s	serious ²	none	67	11	-	MD 5.7 lower (10.99 to 0.41 lower)	VER Y LOW	CRITICAL
Slope F	EV1 (% per ye	ar) (follov	/-up 3 years; ra	nge of scores	: 0-100; Bette	er indicated by h	nigher va	alues)				
1 (Tho mas 2008)	observationa I studies	very serious 3	no serious inconsistency	no serious indirectnes s	serious ²	none	67	11	-	MD 3.3 lower (6.13 to 0.47 lower)	VER Y LOW	CRITICAL
BMI (fo	llow-up 1 year	; Better ir	dicated by hig	her values)								
1 (Van Koolw ijk 2002)	observationa I studies	very serious 1	no serious inconsistency	no serious indirectnes s	no serious imprecisio n	none	41	23	-	MD 0.09 lower (0.42 lower to 0.24 higher)	VER Y LOW	IMPORTAN T

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

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; FEV₁: 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 patie	ents	Effect			
No of studie s	Design	Risk of bias	Inconsistency	Indirectness	Imprecisio n	Other consideration s	CF specialist clinic	Genera I (not CF) clinic	Relativ e (95% CI)	Absolut e	Qual ity	Importan ce
Patient	t satisfaction w	ith care o	verall (Better in	dicated by hig	gher values)							
1 (Walt ers 1994)	observationa I studies	serious 1	no serious inconsistency	no serious indirectness	Not calculable	none	N= 686 ov disaggrega group)	erall (not ated by	-	MD 0.44 higher (0.29 higher to 0.58 higher)	VER Y 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 p	patients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Local care (belo w CF Trust recs)	Shared care (UK equivalent)	Relati ve (95% CI)	Absolut e	Quali ty	Importance
Lung f	unction: chang	ge in FEV	1 % predicted (follow-up 1 ye	ears; range o	f scores: 0-100	; Better	indicated by	higher v	alues)		

Quality No of studi es	<mark>/ assessment</mark> Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	No of p Local care (belo w CF Trust recs)	Shared care (UK equivalent)	Effect Relati ve (95% CI)	Absolut e	Quali ty	Importance
1 (Van Kool wijk 2002)	observation al studies	very serious 1	no serious inconsistenc y	no serious indirectnes s	serious ²	none	23	41	-	MD 3.2 lower (6.84 lower to 0.44 higher)	VER Y LOW	CRITICAL
Lung f	unction: First f	to last FE	V₁ (% per year) (follow-up 1	year; range	of scores: 0-10	0; Better	indicated by	y higher	values)		
1 (Tho mas 2008)	observation al studies	very serious 3	no serious inconsistenc y	no serious indirectnes s	serious ²	none	11	30	-	MD 3.3 higher (2.59 lower to 9.19 higher)	VER Y LOW	CRITICAL
Lung f	unction: Slope	FEV1 (%	per year) (follo	w-up 1 year;	range of sco	res: 0-100; Bett	er indica	ated by lowe	r values)			
1 (Tho mas 2008)	observation al studies	very serious ³	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	11	30	-	MD 1.1 higher (2.69 lower to 4.89 higher)	VER Y LOW	CRITICAL
Nutritio	onal status: ch	ange in E	MI (follow-up '	l year; Better	indicated by	v higher values)						
1 (Van Kool wijk 2002)	observation al studies	very serious 1	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	23	41	-	MD 0.03 lower (0.43 lower to 0.37 higher)	VER Y LOW	IMPORTAN T

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; FEV₁: 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

Quality No of studi es	y assessment Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	No of patie Shared care (above UK equivalent)	ents Shared care (UK equivalen t)	Effect Relati ve (95% CI)	Absolut e	Quali ty	Importan ce
Lung f	unction: First	to last FE	V₁ (% per yea	r) (follow-up :	3 years; rang	ge of scores: 0-	100; Better i	ndicated by	higher v	alues)		
1 (Tho mas 2008)	observation al studies	very serious 1	no serious inconsistenc y	serious ²	serious ³	none	19	30	-	MD 0.5 lower (5.63 lower to 4.63 higher)	VER Y LOW	CRITICAL
Lung f	unction: Slope	e FEV₁ (%	per year) (follo	ow-up 3 years	s; range of s	cores: 0-100; B	etter indicat	ed by highe	r values)			
1 (Tho mas 2008)	observation al studies	very serious 1	no serious inconsistenc y	serious ²	serious ³	none	19	30	-	MD 2.1 lower (6.52 lower to 2.32 higher)	VER Y LOW	CRITICAL

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

Abbreviations: CI: confidence interval; CF: cystic fibrosis; FEV1: 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 patient	ts	Effect				
No of studie s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Home monitoring program with diary and usual care	Usu al care	Relativ e (95% CI)	Absolute	Quali ty	Importan ce
Change	e in FEV 1 (% p	oredicted)	(follow-up 4 ye	ears; range of	scores: 0-10	00; Better indica	ted by higher	values	;)			
1 (Fink elstei n 1992)	observationa I studies	serious 1	no serious inconsistenc y	no serious indirectnes s	serious ²	none	25	25	-	MD 8 lower (17.01 lower to 1.01 higher) ³	VER Y LOW	CRITICAL

Abbreviations: CI: confidence interval; CF: cystic fibrosis; FEV₁: 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	y assessment		No of patient	ts	Effect							
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Telemedicin e	Usual care	Relati ve (95% CI)	Absolu te	Qual ity	Importance
Chang	le in quality of	life- CFC	QOL body (Foll	ow-up: 6 mo	nths; range	of scores: 0-10); Better indica	ated by lo	wer valu	es)		
1 (Wilki	observation al studies	very seriou	no serious inconsistenc	no serious indirectnes	Not calculable	none	4	3	-	Not estima	VER Y	IMPORTAN T
nson 2008)		S ¹	У	S			Significant improvemen t at 6			ble	LOW	

Quality	y assessment					No of patient	S	Effect				
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Telemedicin e	Usual care	Relati ve (95% CI)	Absolu te	Qual ity	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 (FEV₁% predicted at baseline) for prognosis of pulmonary exacerbations and FEV₁ percent predicted at 10 years

Prognostic factors	No of studies	Design	Setting	No of patients	Result (adjRR, MD)	Quality	Notes	Importance
Pulmonary exact	erbations (def	ined as hos	pitalization	s treated w	rith IV AB) (Follo	w-up: 10 years; Bet	ter indicated by lower values)	
FEV1 % predicted, 5- point decrease1 (Sanders 2015)Cohort studyCF centres in Europe60 								
Change/ decline	in FEV₁ % pre	dicted (Fol	low-up: 10 y	ears; Bette	er indicated by l	ower values)		
FEV1 % predicted, 5- point decrease	1 (Sanders 2015)	Cohort study	CF centres in Europe	60	MD: -4.47 (95% CI: -6.48 to -2.76)	$\oplus \oplus \oplus \Theta$ MODERATE ¹	Multiple linear model adjusted for sex, genotype, FEV ₁ and mucoid <i>P</i> 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; FEV₁: 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 FEV₁% 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 increase1 (Sanders 2015)Cohort studyCF centres in Europe60 solutionadjRR: 1.39 (95% CI: 1.15 to 1.67)Multiple Poisson model adjusted for sex, genotype, FEV1 and mucoid P 													
Change/ decline i	n FEV₁ % pre	dicted (Foll	ow-up: 10 yea	ars; Better	indicated by low	er 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, FEV₁ 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; FEV1: 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

Quality No of studie s	assessmen Design	t Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	No of patient s	Effect Relative (95% Cl) FEV1 % predict ed, 5- point decreas e	Brody chest CT score, 1-point increas e	Differenc e between tests P-value	Quality	Importan Ce
Pulmon	ary exacerb	oations (defined as hos	pitalizations	treated with	IV AB) (Follow-	up: 10 ye	ars; Better	indicated	by lower val	ues)	
1 (Sand ers 2015)	Cohort study	seriou s risk of bias ¹	no serious inconsistenc y	no serious indirectnes s	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	MODER ATE	CRITICA L
Change	decline in	FEV1 %	predicted (Fol	low-up: 10 ye	ars; Better i	ndicated by low	er values)				
1 (Sand ers 2015)	Cohort study	seriou s risk of bias ¹	no serious inconsistenc y	no serious indirectnes s	Not calculable 2	none	60	Mean differenc e: -4.47 (95% Cl: -6.48 to -2.76)	Mean differenc e: -4.76 (95% Cl: -7.80 to -1.72)	MD: 0.29*; p-value = 0.4 By F test ²	MODER ATE	CRITICA L

Table 12: Clinical evidence profile: Comparison 1. FEV₁% predicted versus chest CT scan for prognosis of pulmonary exacerbations and FEV₁% predicted at 10 years

Abbreviations: AB: antibiotics; adjRR: adjusted rate ratio; CI: confidence interval; FEV₁: 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

Quality	y assessmen	ıt				No of p	atients	Effect				
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	BAL monit oring	Standa rd monito ring	Relati ve (95% Cl)	Absolute	Quality	Importanc e
FEV ₁ (1	follow-up 5 y	ears; m	easured with: z	z score; Bette	r indicated b	by higher values	s)					
1 (Wai nwrig ht 2011)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	serious ¹	No serious imprecisio n	none	80	77	-	MD 0.15 lower (0.58 lower to 0.28 higher)	MODERA TE	CRITICAL
Cleara	nce of P aeru	uginosa	following 1 or	2 courses of	eradication f	therapy (Follow	up: 5 ye	ars; Bette	r indicate	d by higher	values)	
1 (Wai nwrig ht 2011)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	serious ¹	no serious imprecisio n	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)	MODERA TE	CRITICAL
Weigh	t (follow-up 5	5 years;	measured with	: z scores; B	etter indicate	ed by higher va	lues)					
1 (Wai nwrig ht 2011)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	serious ¹	serious ²	none	80	77	-	MD 0.06 higher (0.21 lower to 0.32 higher)	LOW	IMPORTA NT
Height	(follow-up 5	vears; r	measured with	: z scores; Be	etter indicate	ed by higher val	ues)					

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

Quality	Quality assessment								Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	BAL monit oring	Standa rd monito ring	Relati ve (95% Cl)	Absolute	Quality	Importanc e
1 (Wai nwrig ht 2011)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	serious ¹	no serious imprecisio n	none	80	77	-	MD 0.06 higher (0.23 to 0.35 lower)	MODERA TE	IMPORTA NT
BMI (fo values	ollow-up 5 ye)	ars; me	asured with: z	scores, BMI o	calculated as	s weight in kg di	ivided by	height in	meters s	quared.; Bet	tter indicated	d by higher
1 (Wai nwrig ht 2011)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	serious ¹	no serious imprecisio n	none	80	77	-	MD 0.02 higher (0.25 lower to 0.3 higher)	MODERA TE	IMPORTA NT

Abbreviations: BAL: bronchoalveolar lavage; BMI: body mass index; FEV1: 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 as	ssessmer	nt					No of patients	S	Effect			
No of studies	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Manual physiothera py	Oscillati ng device	Relati ve (95% CI)	Absol ute	Qual ity	Importance
Lung fun values)	ction - FE	V₁ (follov	v-up mean 8.8	days; measu	red with: %	change from ba	iseline; range o	of scores: 0)-100; Be	tter indica	ated by	higher
1 (Homnic k 1998)	random ised trials	very seriou s ¹	no serious inconsistenc y	no serious indirectnes s	serious ²	none	22	22	-	MD 7.9 lower (31.04 lower to 15.24 higher)	VER YLO W	IMPORTAN T
Lung fun values)	ction - FE	V ₁ (follow	v-up mean 1 m	onths; meas	ured with: %	change from b	aseline; range	of scores:	0-100; B	etter indic	cated by	/ higher
1 (Padma n 1999)	random ised trials	very seriou s ³	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	6	6	-	MD 2.59 higher (6.3 lower to 11.48 higher)	VER Y LOW	IMPORTAN T
Lung Fur values)	nction - F\	/C (follow	v-up mean 2 wo	eeks; measu	red with: % o	change from ba	seline; range o	of scores: 0	-100; Bet	ter indica	ited by	higher

.												
Quality as No of studies	ssessmer Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	No of patients Manual physiothera py	s Oscillati ng device	Relati ve (95% CI)	Absol ute	Qual ity	Importance
1 (Homnic k 1998)	random ised trials	very seriou s ¹	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	22	22	-	MD 2.9 higher (14.21 lower to 20.01 higher)	VER Y LOW	IMPORTAN T

Abbreviations: CI: confidence interval; FEV1: 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 assessmen	t		No of patients	5	Effect						
No of Design studies	Risk In of no bias	iconsiste cy	Indirectn ess	Imprecisio n	Other considera tions	Manual physiothera py techniques	HFCW O	Relati ve (95% Cl)	Absol ute	Quality	Importan ce
Sputum weight (dr	/) (follow-up	1-2 weeks; I	measured w	/ith: grams; B	etter indicat	ed by higher v	alues)				
1 randomi (Warwic sed k 2004) trials	seriou no s ¹ ind cy	o serious Iconsisten Y	no serious indirectne ss	serious ²	none	12	12	-	MD 0.13 lower (0.42 lower to 0.16 higher)	LOW	CRITICA L

Quality as	No of patients		Effect									
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Other considera tions	Manual physiothera py techniques	HFCW O	Relati ve (95% Cl)	Absol ute	Quality	Importan ce
1 (Warwic k 2004)	randomi sed trials	seriou s ¹	no serious inconsisten cy	no serious indirectne ss	serious ²	none	12	12	-	MD 4.04 lower (10.77 lower to 2.69 higher)	LOW	CRITICA L

Abbreviations: CI: confidence interval; FEV₁: 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

Quality assessment							No of patients		Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	PEP	No airway clearanc e techniq ue	Relati ve (95% CI)	Absolut e	Quali ty	Importance
Sputur	Sputum dry weight (follow-up mean 2 days; measured with: grams; Better indicated by higher values)											
1 (Placi di 2006)	randomise d trials	no serious risk of bias	no serious inconsistenc y	no serious indirectnes s	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)												

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

Quality assessment Inconsisten Indirectne Imprecisi Other No of studi Design Risk of bias Inconsisten Indirectne Imprecisi Other							No of patients PEP No airway		Effect Relati Absolut ve e			
63						115		e techniq ue	(33 % CI)		Quali ty	Importance
1 (Placi di 2006)	randomise d trials	no serious risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ²	none	17	17	-	MD 1.8 higher (1.72 lower to 5.32 higher)	MOD ERA TE	CRITICAL
Lung function - FEV ₁ (follow-up mean 2 days; measured with: % predicted; range of scores: 0-100; Better indicated by lower values)												
1 (Brag gion 1995)	randomise d trials	very serious 3	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	16	16	-	MD 2.1 higher (11.73 lower to 15.93 higher)	VER Y LOW	IMPORTAN T
Lung function - FEV ₁ (follow-up mean 2 days; measured with: litres; Better indicated by higher values)												
1 (Placi di 2006)	randomise d trials	no serious risk of bias	no serious inconsistenc y	no serious indirectnes s	very serious ¹	none	17	17	-	MD 0.01 higher (0.18 lower to 0.2 higher)	LOW	IMPORTAN T
Lung Function FVC (follow-up mean 2 days; measured with: % predicted; range of scores: 0-100; Better indicated by higher values)												
1 (Brag gion 1995)	randomise d trials	very serious 3	no serious inconsistenc y	no serious indirectnes s	very serious ¹	none	16	16	-	MD 1.2 higher (12.88 lower to 15.28 higher)	VER Y LOW	IMPORTAN T
Quality	/ assessmen	t					No of pati	ents	Effect			
----------------------------	-----------------------	----------------------------------	---------------------------------	--------------------------------	------------------------------	-----------------------------	--------------	--	-----------------------------	--	------------------	---------------
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	PEP	No airway clearanc e techniq ue	Relati ve (95% Cl)	Absolut e	Quali ty	Importance
Lung f	unction - FV	C (follow-	up mean 2 day	s; measured	with: litres; E	Better indicated	by higher v	/alues)				
1 (Placi di 2006)	randomise d trials	no serious risk of bias	no serious inconsistenc y	no serious indirectnes s	very serious ¹	none	17	17	-	MD 0.05 higher (0.35 lower to 0.45 higher)	LOW	IMPORTAN T
Oxyge	n saturation	- Spo2 (fo	llow-up mean	2 days; meas	ured with: %	; range of score	es: 0-100; E	etter indica	ated by h	igher valu	es)	
1 (Placi di 2006)	randomise d trials	no serious risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ²	none	17	17	-	MD 0.3 higher (0.58 lower to 1.18 higher)	MOD ERA TE	IMPORTAN T

Abbreviations: CI: confidence interval; FEV₁: 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.

			-	-	-	<u> </u>	· · · ·			•		
Quality a	ssessmer	nt					No of pat	ients	Effect			
No of studies	Desig n	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisio n	Other considerati ons	PEP	Oscillat ing device	Relati ve (95% Cl)	Absol ute	Quality	Importance
Patient p	reference	: self-witl	hdrawal due to	lack of perc	eived effectiv	eness (follow	-up mean <i>'</i>	1 years; Be	etter indi	cated by I	ower values)	
1 (McIIwai ne 2001)	rando mised trials	seriou s ¹	no serious inconsistenc y	no serious indirectnes s	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
Hospitali values)	zations fo	or respira	tory exacerbat	ions (follow-	up mean 13 n	nonths; measu	ured with:	number pe	er partici	oant; Bett	er indicated b	by lower
1 (Newbol d 2005)	rando mised trials	seriou S ³	no serious inconsistenc y	no serious indirectnes s	serious ⁴	none	21	21	-	MD 0.4 lower (0.92 lower to 0.12 higher)	LOW	CRITICAL
Lung fun	ction - FE	V ₁ (follov	v-up 2-4 weeks	; measured v	with: % chang	ge from baseli	ne; range	of scores:	0-100; B	etter indic	cated by high	er values)
1 (Padma n 1999)	rando mised trials	very seriou s ⁵	no serious inconsistenc y	no serious indirectnes s	serious ⁴	none	6	6	-	MD 4.08 higher (4.66 lower to 12.82 higher)	VERY LOW	IMPORTAN T
Lung fun values)	ction - FE	V ₁ (follov	v-up mean 6-1	2 months; me	easured with:	% change fro	m baseline	e; range of	scores:	0-100; Be	etter indicated	l by higher

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

Quality as	ssessmer	nt					No of pat	ients	Effect			
No of studies	Desig n	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisio n	Other considerati ons	PEP	Oscillat ing device	Relati ve (95% Cl)	Absol ute	Quality	Importance
1 (McIIwai ne 2001)	rando mised trials	seriou s ¹	no serious inconsistenc y	no serious indirectnes s	serious ⁴	none	17	13	-	MD 9.71 higher (2.12 lower to 21.54 higher)	LOW	IMPORTAN T
Lung fun	ction - FE	V ₁ (follow	v-up 1-2 years;	measured w	vith: % change	e from baselin	e; range o	f scores: ()-100; Be	tter indic	ated by highe	r values)
3 (McIlwai ne 2013, Newbol d 2005, Tannen baum 2005)	rando mised trials	seriou S ⁶	no serious inconsistenc y	no serious indirectnes s	serious ⁴	none	78	82	-	MD 2.82 lower (6.36 lower to 0.72 higher)	LOW	IMPORTAN T
Lung fun	ction - FV	C (follow	-up mean 1 ye	ars; measure	ed with: % cha	ange from bas	eline; rang	ge of score	es: 0-100	; Better in	dicated by hi	gher values)
3 (McIlwai ne 2001, McIlwai ne 2013, Newbol d 2005)	rando mised trials	seriou S ⁶	serious ⁷	no serious indirectnes s	no serious imprecision	none	80	80	-	MD - 0.44 lower (6.66 lower to 5.78 higher)	LOW	IMPORTAN T
Lung fun	ction - FV	C (follow	-up 2-4 weeks	; measured w	vith: % predic	ted; range of	scores: 0-1	100; Better	indicate	d by high	er values)	

Quality a	ssessmer	nt					No of pat	ients	Effect			
No of studies	Desig n	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisio n	Other considerati ons	PEP	Oscillat ing device	Relati ve (95% Cl)	Absol ute	Quality	Importance
1 (van Winden 1998)	rando mised trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ⁴	none	22	22	-	MD 2 lower (4.09 lower to 0.09 higher)	MODERAT E	IMPORTAN T
Quality of	f life – CF	Q-R: phy	sical domain (follow-up me	an 1 years; ra	ange of scores	s: 0-100; B	etter indica	ated by h	igher val	ues)	
1 (McIIwai ne 2013)	rando mised trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectnes s	no serious imprecision ⁸	none	51	56	-	MD 2.2 higher (1.32 lower to 5.72 higher)	HIGH	IMPORTAN T
Quality of	f life – CF	Q-R: trea	tment burden	(follow-up m	ean 1 years; r	ange of score	s: 0-100; E	Better indic	ated by	higher va	lues)	
1 (McIlwai ne 2013)	rando mised trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectnes s	no serious imprecision ⁸	none	51	56	-	MD 1.05 higher (6.35 lower to 8.45 higher)	HIGH	IMPORTAN T
Quality of	f life – CF	Q-R: resp	piratory domai	n (follow-up	mean 1 years	; range of sco	res: 0-100;	Better inc	licated b	y higher v	values)	
1 (McIlwai ne 2013)	rando mised trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ^{8,9}	none	51	56	-	MD 2.79 higher (3.68 lower to 9.26 higher)	MODERAT E	IMPORTAN T

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; FEV1: 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 No of studi es	y assessmer Design m volume (fr	nt Risk of bias	Inconsisten cy mean 1 weeks	Indirectne SS	Imprecisi on	Other consideratio ns	No of pat PEP	ients HFCWO	Effect Relati ve (95% Cl)	Absol ute	Quality	Importance
1	randomise	seriou	no serious	no serious	serious ²	none	23	23	-	MD 1.8	LOW	CRITICAL
(Grzi ncich 2008)	d trials	s ¹	inconsistenc y	indirectnes s			20	20		higher (3 lower to 6.6 higher)	2011	
Respir	atory exace	rbations:	number of pat	ients (follow	-up mean 1	years; Better in	dicated by	lower val	ues)			
1 (McII wain e 2013)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectnes s	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)	MODERAT E	CRITICAL
Pulmo	nary exacerl	bations (patients requir	ing antibiotio	cs) (follow-u	p mean 1 years	; Better in	dicated by	lower va	alues)		

Quality	y assessmer	nt					No of pat	ients	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	PEP	HFCWO	Relati ve (95% Cl)	Absol ute	Quality	Importance
1 (McII wain e 2013)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectnes s	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)	MODERAT E	CRITICAL
Lung f	unction - FE	V ₁ (follow	v-up 1 weeks;	measured wi	th: % predic	ted; range of s	cores: 0-10)0; Better i	ndicated	by highe	r values)	
2 (Brag gion 1995; Grzin cich 2008)	randomise d trials	seriou s ³	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	39	39	-	MD 0.67 higher (8.04 lower to 9.38 higher)	VERY LOW	IMPORTAN T
Lung F	Function - FE	EV ₁ (follow	w-up 1-2 week	s; measured	with: % pred	dicted; range of	scores: 0	-100; Bett	er indica	ted by hig	gher values)	
1 (Darb ee 2005)	randomise d trials	seriou s ⁵	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	15	15	-	MD 3 lower (20.54 lower to 14.54 higher)	VERY LOW	IMPORTAN T
Lung f higher	unction F values)	EV₁ (follo	w-up 1 years;	measured wi	ith: change f	from baseline in	n FEV₁ % p	oredicted;	range of	scores: 0	-100; Better i	ndicated by

Quality	/ assessmer	nt					No of pat	ients	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	PEP	HFCWO	Relati ve (95% Cl)	Absol ute	Quality	Importance
1 (McII wain e 2013)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ⁶	none	42	46	-	MD 3.59 lower (9.29 lower to 2.11 higher)	MODERAT E	IMPORTAN T
Lung f	unction - FV	C (follow	-up 1-2 weeks	; measured w	/ith: % predi	cted; Better inc	dicated by	higher val	ues)			
1 (Darb ee 2005)	randomise d trials	seriou s ⁵	no serious inconsistenc y	no serious indirectnes s	very serious ⁷	none	15	15	-	MD 3 lower (16.6 lower to 10.6 higher)	VERY LOW	IMPORTAN T
Lung f	unction - FV	C (follow	-up 1 weeks; r	neasured wit	h: % predict	ed; range of so	ores: 0-10	0; Better ir	ndicated	by highei	r values)	
2 (Brag gion 1995, Grzin cich 2008)	randomise d trials	seriou s ³	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	39	39	-	MD 0.66 higher (7.4 lower to 8.71 higher)	MODERAT E	IMPORTAN T
Lung f values	unction - FV)	C (follow	-up 1 years; m	easured with	1: change fro	om baseline in ^o	% predicte	d; range o	f scores:	0-100; B	etter indicate	d by higher
1 (McII wain e	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ²	none	42	46	-	MD 5 lower (10.3 lower	MODERAT E	IMPORTAN T

 $\ensuremath{\textcircled{\sc online 0.5ex}}$ NICE 2017. All rights reserved. Subject to Notice of rights.

Quality	y assessmei	nt					No of pat	ients	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	PEP	HFCWO	Relati ve (95% Cl)	Absol ute	Quality	Importance
2013)										to 0.3 higher)		

Abbreviations: CI: confidence interval; FEV₁: 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.

Quality No of studi es	y assessmer Design	nt Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	No of pat Oscillati ng device	ients HFCWO	Effect Relati ve (95% Cl)	Absol ute	Qual ity	Importance
Lung f	unction - FE	V ₁ (follow	v-up 2-4 weeks	; measured	with: % prec	dicted; range of	scores: 0-	100; Better indic	cated by	higher va	lues)	
1 (Oer man n 2001)	randomise d trials	seriou s ¹	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	24	24	-	MD 1.6 lower (3.44 lower to 0.24 higher)	MOD ERA TE	IMPORTAN T
Lung f	unction - FV	C (follow	up 2-4 weeks	; measured v	vith: % pred	icted; range of	scores: 0-1	00; Better indic	ated by h	ligher val	ues)	
1 (Oer man n 2001)	randomise d trials	seriou S ¹	no serious inconsistenc y	no serious indirectnes s	serious ²	none	24	24	-	MD 1.4 lower (3.07 lower to 0.27 higher)	LOW	IMPORTAN T

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

Abbreviations: CI: confidence interval; FEV₁: 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.

Quality	/ assessmen	t					No of pati	ents	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	NIV	No airway clearanc e techniqu e	Relati ve (95% Cl)	Absolut e	Qual ity	Importance
Lung f	unction - FE	V ₁ (follow	v-up 6 weeks; r	neasured witl	h: % predicte	ed; range of sco	ores: 0-100;	Better indic	ated by	higher valu	ies)	
1 (You ng 2008)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectnes s	very serious ¹	none	7	8	-	MD 1 higher (8.62 lower to 10.62 higher)	LOW	IMPORTAN T
Lung f	unction - FV	C (follow	-up 6 weeks; m	neasured with	: % predicte	d; range of sco	res: 0-100; I	Better indica	ated by h	ligher valu	es)	
1 (You ng 2008)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectnes s	very serious ²	none	7	8	-	MD 4 higher (10.3 lower to 18.3 higher)	LOW	IMPORTAN T
Oxyge	n saturation	(nocturn	al) (follow-up 6	6 weeks; meas	sured with:	%; range of sco	res: 0-100; I	Better indica	ated by h	igher value	es)	
1 (You ng 2008)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ³	none	7	8	-	MD 3 higher (1.12 lower to 7.12 higher)	MOD ERA TE	IMPORTAN T
Quality	/ of life – CF-	QOL che	est symptom so	core (follow-u	p 6 weeks; r	ange of scores:	: 0-100; Bett	er indicated	l by high	er values)		
1 (You ng 2008)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectnes s	very serious ^{1,4}	none	7	8	-	MD 7 higher (11.73 lower to	LOW	IMPORTAN T

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

Quality	/ assessmen	t					No of patie	ents	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	NIV	No airway clearanc e techniqu e	Relati ve (95% CI)	Absolut e	Qual ity	Importance
										25.73 higher)		
Quality	of life - CF-	QOL trac	litional dyspno	ea index scol	e (follow-up	6 weeks; range	of scores:	0-100; Bette	er indicat	ted by high	er value	es)
1 (You ng 2008)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ^{4,5}	none	7	8	-	MD 2.9 higher (0.71 to 5.09 higher)	MOD ERA TE	IMPORTAN T

Abbreviations: CI: confidence interval; FEV1: 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	/ assessmen	t					No of pa	atients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Mannit ol	Contro I	Relativ e (95% CI)	Absolute	Quality	Impor tance
FEV ₁ %	bredicted (repeated	d measures. ch	ange from ba	aseline) (follo	ow-up 2 weeks:	range of	scores: 0	-100: Bet	ter indicated	ov higher value	s)

Quality	v assessmen	+					No of pa	ationts	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Mannit	Contro	Relativ e (95% CI)	Absolute	Quality	Impor tance
1 (Jaqu es 2008)	randomise d trials ¹	no seriou s risk of bias	no serious inconsistenc y	serious ²	serious ³	none	3	6	-	MD 3.95 higher (0.96 to 6.94 higher)	LOW	CRITI CAL
FEV ₁ %	b predicted (r	repeated	measures, ch	ange from ba	iseline) (follo	w-up 2 months	; range of	f scores:	0-100; Bo	etter indicated	by higher valu	es)
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	no serious imprecisio n	none	361	239	-	MD 2.98 higher (1.04 to 4.92 higher)	MODERATE	CRITI CAL
FEV ₁ %	6 predicted (repeated	measures, ch	ange from ba	iseline) (follo	w-up 4 months	; range of	f scores:	0-100; Bo	etter indicated	by higher valu	es)
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	serious ³	none	361	239	-	MD 3.26 higher (1.16 to 5.35 higher)	LOW	CRITI CAL
FEV ₁ %	6 predicted (repeated	measures, ch	ange from ba	iseline) (follo	w-up 6 months	; range of	f scores:	0-100; B	etter indicated	by higher valu	es)
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	serious ³	none	361	239	-	MD 3.89 higher (1.69 to 6.08 higher)	LOW	CRITI CAL
FEV ₁ %	b predicted in ted by higher	ו childre r values)	n and young p	eople (repeat	ted measure	s, change from	baseline)	(follow-	up 2 mon	ths; range of s	cores: 0-100; E	Better

Quality	/ assessmen	t					No of pa	tients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Mannit ol	Contro I	Relativ e (95% CI)	Absolute	Quality	Impor tance
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	serious ³	none	Total nur children young pe 258 (Nur each gro reported	mber of and cople: nber in up not)	-	MD 2.64 higher (0.73 lower to 6.02 higher)	LOW	CRITI CAL
FEV ₁ %	6 predicted in ed by higher	n childre [.] values)	n and young p	eople (repea	ted measure	s, change from	baseline) (follow-		up 4 mon	ths; range of s	scores: 0-100; E	Better
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	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	CRITI CAL
FEV ₁ %	6 predicted in ted by higher	n childre values)	n and young p	eople (repea	ted measure	s, change from	baseline)	(follow-u	up 6 mon	ths; range of s	scores: 0-100; E	Better
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	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	CRITI CAL
FEV ₁ % values	6 predicted ii)	n adults	(repeated mea	sures, chang	e from base	line) (follow-up	2 months	; range o	of scores:	0-100; Better	indicated by hi	gher
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	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	CRITI CAL

Quality	/ assessmen	t					No of pa	atients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Mannit ol	Contro I	Relativ e (95% CI)	Absolute	Quality	Impor tance
FEV ₁ % values	。predicted ir)	n adults	(repeated mea	sures, chang	e from basel	ine) (follow-up	4 months	; range o	of scores:	0-100; Better	indicated by hi	gher
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	serious ³	none	Total number of adults: 317 (Number in each group not reported) 6 months; range o		-	MD 4.23 higher (0.98 to 7.48 higher)	LOW	CRITI CAL
FEV ₁ % values	。predicted ir)	n adults	(repeated mea	sures, chang	e from basel	ine) (follow-up	6 months	; range o	of scores:	0-100; Better	indicated by hi	gher
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	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	CRITI CAL
Time to	o first protoc	ol define	ed pulmonary o	exacerbation	(follow-up: 6	6 months)						
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	serious ⁴	none	0/361 (0%)	0/239 (0%)	HR 0.7 (0.48 to 1.02)	-	LOW	CRITI CAL
Numbe	er of children	and you	ung people wit	h protocol de	fined exace	bations (proxy	for time t	o next ex	acerbatio	on) (follow-up	: 6 months)	
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	serious⁵	none	No. particip ants with exacer bations	No. partici pants with exacer bation	RR 0.62 (0.35 to 1.09)	-	LOW	CRITI CAL

Quality No of studi es	/ assessmen Design	t Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	No of pa Mannit ol	atients Contro I	Effect Relativ e (95% Cl)	Absolute	Quality	Impor tance
							not reporte d. Total N of particip ants: 154	s not reporte d. Total N of partici pants: 105				
Numbe	er of adults w	ith prot	ocol defined ex	cacerbations	(proxy for til	me to next exac	erbation)	(follow-u	ı <mark>p: 6 mo</mark> n	iths)		
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	serious⁵	none	No. particip ants with exacer bations not reporte d. Total N of particip ants: 207	No. partici pants with exacer bation s not reporte d. Total N of partici pants: 134	RR 0.76 (0.52 to 1.13)	-	LOW	CRITI CAL
Numbe	er of patients	needing	g additional IV	antibiotics (fo	ollow-up 6 m	ionths)						
2 (Aitke n 2012,	randomise d trials	no seriou s risk of bias	serious ⁶	serious ²	serious⁵	none	165/36 1 (45.7%)	134/23 9 (56.1%)	RR 0.81 (0.63 to 1.04)	107 fewer per 1000 (from 28 fewer to 168 fewer)	VERY LOW	CRITI CAL

Quality No of studi es	/ assessmen Design	t Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	No of pa Mannit ol	Contro	Relativ e (95% CI)	Absolute	Quality	Impor tance
Bilton 2011)								56%		106 fewer per 1000 (from 28 fewer to 168 fewer)		
Quality values	/ of life – CF)	QOL res	piratory doma	in (change fr	om baseline)) (follow-up 4 m	onths; ra	nge of sc	ores: 0-1	00; Better indi	cated by highe	r
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s 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	IMPO RTAN T
Quality values	/ of life – CF)	QOL res	piratory doma	in (change fr	om baseline)	(follow-up 6 m	onths; ra	nge of sc	ores: 0-1	00; Better indi	cated by highe	r
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s 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	IMPO RTAN T
Quality	/ of life – CF	QOL vita	ality domain (c	hange from b	oaseline) (fol	low-up 4 month	s; range	of scores	: 0-100; E	Better indicate	d by higher val	ues)
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	serious ³	None	207	154	-	MD 3.42 higher (0.21 lower to 7.04 higher)	LOW	IMPO RTAN T
Quality	/ of life – CF	QOL vita	ality domain (c	hange from b	aseline) (fol	low-up 6 month	s; range	of scores	: 0-100; E	Better indicate	d by higher val	ues)

Quality	/ assessmen	t					No of pa	atients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Mannit ol	Contro I	Relativ e (95% CI)	Absolute	Quality	Impor tance
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	serious ³	None	187	138	-	MD 4.84 higher (0.86 to 8.82 higher)	LOW	IMPO RTAN T
Quality	/ of life – CF0	QOL phy	vsical domain (change from	baseline) (fo	llow-up 4 mont	hs; range	of score	s: 0-100;	Better indicat	ed by higher va	alues)
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	no serious imprecisio n	None	291	214	-	MD 1.8 lower (4.72 lower to 1.11 higher)	MODERATE	IMPO RTAN T
Quality	/ of life – CFC	QOL phy	vsical domain (change from	baseline) (fo	ollow-up 6 mont	hs; range	of score	s: 0-100;	Better indicat	ed by higher va	alues)
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s 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	IMPO RTAN T
Quality	/ of life – CF0	QOL em	otion domain	change from	baseline) (fo	ollow-up 4; rang	je of scor	es: 0-100	; Better i	ndicated by hi	gher values)	
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	no serious imprecisio n	None	292	214	-	MD 2.11 lower (4.56 lower to 0.34 higher)	MODERATE	IMPO RTAN T
Quality	of life - CF	QOL emo	otion domain (change from	baseline) (fo	llow-up 6 week	s; range o	of scores	: 0-100; E	Better indicate	d by higher val	ues)

Quality	/ assessmen	t					No of pa	atients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Mannit ol	Contro I	Relativ e (95% CI)	Absolute	Quality	Impor tance
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	no serious imprecisio n	None	269	196	-	MD 1.27 lower (3.74 lower to 1.2 higher)	MODERATE	IMPO RTAN T
Quality	/ of life – CFC	QOL eati	ng domain (ch	ange from ba	aseline) (follo	ow-up 4 months	; range o	f scores:	0-100; B	etter indicated	l by higher valu	ies)
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	no serious imprecisio n	None	292	213	-	MD 0.81 higher (1.96 lower to 3.58 higher)	MODERATE	IMPO RTAN T
Quality	/ of life – CFC	QOL eati	ng domain (ch	ange from ba	aseline) (follo	ow-up 6 months	; range o	f scores:	0-100; B	etter indicated	l by higher valu	ies)
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	no serious imprecisio n	None	269	197	-	MD 0.68 higher (2.29 lower to 3.65 higher)	MODERATE	IMPO RTAN T
Quality	/ of life – CF0	QOL hea	Ith domain (cl	nange from b	aseline) (foll	ow-up 4 weeks;	range of	scores:	0-100; Be	tter indicated	by higher value	es)
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	no serious imprecisio n	None	208	152	-	MD 0.43 lower (4.18 lower to 3.32 higher)	MODERATE	IMPO RTAN T
Quality	/ of life – CFC	QOL hea	Ith domain (ch	ange from ba	seline) (follo	ow-up 6 months	; range o	f scores:	0-100; B	etter indicated	l by higher valu	ies)

Quality	/ assessmen	t					No of pa	atients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Mannit ol	Contro I	Relativ e (95% CI)	Absolute	Quality	Impor tance
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	no serious imprecisio n	None	186	139	-	MD 0.21 lower (4.14 lower to 3.72 higher)	MODERATE	IMPO RTAN T
Quality	/ of life – CF0	QOL soc	ial domain (ch	ange from ba	seline) (follo	w-up 4 weeks;	range of s	scores: 0	-100; Bet	ter indicated b	oy higher value	s)
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	no serious imprecisio n	None	292	212	-	MD 1.2 lower (3.7 lower to 1.3 higher)	MODERATE	IMPO RTAN T
Quality	/ of life – CF0	QOL soc	ial domain (ch	ange from ba	seline) (follo	w-up 6 months	; range of	f scores:	0-100; Be	etter indicated	by higher valu	es)
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s 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	IMPO RTAN T
Quality	/ of life – CF0	QOL bod	ly domain (cha	nge from bas	eline) (follov	w-up 4 months;	range of	scores: ()-100; Bet	tter indicated	by higher value	es)
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	serious ³	None	290	210	-	MD 3.1 lower (6.49 lower to 0.29 higher)	LOW	IMPO RTAN T
Quality	of life - CFC	OL bod	y domain (cha	nge from bas	eline) (follow	v-up 6 months;	range of s	scores: 0	-100; Bet	ter indicated b	by higher value	s)

Quality	/ assessmen	t					No of pa	atients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Mannit ol	Contro I	Relativ e (95% CI)	Absolute	Quality	Impor tance
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	no serious imprecisio n	None	266	195	-	MD 1.19 lower (4.51 lower to 2.13 higher)	MODERATE	IMPO RTAN T
Quality	/ of life - CFC	OL role	domain (chan	ge from base	line) (follow-	up 4 months; ra	ange of so	cores: 0-	100; Bette	er indicated by	/ higher values)
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	no serious imprecisio n	None	207	151	-	MD 1.22 higher (2.21 lower to 4.66 higher)	MODERATE	IMPO RTAN T
Quality	/ of life - CFC	OL role	domain (chan	ge from base	line) (follow-	up 6 months; ra	ange of so	cores: 0-	100; Bette	er indicated by	/ higher values)
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s 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	IMPO RTAN T
Quality	/ of life - CFC	OL dige	stion domain	change from	baseline) (fe	ollow-up 4 mon	ths; range	e of score	es: 0-100;	; Better indica	ted by higher v	alues)
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	no serious imprecisio n	none	292	213	-	MD 1.49 lower (4.77 lower to 1.78 higher)	MODERATE	IMPO RTAN T
Quality	/ of life - CFC	QOL dige	stion domain	change from	baseline) (fe	ollow-up 6 mon	ths; range	e of score	es: 0-100;	Better indica	ted by higher v	alues)

Quality	/ assessmen	t					No of pa	atients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Mannit ol	Contro I	Relativ e (95% CI)	Absolute	Quality	Impor tance
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	serious ³	None	268	197	-	MD 1.07 lower (5.04 lower to 2.9 higher)	LOW	IMPO RTAN T
Quality	/ of life - CFC	QOL weig	ght domain (ch	ange from ba	seline) (follo	ow-up 4 months	; range o	f scores:	0-100; B	etter indicated	l by higher valu	ies)
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	serious ³	None	207	153	-	MD 4.23 lower (10.28 lower to 1.83 higher)	LOW	IMPO RTAN T
Quality	/ of life - CFC	QOL weig	ght domain (ch	ange from ba	aseline) (follo	ow-up 6 months	; range o	f scores:	0-100; B	etter indicated	l by higher valu	ies)
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	serious ³	None	186	139	-	MD 3.27 lower (9.84 lower to 3.31 higher)	LOW	IMPO RTAN T
Advers	se events: ha	emoptys	sis (mild) (follo	w-up 2 week	s)							
1 (Jaqu es 2008)	randomise d trials ¹	no seriou s risk of bias	no serious inconsistenc y	serious ²	not calculable ª	None	1 (0%)	8 (0%)	RR not estima ble ^b	0 events in each group	MODERATE	IMPO RTAN T
Advers	se events: ha	emopty	sis (severe) (fo	llow-up 2 we	eks)							
				serious ²		None	1	8			VERY LOW	

Quality	/ assessmen	t					No of pa	atients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Mannit ol	Contro I	Relativ e (95% CI)	Absolute	Quality	Impor tance
1 (Jaqu es 2008)	randomise d trials ¹	no seriou s risk of bias	no serious inconsistenc y		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)		IMPO RTAN T
Advers	se events: Br	onchos	basm (mild) (fo	llow-up 6 mo	onths)							
1 (Bilto n 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	not calculable ª	None	0/177 (0%)	0/118 (0%)	RR not estima ble⁵	0 events in each group	MODERATE	IMPO RTAN T
Advers	se events: Ha	emopty	sis (mild) (follo	ow-up 6 mont	hs)							
2 (Aitke n 2012,	randomise d trials	no seriou s risk of	no serious inconsistenc y	serious ²	very serious ⁹	None	6/361 (1.7%)	2/239 (0.84%)	RR 1.73 (0.26 to	6 more per 1000 (from 6 fewer to 89 more)	VERY LOW	IMPO RTAN T
Bilton 2011)		bias						0.9%	11.62)	7 more per 1000 (from 7 fewer to 96 more)		
Advers	se events: Br	onchosp	basm (moderat	te) (follow-up	6 months)							
1 (Bilto n 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	very serious ⁹	None	1/177 (0.56%)	0/118 (0%)	RR 2.01 (0.03 to 133.11)	-	VERY LOW	IMPO RTAN T
Advers	se events: Ha	emopty	sis (moderate)	(follow-up 6	months)							

Quality	/ assessmen	t					No of pa	atients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Mannit ol	Contro I	Relativ e (95% CI)	Absolute	Quality	Impor tance
2 (Aitke n 2012,	randomise d trials	no seriou s risk of	no serious inconsistenc y	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	IMPO RTAN T
Bilton 2011)		bias						0.4%		15 more per 1000 (from 2 fewer to 170 more)		
Advers	se events: Br	onchos	basm (severe)	(follow-up 6 i	months)							
1 (Bilto n 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	very serious ⁹	none	1/177 (0.56%)	0/118 (0%)	RR 2.01 (0.03 to 133.11)	-	VERY LOW	impo Rtan T
Advers	se events: Ha	emopty	sis (severe) (fo	ollow-up 6 mc	onths)							
2 (Aitke n 2012,	randomise d trials	no seriou s risk of	no serious inconsistenc y	serious ²	very serious ⁹	none	3/361 (0.83%)	1/239 (0.42%)	RR 1.55 (0.13 to	2 more per 1000 (from 4 fewer to 75 more)	VERY LOW	IMPO RTAN T
Bilton 2011)		bias						0.4%	18.99)	2 more per 1000 (from 3 fewer to 72 more)		
Advers	se events: Br	onchos	basm in childre	en and young	people (foll	ow-up 6 months	5)					
1 (Bilto n 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	not calculable ª	None	0/63 (0%)	0/42 (0%)	RR not estima ble ^b	0 events in each group	MODERATE	IMPO RTAN T

Quality							No of p	ationto	Effoot			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Mannit ol	Contro I	Relativ e (95% CI)	Absolute	Quality	Impor tance
Adver	se events in a	adults: E	Bronchospasm	in adults (fol	llow-up 6 mo	nths)						
1 (Bilto n 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	very serious ⁹	None	No. particip ants with bronch ospas m not reporte d. Total N of particip ants: 114	No. partici pants with bronch ospas m not reporte d. Total N of partici pants: 76	RR 3.35 (0.16 to 71.50)	-	VERY LOW	IMPO RTAN T
Adver	se events: Ha	aemopty	sis in children	and young p	eople (follow	/-up 6 months)						
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	very serious ⁹	none	No. particip ants with haemo ptysis not reporte d. Total N of particip ants: 154	No. partici pants with haemo ptysis not reporte d. Total N of partici pants: 105	RR 5.48 (0.69 to 43.50)	-	VERY LOW	IMPO RTAN T

 $\ensuremath{\mathbb{C}}$ NICE 2017. All rights reserved. Subject to Notice of rights.

Quality	/ assessmen	t					No of pa	atients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Mannit ol	Contro I	Relativ e (95% CI)	Absolute	Quality	Impor tance
2 (Aitke n 2012, Bilton 2011)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	serious ²	very serious ⁹	none	No. particip ants with haemo ptysis not reporte d. Total N of particip ants: 207	No. partici pants with haemo ptysis not reporte d. Total N of partici pants: 134	RR 1.83 (0.64 to 5.23)	-	VERY LOW	IMPO RTAN T

Abbreviations: CFQOL: cystic fibrosis quality of life questionnaire; CI: confidence interval; FEV₁: 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 (12=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

able 22	. Chinical ev	idence p	rome. Compa	15011 1.2.1.1	viannitor ve	ISUS Dornase	alla					
Quality	assessment						No of patie	nts	Effect			
No of studie s	Design	Risk of bias	Inconsistency	Indirectnes s	Imprecisio n	Other consideration s	Mannitol	Dorn ase alfa	Relativ e (95% CI)	Absolute	Quali ty	Importan ce
FEV ₁ (%	6 change froi	n baselin	e) - Up to 3 mor	ths (follow-u	p 3 months;	range of scores	s: 0-100; Bett	er indica	ated by h	igher values	5)	
1 (Mina sian 2010)	randomise d trials ¹	serious 2	no serious inconsistency	serious ³	serious ⁴	none	20		-	MD 2.8 higher (4.8 lower to 10.4 higher)	VER Y LOW	CRITICAL

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

Abbreviations: CI: confidence interval; FEV1: 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 patien	its	Effect			
No of studie s	Design	Risk of bias	Inconsistency	Indirectnes s	Imprecisio n	Other consideration s	Mannitol + dornase alfa <i>versus</i>	Dorn ase alfa alone	Relativ e (95% CI)	Absolute	Quali ty	Importan ce
FEV 1 (%	% change fro	m baselin	e) (follow-up 3	months; rang	je of scores:	0-100; Better in	dicated by hi	gher val	ues)			
1 (Mina sian 2010)	randomise d trials1	serious 2	no serious inconsistency	serious ³	very serious ⁴	none	20		-	MD 4.3 lower (14.1 lower to 5.5 higher)	VER Y LOW	CRITICAL

Abbreviations: CI: confidence interval; FEV₁: 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	assassman	•					No of p	ationte	Effoct			
No of studies	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Dornas e alfa	Place bo	Relative (95% CI)	Absolute	Qualit y	Importan ce
Lung fu	nction: rela	tive mear	n % change in	FEV ₁ (follow-	up 10 days;	range of scores	s: 0-100; E	Better inc	licated by	higher values)		
Shah 1996	randomis ed trials	very serious	no serious inconsistenc y	no serious indirectnes s	serious ⁷	none	20	21	-	MD 13.17 higher (0.70 to 25.64 higher)	VERY LOW	CRITICA L
Lung fu	nction: rela	tive mear	n % change in	FEV1 (follow-	up 1 months	; range of score	es: 0-100;	Better i	ndicated b	y higher values	;)	
4 (Laube 1996, Ramse y 1993a, Ranasi nha 1993,	randomis ed trials	very serious ³	very serious ⁴	no serious indirectnes s	serious ⁷	none	121	127	-	MD 9.52 higher (0.59 to 18.46 higher)	VERY LOW	CRITICA L

Quality	assessmen	t					No of pa	atients	Effect			
No of studies	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Dornas e alfa	Place bo	Relative (95% CI)	Absolute	Qualit y	Importan ce
Shah 1995)												
Lung fu	nction: rela	tive mear	n % change in	FEV ₁ (follow-	up 3 months	; range of score	es: 0-100;	Better in	ndicated by	y higher values)	
2 (Amin 2011, McCoy 1996)	randomis ed trials⁵	very serious 6	no serious inconsistenc y	no serious indirectnes s	serious ⁷	none	175	144	-	MD 6.7 higher (3.72 to 9.67 higher)	VERY LOW	CRITICA L
Lung fu	nction: rela	tive mear	n % change in	FEV ₁ (follow-	up 6 months	; range of score	es: 0-100;	Better in	ndicated by	y higher values)	
1 (Fuchs 1994)	randomis ed trials	serious ⁸	no serious inconsistenc y	no serious indirectnes s	serious ⁷	none	322	325	-	MD 5.8 higher (4.41 to 7.19 higher)	LOW	CRITICA L
subgrou range o	up analysis f scores: 0-	based on 100; Bette	disease sever er indicated by	rity: participa higher value	nts with mod s)	derate disease l	FEV₁ relat	tive mear	n % change	e in FEV ₁ (follow	w-up 1 m	onths;
3 (Laube 1996, Ramse y 1993a, Ranasi nha 1993)	randomis ed trials	very serious 9	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	90	93	-	MD 14.32 higher (10.81 to 17.83 higher)	LOW	CRITICA L
subgrou indicate	up analysis ed by higher	based on values)	i disease sevei	rity: participa	nts with sev	ere disease FE\	/₁ relative	e mean %	change ir	n FEV₁ (follow-u	ıp 1 mont	hs; Better
1 (Shah 1995)	randomis ed trials	very serious	no serious inconsistenc y	no serious indirectnes s	serious ⁷	none	31	34	-	MD 2.8 lower (8.76 lower to 3.16 higher)	VERY LOW	CRITICA L

Quality	assessmen	+					No of pa	atients	Effect			
No of studies	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Dornas e alfa	Place bo	Relative (95% CI)	Absolute	Qualit y	Importan ce
subgrou range of	up analysis f scores: 0-	based on 100; Bette	disease sever er indicated by	rity: participa higher value	nts with acu s)	te pulmonary e	xacerbati	on mean	% change	in FEV ₁ (follow	/-up 1 mo	onths;
1 (Wilmo tt 1996)	randomis ed trials	very serious	no serious inconsistenc y	no serious indirectnes s	very serious ²	none	43	37	-	MD 1 higher (13.93 lower to 15.93 higher)	VERY LOW	CRITICA L
Lung fu	nction: abs	olute mea	an % change ir	FEV ₁ (follow	/-up 2 years;	range of score	s: 0-100;	Better in	dicated by	higher values)		
1 (Quan 2001)	randomis ed trials	no serious risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ⁷	none	204	206	-	MD 3.24 higher (1.03 to 5.45 higher)	MODE RATE	CRITICA L
Number	of people e	experienc	ing exacerbati	ons (follow-u	p 6 month)							
1 (Fuchs 1994)	randomis ed trials	serious ⁸	no serious inconsistenc y	no serious indirectnes s	serious ¹²	none	71/322 (22%)	89/32 5 (27.4 %)	RR 0.81 (0.61 to 1.06)	52 fewer per 1000 (from 107 fewer to 16 more)	LOW	CRITICA L
Number	of people e	experienc	ing exacerbati	ons (follow-u	ip 2 years)							
1 (Quan 2001)	randomis ed trials	no serious risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ¹²	none	40/236 (16.9%)	56/23 4 (23.9 %)	RR 0.71 (0.49 to 1.02)	69 fewer per 1000 (from 122 fewer to 5 more)	MODE RATE	CRITICA L
Number	of days of	IV antibio	otic use (follow	-up 3 months	; Better indi	cated by lower	values)					
1 (McCo y 1996)	randomis ed trials	serious ¹³	no serious inconsistenc y	no serious indirectnes s	very serious ¹⁴	none	158	162	-	MD 2.96 lower (7.29 lower to 1.37 higher)	VERY LOW	CRITICA L
Adverse	events: ha	emoptys	is (follow-up 1	months)								
2 (Rana	randomis ed trials				very serious ¹⁴	none	4/71 (5.6%)	3/70 (4.3%)		10 more per 1000 (from	VERY LOW	IMPORT ANT

Quality	assessmen	t					No of pa	atients	Effect			
No of studies	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Dornas e alfa	Place bo	Relative (95% CI)	Absolute	Qualit y	Importan ce
sinha 1993, Shah 1995)		very serious ¹⁵	no serious inconsistenc y	no serious indirectnes s				4.3%	RR 1.23 (0.20 to 7.63)	34 fewer to 284 more) 10 more per 1000 (from 34 fewer to 285 more)		
Adverse	events: ha	emoptys	is (follow-up 6	months)								
1 (Fuchs 1994)	randomis ed trials	serious ⁸	no serious inconsistenc y	no serious indirectnes s	very serious ¹⁴	none	17/322 (5.3%)	21/32 5 (6.5%)	RR 0.82 (0.44 to 1.52)	12 fewer per 1000 (from 36 fewer to 34 more)	VERY LOW	IMPORT ANT
Adverse	events: vo	oice altera	tion (follow-up	o 1 months)								
3 (Rams ey 1993a,	randomis ed trials	very serious	very serious ¹⁷	no serious indirectnes s	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	IMPORT ANT
Ranasi nha 1993, Shah 1995)								0%		-		
Adverse	events: vo	oice altera	tion (follow-up	o 3 months)								
1 (McCo y 1996)	randomis ed trials	serious ¹³	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	28/158 (17.7%)	10/16 2 (6.2%)	RR 2.87 (1.44 to 5.71)	115 more per 1000 (from 27 more to 291 more)	MODE RATE	IMPORT ANT
Adverse	events: vo	oice altera	tion (follow-up	6 months)								

Quality	assessmen	t					No of pa	atients	Effect			
No of studies	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Dornas e alfa	Place bo	Relative (95% CI)	Absolute	Qualit y	Importan ce
1 (Fuchs 1994)	randomis ed trials	serious ⁸	no serious inconsistenc y	no serious indirectnes s	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	IMPORT ANT
Adverse	events: vo	ice altera	tion (follow-up	o 2 years)								
1 (Quan 2001)	randomis ed trials	no serious risk of bias	no serious inconsistenc y	no serious indirectnes s	very serious ¹⁴	none	26/236 (11%)	27/23 4 (11.5 %)	RR 0.95 (0.57 to 1.59)	6 fewer per 1000 (from 50 fewer to 68 more)	LOW	IMPORT ANT
Quality	of life: char	nge in QF	Q-R parents (fe	ollow-up 3 m	onths; range	of scores: 0-10	0; Better	indicate	d by highe	r values)		
1 (Amin 2011)	randomis ed trials⁵	no serious risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ⁷	none	00; Better indicate 17		-	MD 5.45 lower (15.23 lower to 4.33 higher)	MODE RATE	IMPORT ANT
Quality	of life: char	nge in QF	Q-R 14+ (follow	v-up 3 month	s; range of s	scores: 0-100; E	etter indi	cated by	higher va	lues)		
1 (Amin 2011)	randomis ed trials⁵	no serious risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ⁷	none	; Better indicated b 17		-	MD 5.21 lower (15.5 lower to 5.08 higher)	MODE RATE	IMPORT ANT

Abbreviations: CFQ-R: cystic fibrosis questionnaire revised; CI: confidence interval; FEV₁: 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 (12=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	y assessmer	nt					No of pa	atients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Dorna se alfa	Nebulis ed sodium chlorid	Relat ive (95% CI)	Absolute		
Lung	unctionumo	on ⁰ / oho	ngo in EEV. (fr). Bottor i	e	hy high		Quality	Importance
Lung	unction: me	an % cna	nge in FEV ₁ (fo	bliow-up 3 we	eeks; range	of scores: 0-100); Better i	ndicated	by nign	er values)		
1 Ballm an 1998	randomise d trials ¹	seriou s ²	no serious inconsistenc y	no serious indirectnes s	very serious ³	none	48		-	MD 1.6 higher (7.96 lower to 11.16 higher)	VERY LOW	CRITICAL
Lung f	unction: me	an % cha	nge in FEV ₁ (fo	ollow-up 3 m	onths; range	of scores: 0-10	00; Better	^r indicated	l by hig	her values)		
1 Suri 2001	randomise d trials ¹	seriou s ²	no serious inconsistenc y	no serious indirectnes s	serious ⁴	none	00; Better indicate 14		-	MD 8 higher (2 to 14 higher)	LOW	CRITICAL
Numbe	er of days in	patient tr	eatment (follow	w-up 3 month	ns; Better ind	dicated by lowe	r values)					
1 Suri 2001	randomise d trials	seriou s ²	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	ver values) 14		-	MD 0.4 lower (2.32 lower to 1.52 higher)	MODER ATE	CRITICAL

Abbreviations: CI: confidence interval; FEV₁: 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%)

Qualit No of studi es	y assessmer Design	nt Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	No of pat High concentr ation (>3% sodium chloride)	ients Low conce ntratio n(≤3% sodiu m	Effect Relative (95% CI)	Absolu te		
								de)			Quality	Importance
Failed	to regain pro	e-exace	rbation FEV₁%	predicted (fo	ollow-up: at l	hospital discha	rge; range	of score	s: 0-100; B	etter indi	cated by high	er values)
1 (Dent ice 2016)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	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)	MODERAT E	CRITICAL
Lung	function: % c	hange i	in FEV ₁ (follow	-up 2 weeks;	range of sco	ores: 0-100; Bet	tter indicat	ed by hig	gher value	s)		
1 (Gupt a 2012)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ¹	none	15	15	-	MD 14.35 lower (27.8 to 0.9 lower)	MODERAT E	CRITICAL
Lung	function: % c	hange i	n FEV ₁ (follow	-up 4 weeks;	range of sco	ores: 0-100; Bet	ter indicat	ed by hig	gher values	s)		

Quality	/ assessmen	ıt					No of pat	ients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	High concentr ation (>3% sodium chloride)	Low conce ntratio n(≤3% sodiu m chlori de)	Relative (95% CI)	Absolu te	Quality	Importance
2 (Gupt a 2012, Main z 2016)	randomise d trials ²	very serio us ³	very serious ⁴	no serious indirectnes s	very serious⁵	none	75	78	-	MD 4.92 lower (17.69 lower to 7.86 higher)	VERY LOW	CRITICAL
Lung f	unction: % c	hange i	n FEV ₁ (follow	-up 12 weeks	; range of so	cores: 0-100; Be	etter indica	ted by h	igher value	es)		
1 (Elkin s 2006)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ¹	none	76	73	-	MD 4.1 higher (0.08 lower to 8.28 higher)	MODERAT E	CRITICAL
Lung f	unction: % c	hange i	n FEV₁ (follow	-up 24 weeks	; range of so	cores: 0-100; B	etter indica	ated by h	ligher valu	es)		
1 (Elkin s 2006)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ¹	none	75	65	-	MD 5.37 higher (1.03 to 9.71 higher)	MODERAT E	CRITICAL
Lung f	unction: % c	hange i	n FEV₁ (follow	-up 36 weeks	; range of so	cores: 0-100; Be	etter indica	ted by h	igher value	es)		
1 (Elkin s	randomise d trials	no serio us	no serious inconsistenc y	no serious indirectnes s	serious ¹	none	69	65	-	MD 3.63 higher	MODERAT E	CRITICAL

Quality assessment							No of patients		Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	High concentr ation (>3% sodium chloride)	Low conce ntratio n(≤3% sodiu m chlori de)	Relative (95% CI)	Absolu te	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 (Elkin s 2006)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ¹	none	68	66	-	MD 2.31 higher(2.72 lower to 7.34 higher)	MODERAT E	CRITICAL
Time to first pulmonary exacerbation (follow-up: > 1 year)												
2 (Dent ice 2016, Rose nfeld 2012)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ⁶	none	225	228	HR 0.92 (0.74 to 1.14)	-	MODERAT E	CRITICAL
Number of days of treatment for a pulmonary exacerbation (follow-up 48 weeks; Better indicated by lower values)												
1 (Ros endfe Id	randomise d trials	no serio us risk	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	158	163	-	MD 1.11 higher (0.89	HIGH	CRITICAL

 $\ensuremath{\textcircled{\sc online 0.5ex}}$ NICE 2017. All rights reserved. Subject to Notice of rights.

Quality assessment							No of patients		Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	High concentr ation (>3% sodium chloride)	Low conce ntratio n(≤3% sodiu m chlori de)	Relative (95% CI)	Absolu te	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 (Dent ice 2016)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ¹	none	67	65	-	MD 2.00 higher (3.12 lower to 7.12 higher)	MODERAT E	IMPORTAN T
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 (Dent ice 2016)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	67	65	-	MD 0.00 higher (4.78 lower to 4.78 higher)	HIGH	IMPORTAN T
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 (Dent ice	randomise d trials	no serio us risk	no serious inconsistenc y	no serious indirectnes s	serious ¹	none	67	65	-	MD 2.00 lower (8.15 lower	MODERAT E	IMPORTAN T
Quality	y assessmen	it					No of pat	ients	Effect			
--------------------------------	-----------------------	---	---------------------------------	--------------------------------	----------------------	-----------------------------	--	---	-------------------------	--	-----------------	---------------
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	High concentr ation (>3% sodium chloride)	Low conce ntratio n(≤3% sodiu m chlori de)	Relative (95% CI)	Absolu te	Quality	Importance
2016)		of bias								to 4.15 higher)		
Chang values	e in quality o	of life fo	llowing treatm	ent – CFQOL	, respiratory	domain (follow	/-up 7 days	; range (of scores:	0-100; Be	tter indicated	by higher
1 (Dent ice 2016)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ¹	none	67	65	-	MD 1.00 higher (4.99 lower to 6.99 higher)	MODERAT E	IMPORTAN T
Chang values	e in quality o	of life fo	llowing treatm	ent – CFQOL	, physical do	omain (at hospi	tal dischar	ge; rang	e of score	s: 0-100; I	Better indicate	ed by higher
1 (Dent ice 2016)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ¹	none	67	65	-	MD 2.00 higher (4.15 lower to 8.15 higher)	MODERAT E	IMPORTAN T
Chang values	e in quality o	of life fo	llowing treatm	ent – CFQOL	, burden dor	main (at hospita	al discharg	e; range	of scores:	0-100; B	etter indicated	d by higher
1 (Dent ice	randomise d trials	no serio us risk	no serious inconsistenc y	no serious indirectnes s	serious ¹	none	67	65	-	MD 2.00 higher (4.04 lower	MODERAT E	IMPORTAN T

Quality	y assessmer	nt					No of pat	ients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	High concentr ation (>3% sodium chloride)	Low conce ntratio n(≤3% sodiu m chlori de)	Relative (95% CI)	Absolu te	Quality	Importance
2016)		of bias								to 8.04 higher)		
Chang values	e in quality (of life fo	llowing treatm	ent — CFQOI	L, health dor	nain (at hospita	I discharge	e; range	of scores:	0-100; Be	etter indicated	l by higher
1 (Dent ice 2016)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ¹	none	67	65	-	MD 2.00 higher (4.99 lower to 8.99 higher)	MODERAT E	IMPORTAN T
Chang higher	e in quality (values)	of life fo	llowing treatm	ent – CFQOL	, respiratory	domain (at hos	spital disch	narge; ra	nge of sco	ores: 0-100	0; Better indic	ated by
1 (Dent ice 2016)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ¹	none	67	65	-	MD 2.00 lower (8.67 lower to 4.67 higher)	MODERAT E	IMPORTAN T
Quality	y of life: CFC) parent	, CFQ-R respir	atory (follow-	up 4 week; ı	range of scores	: 0-100; Be	tter indic	cated by h	igher valu	ies)	
1 (Ami n 2010)	randomise d trials ⁷	no serio us risk	no serious inconsistenc y	no serious indirectnes s	serious ¹	none	20		-	MD 5.9 higher (3.1 lower	MODERAT E	IMPORTAN T

Quality	y assessmen	it					No of pat	ients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	High concentr ation (>3% sodium chloride)	Low conce ntratio n(≤3% sodiu m chlori de)	Relative (95% CI)	Absolu te	Quality	Importance
		of bias								to 14.9 higher)		
Quality	y of life: CFQ	14+, CI	FQ-R respirato	ry (follow-up	4 weeks; Be	etter indicated b	y higher v	alues)				
1 (Ami n 2010)	randomise d trials ⁷	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	very serious⁵	none	20		-	MD 5.2 higher (7 lower to 17.4 higher)	LOW	IMPORTAN T
Chang	e in quality o	of life: C	FQ-R parents	(follow-up 48	weeks; rang	ge of scores: 0-	100; Better	indicate	d by highe	er values)		
1 (Elkin s 2006)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	very serious⁵	none	34	33	-	MD 1.13 lower (7.49 lower to 5.23 higher)	LOW	IMPORTAN T
Chang	e in quality o	of life: C	FQ-R 14+ (follo	ow-up 48 wee	eks; range o	f scores: 0-100;	Better ind	icated by	y higher va	lues)		
1 (Elkin s 2006)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ¹	none	46	46	-	MD 7.77 higher(1.86 to 13.68 higher)	MODERAT E	IMPORTAN T
Chang	e in quality o	of life: C	FQ-R respirato	ory domain (f	ollow-up 48	weeks; range o	f scores: 0	-100; Be	tter indicat	ted by hig	pher values)	

Quality	y assessmer	nt					No of pat	ients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	High concentr ation (>3% sodium chloride)	Low conce ntratio n(≤3% sodiu m chlori de)	Relative (95% CI)	Absolu te	Quality	Importance
1 (Ros enfel d 2012)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ¹	none	158	163	-	MD 3.3 higher (0 to 6.6 higher)	MODERAT E	IMPORTAN T

Abbreviations: CFQ-R: cystic fibrosis questionnaire revised; CI: confidence interval; FEV₁: 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

Qualit	v accoccimo	nt —					No of patient		Effoct			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectne ss	Imprecisi on	Other consideration s	Acetylcystei ne	Place bo	Relati ve (95% CI)	Absolu te	Quality	Importanc e
Lung	function: cha	ange in	FEV ₁ (% predic	cted) (follow-	up 4 weeks;	range of score	es: 0-100; Bett	er indica	ted by hi	igher valu	ies)	
1 (Sko v 2015)	randomise d trials	very serio us ¹	no serious inconsistenc y	no serious indirectnes s	serious ²	none	10	9	-	MD 3.51 higher (0.65 lower to 7.67 higher)	VERY LOW	CRITICAL
Lung	function: cha	ange in	FEV ₁ (% predic	cted) (follow-	up 12 weeks	s; range of sco	res: 0-100; Bet	ter indic	ated by I	higher val	lues)	
1 (Ratj en 1985)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	very serious ³	none	10	11	-	MD 5 higher (10.84 lower to 20.84 higher)	LOW	CRITICAL
Lung	function: cha	ange in	FEV ₁ (% predic	cted) (follow-	up 24 weeks	s; range of sco	res: 0-100; Bet	ter indic	ated by I	higher val	lues)	
1 (Con rad 2015)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ²	none	36	34	-	MD 4.4 higher (0.83 to 7.97 higher)	MODERAT E	CRITICAL
Inflam	matory mark	kers: ch	ange in sputu	m IL-8 (log10) (follow-up	24 weeks; Bett	er indicated by	y lower v	alues)			

Quality	y assessmer	nt					No of patient	S	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectne ss	Imprecisi on	Other consideration s	Acetylcystei ne	Place bo	Relati ve (95% CI)	Absolu te	Quality	Importanc e
1 (Con rad 2015)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	not calculable 4	none	36	34	-	MD 0.19 higher (0.03 lower to 0.42 higher)	HIGH	IMPORTAN T
Incide	nce of pulmo	onary e	xacerbations (f	follow-up 24	weeks)							
1 (Con rad 2015)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	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	y of life: QFC	Q-R resp	oiratory (follow	v-up 24 week	s; range of s	scores: 0-100; E	Better indicate	d by hig	her value	es)		
1 (Con rad 2015)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	very serious ³	none	36	34	-	MD 0.34 lower (6.3 lower to 5.62 higher)	LOW	IMPORTAN T

Abbreviations: CFQ-R: cystic fibrosis questionnaire revised; CI: confidence interval; FEV1: 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	y assessmen	t					No of patients	s	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne SS	Imprecisi on	Other consideratio ns	Continuous oral Flucloxacilli n, antibiotic prophylaxis	Antibi otics as requir ed	Relati ve (95% Cl)	Absolu te	Quality	Importan ce
Numbe	er of children	from wh	om S aureus	isolated at lea	ast once (foll	ow-up mean 1 y	/ears)					
1 (Chat field 1991)	randomise d trials	very serious 1	no serious inconsistenc y	no serious indirectnes s	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	IMPORT ANT
Numbe	er of children	from wh	om <i>S aureus</i> is	solated at lea	st once (follo	ow-up mean 2 y	ears)					
2 (Chat field 1991, Weav er 1994)	randomise d trials	very serious ³	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	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	IMPORT ANT
								48.3%		270 fewer per 1000 (from 111		

© NICE 2017. All rights reserved. Subject to Notice of rights.

Quality No of studi es	/ assessmen Design	t Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	No of patients Continuous oral Flucloxacilli n, antibiotic prophylaxis	Antibi otics as requir ed	Effect Relati ve (95% CI)	Absolu te	Quality	Importan ce
										fewer to 362 fewer)		
Numbe	er of children	from wh	om S <i>aureus</i> i	solated at lea	ist once (foll	ow-up mean 3 y	vears)					
1 (Chat field 1991)	randomise d trials	very serious 1	no serious inconsistenc y	no serious indirectnes s	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	IMPORT ANT
Numbe	er of children	from wh	om <i>P aerugino</i>	sa isolated a	t least once	(follow-up mear	n 1 years)					
1 (Chat field 1991)	randomise d trials	very serious 1	no serious inconsistenc y	no serious indirectnes s	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	CRITICA L
Numbe	er of children	from wh	om <i>P aerugino</i>	sa isolated a	t least once	(follow-up mear	n 2 years)					
2 (Chat field 1991, Weav	randomise d trials	very serious ³	no serious inconsistenc y	no serious indirectnes s	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	CRITICA L

Quality	v assessmen	t					No of patients	S	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Continuous oral Flucloxacilli n, antibiotic prophylaxis	Antibi otics as requir ed	Relati ve (95% CI)	Absolu te	Quality	Importan ce
er 1994)								21 7%		fewer to 107 more)		
								21.770		fewer per 1000 (from 143 fewer to 132 more)		
Numbe	er of children	from wh	om <i>P aerugino</i>	sa isolated a	t least once	(follow-up mean	n 3 years)					
1 (Chat field 1991)	randomise d trials	very serious 1	no serious inconsistenc y	no serious indirectnes s	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	CRITICA L
Numbe	er of children	requiring	g admission dι	ie to pulmon	ary exacerba	ations (annualis	ed rates) (follo	w-up me	an 3 year	s)		
2 (Chat field 1991, Weav er 1994)	randomise d trials	very serious ³	no serious inconsistenc y	no serious indirectnes s	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	CRITICA L

Quality	y assessmen	t					No of patients	S	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Continuous oral Flucloxacilli n, antibiotic prophylaxis	Antibi otics as requir ed	Relati ve (95% CI)	Absolu te	Quality	Importan ce
										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'

Qualit	y assessme	nt					No of patie	ents	Effect			
No of studi es	Design	Risk of bias	Inconsiste ncy	Indirectne ss	Imprecision	Other considerati ons	Continuo us oral Cephalex in, antibiotic prophyla xis	Antib iotics as requi red	Relati ve (95% Cl)	Absol ute	Quality	Importanc e
Numb	er of childre	n from w	hom S aureus	isolated at	least once (fol	low-up mean 1	years; asse	ssed wit	h: Respi	ratory cu	ltures)	
1 (Stut man 2002)	randomis ed trials	seriou s ¹	no serious inconsisten cy	no serious indirectne ss	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	MODERAT E	IMPORTAN T

© NICE 2017. All rights reserved. Subject to Notice of rights.

Quality No of studi es	y assessmei Design	nt Risk of bias	Inconsiste ncy	Indirectne ss	Imprecision	Other considerati ons	No of patie Continuo us oral Cephalex in, antibiotic prophyla xis	nts Antib iotics as requi red	Effect Relati ve (95% Cl)	Absol ute	Quality	Importanc e
										fewer)		
Numbe	er of childre	n from w	hom S aureus	isolated at lo	east once (foll	ow-up mean 2	years; asses	sed with	n: Respir	atory cul	tures)	
1 (Stut man 2002)	randomis ed trials	seriou s ²	no serious inconsisten cy	no serious indirectne ss	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)	MODERAT E	IMPORTAN T
Numbe	er of childre	n from w	hom S aureus	isolated at lo	east once (foll	ow-up mean 3 y	years; asses	sed with	n: Respir	atory cult	tures)	
1 (Stut man 2002)	randomis ed trials	seriou s ³	no serious inconsisten cy	no serious indirectne ss	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)	MODERAT E	IMPORTAN T
Numbe	er of childre	n from w	hom S aureus	isolated at l	east once (foll	ow-up mean 4 y	years; asses	sed with	n: Respir	atory cul	tures)	
1 (Stut man	randomis ed trials	seriou s ⁴	no serious inconsisten cy	no serious indirectne ss	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	MODERAT E	IMPORTAN T

Risk of bias	Inconsiste ncy	Indirectne ss	Imprecision	Other considerati ons	No of paties Continuo us oral Cephalex in, antibiotic prophyla xis	nts Antib iotics as requi red	Effect Relati ve (95% Cl)	Absol ute	Quality	Importanc e
								344 fewer to 587 fewer)		
from wh	nom S aureus	isolated at le	east once (follo	ow-up mean 5 y	/ears; asses	sed with	: Respir	atory cult	tures)	
very seriou s ⁵	no serious inconsisten cy	no serious indirectne ss	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	IMPORTAN T
from wh	nom S aureus	isolated at le	east once (follo	ow-up mean 6 y	/ears; asses	sed with	: Respir	atory cult	tures)	
very seriou s ⁶	no serious inconsisten cy	no serious indirectne ss	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	IMPORTAN T
f vsss f vsss	rom wł ery eriou ⁵ rom wł ery eriou f	kisk f iasInconsiste ncyf iasInconsiste ncyrom whom S aureus ery eriou 5no serious inconsisten cyrom whom S aureus ery eriou ery eriou ery ery eriou fno serious erious inconsisten cyrom whom S aureus ery ery eriou fno serious inconsisten cyrom whom S aureus ery eriou fno serious inconsisten cyinconsisten fno serious inconsisten cyintres (follow-up meal	kisk f iasInconsiste ncyIndirectne ssrom whom S aureusisolated at le overious inconsisten cyNo serious indirectne ssrom whom S aureusno serious indirectne ssNo serious indirectne ssrom whom S aureusisolated at le indirectne ssrom whom S aureusno serious indirectne ssrom whom S aureusno serious indirectne ssrom whom S aureusisolated at le ssrom whom S aureusisolated at le sseriou 6no serious inconsisten cyno serious eriou 6no serious indirectne ssinteres (follow-up mean 6 years; Be	Isk f iasInconsiste ncyIndirectne ssImprecisioniasInconsiste ncyImprecisionrom whom S aureusisolated at least once (followers) inconsisten syno serious indirectne ssno serious imprecisionrom whom S aureusno serious inconsisten cyno serious indirectne ssno serious imprecisionrom whom S aureusisolated at least once (followers) inconsisten ssno serious imprecisionrom whom S aureusisolated at least once (followers) inconsisten indirectne ssrom whom S aureusisolated at least once (followers) indirectne indirectne ssrom whom S aureusisolated at least once (followers) indirectne ssrom whom S aureusno serious indirectne ssrom whom S aureusno serious indirectne ss<	Lisk f iasInconsiste ncyIndirectne ssImprecisionOther considerati onsrom whom S aureus isolated at least once (follow-up mean 5 y eriou sno serious inconsisten cyno serious indirectne ssno serious imprecisionnonerom whom S aureus isolated at least once (follow-up mean 5 y inconsisten cyno serious indirectne ssno serious imprecisionnonerom whom S aureus isolated at least once (follow-up mean 6 y eriou inconsisten cyno serious indirectne ssno serious imprecisionnonerom whom S aureus isolated at least once (follow-up mean 6 y eriou eriou for serious inconsisten cyno serious indirectne ssno serious imprecisionnonerom whom S aureus isolated at least once (follow-up mean 6 y eriou for serious indirectne ssno serious imprecisionnone	Inconsiste fias Inconsiste ncy Indirectne ss Imprecision Other considerati ons Continuo us oral Cephalex in, antibiotic prophyla xis rom whom S aureus isolated at least once (follow-up mean 5 years; asses ery eriou s5 no serious inconsisten cy no serious indirectne ss no serious imprecision none 20/58 (34.5%) rom whom S aureus isolated at least once (follow-up mean 5 years; asses ery eriou s no serious indirectne ss no serious imprecision none 20/58 (34.5%) rom whom S aureus isolated at least once (follow-up mean 6 years; asses ery eriou s no serious indirectne ss no serious imprecision none 7/25 (28%) inconsisten s no serious indirectne s no serious imprecision none 7/25 (28%)	Isk fias Inconsiste ncy Indirectne ss Imprecision Other considerati ons Continuo us oral considerati ons Antibiotic as required as a conserved as a conser	Inconsiste f Indirectne ss Imprecision Other considerati ons Continuo us oral Cephalex in, antibiotic prophyla Antib iotis as requi red Relati ve ss rom whom S aureus isolated at least once (follow-up mean 5 years; assested with: noserious inconsisten cy no serious indirectne ss no serious indirectne ss no serious imprecision none 20/58 (34.5%) 34/40 (85%) RR 0.41 (0.28 to 0.59) rom whom S aureus isolated at least once (follow-up mean 6 years; assested with: Respir respir to 0.59) rom whom S aureus isolated at least once (follow-up mean 6 years; assested with: Respir (34.5%) rom whom S aureus isolated at least once (follow-up mean 6 years; assested with: Respir (0.28 to 0.59) rom whom S aureus isolated at least once (follow-up mean 6 years; assested with: Respir (0.28 to 0.59) rom whom S aureus isolated at least once (follow-up mean 6 years; assested with: Respir (0.18 to 0.71) reriou 6 no serious indirectne ss no serious indirectne ss none 7/25 (28%) 14/18 (77.8 %) RR 0.36 %) reriou 6 reriou ss ss serious indirectne ss no serious indirectne ss none 7/25 (28%) 14/18 (77.8 %) no.36 (0.18 to 0.71)	Inconsiste f Inconsiste ncy Indirectne ss Imprecision Other considerati ons Continuo us oral cephalex in, antibiotic prophyla xis Antib iotics requi red Relati ve (95% CI) Absol ute Imprecision Other considerati ons Soral cephalex in, antibiotic prophyla Antib iotics requi red Relati ve (95% CI) Absol ve (95% CI) Imprecision Imprecision Soral cephalex Soral cephalex Antib iotics requi red Relati ve (95% CI) Adve (95% CI) Imprecision Imprecision Imprecision Imprecision Imprecision Imprecision Imprecision Indirectne s no serious inconsisten no serious indirectne s no serious indirectne indirectne s no serious indirectne s no serious indirectne s no serious indirectne s none 7/25 (28%) 14/18 (77.8 %) Re s 498 fewer eriou No serious indirectne s no serious indirectne s no serious indirectne s none 7/25 (28%) 14/18 (77.8 %) Re s 498 fewer 0.30 (0.18 (700) 0.71) 1000 (2.71) 0.36 fewer fewer to 633 fewer 1000	Inconsiste f Inconsiste ncy Indirectne ss Imprecision ss Imprecision ss Other considerati ons Continuo to snaition ons Anthis cephalex in, antibiotic prophyla xis Relati set (95% (1) Absoi ute (95% (1) Quality Quality Verephalex in, antibiotic prophyla xis Relati set (10) 344 fewer to 587 fewer Verephalex inconsiderati prophyla xis 344 fewer to 587 fewer Quality Imprecision Imprecision Imprecision Imprecision Verephalex inconsiderati prophyla xis 344 fewer to 587 fewer Continuo (100 (100) 344 fewer to 587 fewer Imprecision s Imprecision indirectne cy Imprecision indirectne ss no serious imprecision none 20/58 (34.5%) 34/40 (85%) RR 0.41 fewer to 612 fewer COV rom w-m S aureus isolated at least once (follow-up mean 6 years; assested with ss Imprecision imprecision none 7/25 (28%) 14/18 (77.8 %) RR 0.36 (0.18 per to 1000 (0.71) 498 fewer to 633 fewer eriou s Imprecision indirectne cy Imprecision imprecision none 7/25 (28%) 14/18 (77.8 %) RR 0.36 (0.18 per to 6.038 fewer 498 to 6.038 fewer

© NICE 2017. All rights reserved. Subject to Notice of rights.

Qualit No of studi es	y assessme Design	nt Risk of bias	Inconsiste ncy	Indirectne ss	Imprecision	Other considerati ons	No of patie Continuo us oral Cephalex in, antibiotic prophyla xis	nts Antib iotics as requi red	Effect Relati ve (95% CI)	Absol ute	Quality	Importanc e
1 (Stut man 2002)	randomis ed trials	seriou s ⁷	no serious inconsisten cy	no serious indirectne ss	very serious ⁸	none	68	51	-	MD 2.3 lower (13.59 lower to 8.99 higher)	VERY LOW	IMPORTAN T
Any p	ulmonary ex	acerbatio	ons (follow-up	mean 6 year	s; measured v	vith: %; Better	indicated by	lower va	alues)			
1 (Stut man 2002)	randomis ed trials	seriou s ⁷	no serious inconsisten cy	no serious indirectne ss	very serious ⁹	none	68	51	-	MD 4.9 lower (22.24 lower to 12.44 higher)	VERY LOW	CRITICAL
Numb	er of childre	n requiriı	ng admission	due to pulmo	onary exacerba	ations (annuali	sed rates) (fo	ollow-up	mean 6	years; as	sessed with:	not
1 (Stut man 2002)	randomis ed trials	seriou s ⁷	no serious inconsisten cy	no serious indirectne ss	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
Adner	ence to trea	unent (to	now-up mean	o years; mea	isurea with: Pa	arents selt-repo	ort; better in	ulcated	by nighe	r values)		

Quality No of studi es	y assessmei Design	nt Risk of bias	Inconsiste ncy	Indirectne ss	Imprecision	Other considerati ons	No of patie Continuo us oral Cephalex in, antibiotic prophyla xis	nts Antib iotics as requi red	Effect Relati ve (95% CI)	Absol ute	Quality	Importanc e
1 (Stut man 2002)	randomis ed trials	seriou s ⁷	no serious inconsisten cy	no serious indirectne ss	Not calculable ¹⁰	none	68	51	-	MD 5 higher (0 to 0 higher)	MODERAT E	IMPORTAN T
Minor	adverse eve	ents - gen	eralised rash	(follow-up m	ean 6 years; n	neasured with:	Parents self	-report;	Better in	dicated b	y lower value	es)
1 (Stut man 2002)	randomis ed trials	seriou s ⁷	no serious inconsisten cy	no serious indirectne ss	no serious imprecision	none	68	51	-	MD 0.4 higher (0.07 lower to 0.87 higher)	MODERAT E	IMPORTAN T
Minor	adverse eve	ents - nap	py rash (follo	w-up mean 6	years; measu	red with: Parer	nts self-repoi	rt; Bettei	r indicate	ed by low	er values)	
1 (Stut man 2002)	randomis ed trials	seriou S ⁷	no serious inconsisten cy	no serious indirectne ss	no serious imprecision	none	68	51	-	MD 0.9 higher (1.06 lower to 2.86 higher)	MODERAT E	IMPORTAN T
Minor	adverse eve	nts - inci	reased stool f	requency (fol	low-up mean	6 years; measu	red with: Pa	rents se	lf-report;	Better in	dicated by lo	wer values)
1 (Stut man 2002)	randomis ed trials	seriou s ⁷	no serious inconsisten cy	no serious indirectne ss	no serious imprecision	none	68	51	-	MD 0.2 higher (2.18 lower	MODERAT E	IMPORTAN T

Quality No of studi es	y assessme Design	nt Risk of bias	Inconsiste ncy	Indirectne ss	Imprecision	Other considerati ons	No of patie Continuo us oral Cephalex in, antibiotic prophyla xis	nts Antib iotics as requi red	Effect Relati ve (95% CI)	Absol ute	Quality	Importanc e
Number	or of obildre	n from	hom Deerwei	ange identifie	d at lacat area					higher)		
1 (Stut man 2002)	randomis ed trials	seriou s ¹	nom <i>P aerugii</i> no serious inconsisten cy	no serious indirectne ss	ed at least onc 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
Numbe	er of childre	n from w	hom <i>P aerugii</i>	nosa identifie	ed at least onc	e (follow-up me	ean 2 years)					
1 (Stut man 2002)	randomis ed trials	seriou s ²	no serious inconsisten cy	no serious indirectne ss	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
Numbe	er of childre	n from w	hom <i>P aerugii</i>	nosa identifie	ed at least onc	e (follow-up me	ean 3 years)					
1 (Stut man	randomis ed trials	seriou s ³	no serious inconsisten cy	no serious indirectne ss	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

 $\ensuremath{\textcircled{\sc online 0.5ex}}$ NICE 2017. All rights reserved. Subject to Notice of rights.

Quality No of studi es	y assessme Design	nt Risk of bias	Inconsiste ncy	Indirectne ss	Imprecision	Other considerati ons	No of patie Continuo us oral Cephalex in, antibiotic prophyla xis	nts Antib iotics as requi red	Effect Relati ve (95% Cl)	Absol ute	Quality	Importanc e
)										fewer to 178 more)		
Numb	er of childre	n from w	hom <i>P aerugii</i>	nosa identifie	ed at least onc	e (follow-up m	ean 4 years)					
Numbe 1 (Stut man 2002)	randomis ed trials	seriou S ⁴	no serious inconsisten cy	no serious indirectne ss	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)		
Numb	er of childre	n from w	hom <i>P aerugiı</i>	nosa identifie	ed at least onc	e (follow-up m	ean 5 years)					
1 (Stut man	randomis ed trials	very seriou s⁵	no serious inconsisten cy	no serious indirectne ss	serious ¹¹	none	41/58 (70.7%)	22/40 (55%)	RR 1.29 (0.93	159 more per 1000	VERY LOW	CRITICAL

Qualit No of studi es	y assessme Design	nt Risk of bias	Inconsiste ncy	Indirectne ss	Imprecision	Other considerati ons	No of patie Continuo us oral Cephalex in, antibiotic prophyla xis	nts Antib iotics as requi red	Effect Relati ve (95% CI)	Absol ute	Quality	Importanc e
2002)									to 1.78)	(from 38 fewer to 429 more)		
Numb	er of childre	n from w	hom <i>P aerugii</i>	nosa identifie	ed at least onc	e (follow-up me	ean 6 years)					
1 (Stut man 2002)	randomis ed trials	very seriou s ⁶	no serious inconsisten cy	no serious indirectne ss	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; FEV1: 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 patie	ents	Effect			
No of studie	Design	Risk of bias	Inconsistenc y	Indirectness	Imprecision	Other consideration	Single IV agent	Singl e IV	Relativ e	Absolute		
S						S		agent	(95% CI)		Quali ty	Importan ce
FEV ₁ (a	bsolute char	nge) (follo	w-up 2 weeks;	measured wit	th: litres ; Bet	ter indicated by	higher valu	es) [ceft	azidime	versus aztre	onam]	
2 (Elbor n 1992, Salh 1992)	randomise d 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	CRITICA L

Abbreviations: CI: confidence interval; FEV1: 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	assessmen	t					No of patients	5	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne SS	Imprecisi on	Other considera tions	Single IV antibiotic (with placebo)	Combi nation IV antibio tic	Relati ve (95% CI)	Absolut e	Quali ty	Importance
FEV₁ % ceftazi	。predicted(a dime]	absolute (change) (follow	-up 10 days;	Better indica	ated by highe	er values) [tobr	amycin +	placebo v	ersus tobi	ramycin	+
1 (Mast er 2001)	randomise d trials	serious 1	no serious inconsistenc y	no serious indirectnes s	serious ²	none	47	51	-	MD 2.2 lower (6.63 lower to 2.23 higher)	LOW	CRITICAL
FEV₁% tobram	predicted (re	elative ch	ange) (follow-u	ıp 2 weeks; B	etter indicat	ed by higher	values) [tobrai	nycin + pl	acebo ve	ersus IV pip	oeracillir	ı +
1(Ma cfarla ne 1985)	randomise d trials	serious 3	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	4	5	-	MD 4.2 lower (26.5 lower to 18.1 higher)	VER Y LOW	CRITICAL
FEV ₁ %	predicted (r	elative ch	ange) (follow-ւ	ip 2 weeks; B	etter indicat	ed by higher	values) [tobrai	nycin + pl	acebo ve	rsus piper	acillin +	tobramycin]
1(Ma cfarla ne 1985)	randomise d trials	serious 3	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	4	5	-	MD 7.95 higher (8.78 lower to 24.68 higher)	VER Y LOW	CRITICAL
Advers regime	se effects - se ens]	ensitivity	reaction (follow	w-up 2 weeks	; assessed v	vith: number	of participants) [tobram	ycin + pla	acebo vers	us pipe	racillin all
1(Ma cfarla ne 1985)	randomise d trials	serious 3	no serious inconsistenc y	no serious indirectnes s	serious⁵	none	0/8 (0%)	3/10 (30%)	RR 0.17 (0.01	249 fewer per 1000	LOW	IMPORTAN T

Quality No of studi es	/ assessmen Design	t Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other considera tions	No of patients Single IV antibiotic (with placebo)	Combi nation IV antibio tic	Effect Relati ve (95% Cl) to 2.96)	Absolut e (from 297 fewer to 588 more)	Quali ty	Importance
Advers	se effects - N	umber of	hospital admis	ssions due to	tinnitus (fol	low-up 2 wee	ks) [tobramvci	n + placeb	o versus	tobramyc	in + ceft	azidime1
1(Ma ster 2001)	randomise d trials	serious 1	no serious inconsistenc y	no serious indirectnes s	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)	VER Y LOW	IMPORTAN T
Advers	se effects - se	erum crea	atinine (follow-	up 2 weeks; E	Better indicat	ted by lower	values) [tobram	nycin + pla	acebo <i>vei</i>	rsus tobrar	nycin +	ceftazidime]
1(Ma ster 2001)	randomise d trials	serious 1	no serious inconsistenc y	no serious indirectnes s	very serious ⁶	none	21	23	-	MD 4 lower (9.38 lower to 1.38 higher)	VER Y LOW	IMPORTAN T
Advers	se effects - se	erum NAC	G (follow-up 2 v	weeks; Better	indicated by	/ lower value	s) [tobramycin	+ placebo	versus t	obramycin	+ cefta	zidime]
1(Ma ster 2001)	randomise d trials	serious 1	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	21	23	-	MD 2.1 lower (3.46 lower to 0.74 lower)	MOD ERA TE	IMPORTAN T

Abbreviations: CI: confidence interval; FEV1: 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

© NICE 2017. All rights reserved. Subject to Notice of rights.

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

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

Qualit No of studi es	y assessmei Design	nt Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	No of patie Single IV antibiotic	nts Comb inatio n IV antibi otic	Effect Relati ve (95% CI)	Absol ute	Quality	Importance
Eradio pipera	ation: numb	er of peo amycin]	ple in whom p	seudomonas	s isolates we	ere eradicated a	t end of cou	rse (follo	ow-up 10	days) [Pi	peracillin ver	sus
1(Mc Carty 1988)	randomise d trials	very seriou s ¹	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n 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 char	nge) (follo	ow-up 10 - 14 c	lays; measur	ed with: %;	Better indicate	d by higher v	values) [o	ceftazidir	ne versus	s tobramycin	+ ticarcillin]
1 (Gold 1985)	randomise d trials	seriou S ³	no serious inconsistenc y	no serious indirectnes s	serious imprecisio n ⁴	none	17	13	-	MD 19.6 lower (38.26 to 0.94 lower)	LOW	CRITICAL
FEV ₁ (absolute cha	ange) (fol	llow-up 12 day	s; measured	with: ml; B	etter indicated	by higher va	lues) [Co	olistin ve	rsus colis	stin & "other"	
1 (Con way	randomise d trials	very seriou s ⁵	no serious inconsistenc y	no serious indirectnes s	no serious	none	36	35	-	MD 160 lower	LOW	CRITICAL

© NICE 2017. All rights reserved. Subject to Notice of rights.

Quality No of studi es	/ assessmer Design	nt Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	No of patien Single IV antibiotic	nts Comb inatio n IV antibi otic	Effect Relati ve (95% Cl)	Absol ute	Quality	Importance
)					n					2 to 10.28 lower)		
FEV ₁ %	6 predicted ((absolute	change) (follo	w-up: 14 day	vs; Better ind	dicated by high	er values) [c	eftazidin	ne versus	s tobramy	cin + piperac	illin]
1 (De Boec k 1989)	randomise d trials	seriou S ³	no serious inconsistenc y	no serious indirectnes s	very serious ⁶	none	11	10	-	MD 1 higher (8.85 lower to 10.85 higher)	VERY LOW	CRITICAL
Time t	o readmissio	on (follow	/-up: 24 to 26 r	nonths; Bett	er indicated	by lower value	s) [ceftazidin	ne versu	s tobram	ycin + pi	peracillin]	
1 (De Boec k 1989)	randomise d trials	seriou s ³	no serious inconsistenc y	no serious indirectnes s	very serious ⁷	none	9	10	-	MD 1 lower (5.52 lower to 3.52 higher)	VERY LOW	IMPORTAN T
Numbe	er of admiss	ions, req	uiring IV antibi	otics or deat	h (follow-up	3 months) [cef	ftazidime ver	s <i>us</i> tobr	amycin +	ticarcilli	n]	
1 (Wes ley 1988)	randomise d trials	seriou s ⁸	no serious inconsistenc y	no serious indirectnes s	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	IMPORTAN T

Quality	/ assessmer	nt					No of patier	nts	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Single IV antibiotic	Comb inatio n IV antibi otic	Relati ve (95% CI)	Absol ute	Quality	Importance
Mortal	ity (follow-u	p 4 montl	hs) [ceftazidim	e <i>versus</i> tob	ramycin & ti	carcillin]						
1 (De Boec k 1989)	randomise d trials	seriou S ⁹	no serious inconsistenc y	no serious indirectnes s	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	IMPORTAN T
Mortal	ity (follow-u	p 12 weel	ks) [Colistin <i>ve</i>	ersus colistin	+ "other"]							
1 (Con way 1997)	randomise d trials	very seriou s ⁵	no serious inconsistenc y	no serious indirectnes s	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	IMPORTAN T
Advers	se effects: liv	ver trans	aminase enzyn	ne elevation	(follow-up 1	0-14 days) [cef	tazidime vers	sus tobra	amycin +	ticarcillin	1]	
2 (Gold 1987 and Wesl ey 1988)	randomise d trials	seriou s ¹¹	no serious inconsistenc y	no serious indirectnes s	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	IMPORTAN T

Quality	y assessmer	nt					No of patier	nts	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Single IV antibiotic	Comb inatio n IV antibi otic	Relati ve (95% Cl)	Absol ute	Quality	Importance
Advers	se effects: n	eurologic	al adverse eff	ects (follow-u	up 12 days)	[Colistin versus	s combinatio	n anti-ps	seudo]			
1 (Con way 1997)	randomise d trials	very seriou s ⁵	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	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	IMPORTAN T
Advers	se effects: ra	ash (follo	w-up 10 days)	[piperacillin	versus pipe	racillin + tobrar	nycin]					
1 (McC arty 1988)	randomise d trials	very seriou s ¹	no serious inconsistenc y	no serious indirectnes s	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	IMPORTAN T
Advers	se effects: fe	ever (follo	ow-up 10 days)	[piperacillin	versus pipe	eracillin + tobra	mycin]					
1 (McC arty 1988)	randomise d trials	very seriou s ¹	no serious inconsistenc y	no serious indirectnes s	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	IMPORTAN T

Quality	y assessmer	nt					No of patients Effect					
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Single IV antibiotic	Comb inatio n IV antibi otic	Relati ve (95% CI)	Absol ute	Quality	Importance
										1000 more)		
Adver	se effects: p	roteinuria	a (follow-up 10	- 14 days) [c	eftazidime v	versus tobramy	cin+ticarcilli	n]		,		
1 (Gold 1985)	randomise d trials	seriou S ³	no serious inconsistenc y	no serious indirectnes s	very serious ⁷	none	1/17ª (5.9%)	1/17ª (5.9%)	RR 1 (0.07 to 14.72)	0 fewer per 1000 (from 55 fewer to 807 more)	VERY LOW	IMPORTAN T
Advers anti-ps	se effects: re seudo]	enal toxic	ity - Change ir	l blood urea	(mmol/l) (fol	low-up 12 days	; Better indic	ated by	lower va	lues) [col	listin <i>versus</i> o	combination
1 (Con way 1997)	randomise d trials	very seriou s ⁵	no serious inconsistenc y	no serious indirectnes s	serious ¹²	none	36	35	-	MD 0.26 lower (0.93 lower to 0.41 higher)	VERY LOW	IMPORTAN T
Advers combi	se effects: re nation anti-p	enal toxic [] [] [] [] [] [] [] [] [] [] [] [] [] [ity - Change ir	n serum creat	tinine (mmo	l/l) (follow-up 1	2 days; Bette	er indicat	ed by lov	wer value	es) [colistin ve	ersus
1 (Con way 1997)	randomise d trials	very seriou s ⁵	no serious inconsistenc y	no serious indirectnes s	very serious ⁷	none	36	35	-	MD 8.85 higher (0.66 lower to	VERY LOW	IMPORTAN T

Quality	y assessmer	nt					No of patie	nts	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Single IV antibiotic	Comb inatio n IV antibi otic	Relati ve (95% CI)	Absol ute	Quality	Importance
										18.36 higher)		

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: intravenous; MD: mean difference; mmol/ I: 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 as No of studies	sessmen Desig n	t Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	No of patient Combinati on IV AB	s comb inatio n IV AB	Effect Relati ve (95% Cl)	Absolut e	Quali ty	Importance
Eradicatio	n of path	ogen (fol	low-up 2 weeks	s) [aztreonam	+ amikacin	versus ceftazid	ime + amikaci	n]				
1(Schaad 1989)	rando mised trials	serious	no serious inconsistenc y	no serious indirectnes s	very serious ²	none	17/28ª (60.7%)	16/28ª (57.1 %)	RR 1.06 (0.69	34 more per 1000 (from	VER Y LOW	CRITICAL

© NICE 2017. All rights reserved. Subject to Notice of rights.

Quality as	sessmen	t					No of patients Effect					
No of studies	Desig n	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Combinati on IV AB	comb inatio n IV AB	Relati ve (95% Cl)	Absolut e	Quali ty	Importance
									to 1.65)	177 fewer to 371 more)		
FEV ₁ % pr	edicted (a	absolute o	change) (follow	v-up 2 weeks;	Better indic	ated by lower v	alues) [aztreo	nam + ve	ersus ceft	azidime +	amikaci	n]
1 Schaad (1989)	rando mised trials	serious 1	no serious inconsistenc y	no serious indirectnes s	serious ³	none	24 ^a	25ª	-	MD 4 higher (0.25 lower to 8.25 higher)	LOW	CRITICAL
FEV ₁ % protocol tobramyci	edicted (a n]	absolute	change) (follow	/-up 2 - 4 wee	ks ^ь ; Better i	ndicated by hig	her values) [m	eropene	m + tobra	amycin <i>vel</i>	rs <i>us</i> cef	tazidime +
1 (Blumer 2005)	rando mised trials	serious 4	no serious inconsistenc y	no serious indirectnes s	serious ³	none	47	50	-	MD 2.7 higher (0.76 lower to 6.16 higher)	LOW	CRITICAL
FEV ₁ % protocol tobramyci	edicted (ı n]	relative %	change) (follo	w-up 2-4 wee	ks ^b ; Better i	ndicated by hig	her values) [m	eropene	m + tobra	amycin <i>vei</i>	rsus cef	tazidime +
1 (Blumer 2005)	rando mised trials	serious 4	no serious inconsistenc y	no serious indirectnes s	very serious⁵	none	47	50	-	MD 9.4 higher (8.44 lower to 27.24 higher)	VER Y LOW	CRITICAL
Adverse e	ffects - R	ash (follo	w-up 2 weeks)	[aztreonam +	- amikacin <i>v</i>	ersus ceftazidin	ne + amikacin]					

Quality as	sessmen	t				No of patients Effect						
No of studies	Desig n	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Combinati on IV AB	comb inatio n IV AB	Relati ve (95% Cl)	Absolut e	Quali ty	Importance
1 (Schaad 1989)	rando mised trials	serious 1	no serious inconsistenc y	no serious indirectnes s	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)	VER Y LOW	IMPORTAN T
Adverse e	ffects - L	iver trans	aminases - AS	T & ALT (follo	ow-up 2 wee	ks) [aztreonam	+ amikacin ve	<i>rsus</i> ceft	azidime -	⊦ amikacin]	
1 (Schaad 1989)	rando mised trials	serious 1	no serious inconsistenc y	no serious indirectnes s	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)	VER Y LOW	IMPORTAN T
Adverse et	ffects - T	hrombocy	ytopenia (follov	w-up 2 weeks) [aztreonam	n + amikacin <i>vel</i>	rsus ceftazidin	ne + amil	kacin]			
1 (Schaad 1989)	rando mised trials	serious	no serious inconsistenc y	no serious indirectnes s	very serious ⁶	none	3/28 (10.7%)	0/28 (0%)	RR 7 (0.38 to 129.55)	-	VER Y LOW	IMPORTAN T

Abbreviations: AST: aminotransferase, ALT: alanine aminotransferase; CI: confidence interval; FEV1: 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.

linout	innaida ant					aginoou						
Quality	/ assessmen	t					No of patie	ents	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	2 IV antibiotic + inhaled antibiotic	2 IV witho ut inhale d antibi	Relativ e (95% CI)	Absolut e	Quali	Importanco
Fradic	ation of P ao	ruginosa	- (follow-up 15	days) [IV cof	itazidime + I\	/ amikacin + inh	aled amikac	in versu	evoreue l	V coftazidir	uy no + IV :	amikacinl
1(Sch aad 1987)	randomise d trials	serious 1	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	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)	MOD ERA TE	CRITICAL
Advers ceftazi	se effects: ra dime + IV am	ised liver likacin]	transaminases	(follow-up: 4	to 6 weeks)	[IV ceftazidime	+ IV amikac	in + inha	aled amika	acin versus	versus	IV
1 (Scha ad 1987)	randomise d trials	serious 1	no serious inconsistenc y	no serious indirectnes s	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)	VER Y LOW	IMPORTAN T

Table 34:	linical evidence profile: Comparison 5. Combination of 2 IV antibiotics + inhaled antibiotic versus 2 IV antibiotics
without inhal	d antibiotic for pulmonary exacerbations with <i>P aeruginosa</i>

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 No	Quality assessment No Design Risk Inconsisten Indirectne Imprecisi Other of cy ss on consideratio							No of patients IV oral ceftazidim ciprof		Absol		
or studi es		of bias	су	SS	on	ns	e + IV tobramyci n	ciprof loxaci n	ve (95% CI)	ute	Quality	Importance
Eradic	ation of P a	eruginosa	a (follow-up 2	weeks)								
1 (Rich ard 1997)	randomise d trials	seriou s ¹	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	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)	MODERAT E	CRITICAL
Adver	se effects - 1	Freatmen	t-related event	s (follow-up	2 weeks)							
1(Ric hard 1997)	randomise d trials	seriou s ¹	no serious inconsistenc y	no serious indirectnes s	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	IMPORTAN T

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 studi es Design of bias Risk of bias Inconsisten cy Indirectne ss Imprecisi on Other considerants Adverse events: severe cough (follow-up 3 months) Adverse events: severe cough (follow-up 3 months) State of the state							No of patient Oral ciprofloxaci n + inhaled colistin	s inhal ed tobra myci n	Effect Relati ve (95% CI)	Absolut e	Quali ty	Importance
Advers	se events: se	vere cou	gh (follow-up 3	months)								
1 (Proe sman s 2013)	randomise d trials	serious 1	no serious inconsistenc y	no serious indirectnes s	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)	VER Y LOW	IMPORTAN T

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 No of studi es	/ assessmen Design	t Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	No of patients Inhaled colistin + oral ciprofloxacin	inhale d tobra mycin + oral ciprof loxaci n	Effect Relati ve (95% CI)	Absol ute	Qual ity	Importance
Relativ	e change in	% predict	ted FEV ₁ from	baseline (foll	ow-up 54 da	ys; Better indic	ated by higher v	alues)				
1 (Tacc etti 2012)	randomise d trials	serious 1	no serious inconsistenc y	no serious indirectnes s	very serious ²	none	60	68	-	MD 2.4 lower (5.885 lower to 1.0855 higher)	VER Y LOW	CRITICAL
Treatm	ent failure: t	rial disco	ntinuation due	e to lack of co	ompliance (f	ollow-up 28 day	s)					
1(Tac cetti 2012)	randomise d trials	serious 1	no serious inconsistenc y	serious ³	very serious ⁴	none	11/105 (10.5%)	13/11 8 (11%)	RR 0.95 (0.45 to 2.03)	6 fewer per 1000 (from 61 fewer to 113 more)	VER Y LOW	IMPORTAN T
Advers	se events: vo	omiting (fo	ollow-up 28 da	ys)								
1(Tac cetti 2012)	randomise d trials	serious 1	no serious inconsistenc y	no serious indirectnes s	very serious⁵	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)	VER Y LOW	IMPORTAN T

Advers	se events: pl	hotosensi	itivity (follow-ເ	ıp 28 days)								
1(Tac cetti 2012)	randomise d trials	serious 1	no serious inconsistenc y	no serious indirectnes s	very serious ⁵	none	1/105 (0.95%)	0/118 (0%)	RR 3.37 (0.14 to 81.79)	-	VER Y LOW	IMPORTAN T
Advers	se events: w	heeze (fo	llow-up 28 day	s)								
1(Tac cetti 2012)	randomise d trials	serious 1	no serious inconsistenc y	no serious indirectnes s	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)	VER Y LOW	
Advers	se events lea	ading to t	rial discontinu	ation - pulmo	nary exacer	bation during e	arly eradication	treatmen	t (follow	-up 28 da	ys)	
1(Tac cetti 2012)	randomise d trials	serious 1	no serious inconsistenc y	no serious indirectnes s	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)	VER Y LOW	IMPORTAN T

Abbreviations: CI: confidence interval; FEV1: 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		
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Other considerat ions	Aztre onam Ivsine	Plac ebo	Relati ve (95%	Absolute	Qualit	Importa
									CI)		у	nce
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)	randomis ed trials	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	serious ¹	none	76	81	-	MD 2.79 higher (0.48 TO 5.10 higher)	MODE RATE	CRITICA L
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)	randomis ed trials	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	no serious imprecisio n	none	156	165	-	MD 1.40 lower (1.94 lower to 0.85 higher)	HIGH	IMPORT ANT
Nutritional status (follow-up 28 days; measured with: % weight change (kg) ; Better indicated by higher values)												

Quality assessment No of studies Design bias Risk of bias Inconsiste ncy Indirectn ess Imprecisi on Other considerat								Plac ebo	Effect Relati ve	Absolute	Qualit	Importa
						10113	Tysine		(30 / i CI)		y	nce
1 1 (Retsch- Bogart 2009)	randomis ed trials	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	no serious imprecisio n	none	80	84	-	MD 1 higher (0.33 to 1.67 higher)	HIGH	IMPORT ANT
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)	randomis ed trials	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	serious ¹	none	156	164	-	MD 2.44 higher (0.35 lower to 5.23 higher)	MODE RATE	IMPORT ANT
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)	randomis ed trials	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	no serious imprecisio n	none	156	165	-	MD 0.45 lower (3.53 lower to 2.63 higher)	HIGH	IMPORT ANT
Quality of life	: CFQ-R eati	ing (follow	-up 28 days; I	range of sco	res: 0-100; l	Better indicat	ed by hig	jher va	lues)			
2 (Retsch- Bogart 2009, Wainwright 2011)	randomis ed trials	no serious risk of bias	very serious ²	no serious indirectne ss	serious ¹	none	156	165	-	MD 4.99 higher (1.47 lower to 711.46higher)	VERY LOW	IMPORT ANT
Quality of life	: CFQ-R em	otional fun	ctioning (foll	ow-up 28 da	ys; range of	scores: 0-10	0; Better	indicat	ed by hig	gher values)		
2 (Retsch- Bogart 2009, Wainwright 2011)	randomis ed trials	no serious risk of bias	very serious ²	no serious indirectne ss	serious ¹	none	156	164	-	MD 2.36 higher (3.13 lower to 7.84 higher)	VERY LOW	IMPORT ANT
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)	randomis ed trials	no serious risk of bias	very serious ²	no serious indirectne ss	serious ¹	none	134	138	-	MD 6.82higher (0.75 to 12.89 higher)	VERY LOW	IMPORT ANT

Quality assessment								No of patients		Effect		
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Other considerat ions	Aztre onam lysine	Plac ebo	Relati ve (95% Cl)	Absolute	Qualit y	Importa nce
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)	randomis ed trials	no serious risk of bias	very serious ²	no serious indirectne ss	serious ¹	none	156	164	-	MD 5.60 higher (0.96 lower to 12.15 higher)	VERY LOW	IMPORT ANT
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)	randomis ed trials	no serious risk of bias	very serious ²	no serious indirectne ss	serious ¹	none	156	165	-	MD 4.81 higher (4.60 lower to 14.21 higher)	VERY LOW	IMPORT ANT
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)	randomis ed trials	no serious risk of bias	very serious ²	no serious indirectne ss	serious ¹	none	133	139	-	MD 2.97 higher (3.20lower to 9.13 higher)	VERY LOW	IMPORT ANT
Quality of life	CFQ-R soc	ial functio	ning (follow-ເ	ıp 28 days; ı	range of sco	ores: 0-100; B	etter indi	cated b	oy higher	values)		
2 (Retsch- Bogart 2009, Wainwright 2011)	randomis ed trials	no serious risk of bias	No serious inconsisten cy	no serious indirectne ss	serious ¹	none	155	164	-	MD 3.54 higher (0.78 to 6.31 higher)	MODE RATE	import Ant
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)	randomis ed trials	no serious risk of bias	very serious ²	no serious indirectne ss	very serious ³	none	156	165	-	MD 0.36 lower (7.42 lower to 6.69 higher)	VERY LOW	IMPORT ANT
Quality of life: CFQ-R vitality (follow-up 28 days; range of scores: 0-100; Better indicated by higher values)												
2 (Retsch- Bogart 2009,	randomis ed trials	no serious	serious ²	no serious	serious ¹	none	134	138	-	MD 5.46 higher (0.16 to 10.76 higher)	LOW	IMPORT ANT
Quality asses	sment Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Other considerat	No of patients Aztre onam	Plac ebo	Effect Relati ve (95%	Absolute	Qualit	Importa
--	-----------------------	----------------------------------	---------------------------------	-----------------------------------	------------------------------	---------------------	------------------------------------	---------------------------	------------------------------------	--	--------------	---------------
Wainwright		risk of		indirectne			lysine		CI)		y	nce
Quality of life	CEO_R woi	abt (follow	un 28 dave:	ss range of sco	ores: 0-100.	Bottor indicat	ed by hi	nhor va	luos)			
2 (Retsch- Bogart 2009, Wainwright 2011)	randomis ed trials	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	serious ¹	none	133	139	-	MD 2.58 higher (2.83 lower to 7.98 higher)	MODE RATE	import Ant
Minor adverse	e events: ch	est discon	nfort (follow-u	ıp 28 days)								
1 (Retsch- Bogart 2009)	randomis ed trials	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	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	IMPORT ANT
Minor adverse	e events: co	ugh (follov	w-up 28 days)									
3 (McCoy 2009, Retsch- Bogart 2009, Waipwright	randomis ed trials	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	very serious ⁴	none	106/29 1 (36.4 %)	82/2 41 (34 %)	RR 1.09 (0.87 to 1.38)	31 more per 1000 (from 44 fewer to 129 more)	LOW	import Ant
2011)								34.2 %	1.50)	31 more per 1000 (from 44 fewer to 130 more)		
Minor adverse	e events: he	adache (fo	llow-up 28 da	iys)								
2 (Retsch- Bogart 2009, Wainwright 2011)	randomis ed trials	no serious risk of bias	serious ⁶	no serious indirectne ss	very serious ⁴	none	19/156 (12.2 %)	20/1 65 (12. 1%)	RR 0.94 (0.34 to 2.61)	7 fewer per 1000 (from 80 fewer to 195 more) 7 fewer per	VERY LOW	IMPORT ANT
								%	,	1000 (from 80		

 $\ensuremath{\textcircled{\sc online 0.5ex}}$ NICE 2017. All rights reserved. Subject to Notice of rights.

Quality asses	sment Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Other considerat ions	No of patients Aztre onam lysine	Plac ebo	Effect Relati ve (95% Cl)	Absolute	Qualit v	Importa nce
										fewer to 195 more)		
Major adverse	e events: dy	spnoea (fo	ollow-up 28 da	ays)								
1 (Retsch- Bogart 2009)	randomis ed trials	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	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	IMPORT ANT
Major adverse	e events: ha	emoptysis	(follow-up 28	8 days)								
Major adverse2 (McCoyra2009,Retsch-Bogart 2009)	randomis ed trials	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	very serious ⁴	none	18/215 (8.4%)	15/1 60 (9.4 %)	RR 0.86 (0.44 to 1.7)	13 fewer per 1000 (from 53 fewer to 66 more)	LOW	IMPORT ANT
								9.4 %		13 fewer per 1000 (from 53 fewer to 66 more)		
Mortality (foll	ow-up 28 da	iys)										
1 (McCoy 2009)	randomis ed trials	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	Not calculable	none	0/135 (0%)	0/76 (0%)	-	-	HIGH	IMPORT ANT
Emergence of	f resistant o	rganisms:	persistent iso	olation of S	aureus (follo	ow-up 42 days	5)					
1 (Retsch- Bogart 2009)	randomis ed trials	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	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)	MODE RATE	IMPORT ANT
Emergence of	f resistant o	rganisms	: persistent is	olation of B	cepacia (fo	llow-up 42 da	vs)					

Quality asses	sment Design	Risk of	Inconsiste	Indirectn	Imprecisi	Other	No of patients Aztre	s Plac	Effect Relati	Absolute		
		bias	ncy	ess	on	considerat ions	onam lysine	ebo	ve (95% CI)		Qualit y	Importa nce
1 (Retsch- Bogart 2009)	randomis ed trials	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	Not calculable	none	0/74 (0%)	0/81 (0%)	-		HIGH	IMPORT ANT
Emergence of	f resistant o	rganisms:	persistent iso	olation of S	maltophilia	(follow-up 42	days)					
1 (Retsch- Bogart 2009)	randomis ed trials	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	very serious ⁴	none	2/74 (2.7%)	0/81 (0%)	RR 5.47 (0.27 to 112.0 4)	-	LOW	IMPORT ANT
Emergence of	f resistant o	rganisms:	persistent iso	olation of A	xilosidans (follow-up 42 d	days)					
1 (Retsch- Bogart 2009)	randomis ed trials	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	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	IMPORT ANT

Abbreviations: CFQ-R: cystic fibrosis questionnaire revised; CI: confidence interval; FEV₁: 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%)

able 53		nuence	prome. comp	anson 2. O	pronozacii	i versus place	00					
Quality	/ assessmen	t					No of patients	5	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Ciprofloxaci n	Place bo	Relati ve (95% CI)	Absolu te	Quali ty	Importance
Lung f	unction: FEV	/ ₁										
Not rep	orted											CRITICAL
Numbe	er of people v	with 1 or I	more exacerba	tions								
NMA c	outcome											CRITICAL
Nutriti	onal status:	weight (fo	llow-up 6 to 1	2 months; me	asured with	: kg; Better indi	cated by highe	r values))			
1 (Shel don 1993)	randomise d trials	very serious 1	no serious inconsistenc y	no serious indirectnes s	serious ²	none	15	16	-	MD 4.4 higher (3.7 lower to 12.5 higher)	VER Y LOW	IMPORTAN T
Minor	adverse ever	nts: gastr	ointestinal (fol	low-up 12 mc	onths)							
1 (Shel don 1993)	randomise d trials	very serious	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	2/20 (10%)	0/20 (0%)	RR 5 (0.26 to 98)	-	VER Y LOW	IMPORTAN T
Mortal	ity (follow-up	o 12 mont	hs)									
1 (Shel don 1993)	randomise d trials	no serious risk of bias	no serious inconsistenc y	no serious indirectnes s	very serious⁵	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	IMPORTAN T
Emerg	ence of resis	stant orga	inisms - isolati	on of resista	nt strains of	P aeruginosa (1	follow-up 12 m	onths)				

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

© NICE 2017. All rights reserved. Subject to Notice of rights.

Quality	y assessmen	t					No of patients	5	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Ciprofloxaci n	Place bo	Relati ve (95% Cl)	Absolu te	Quali ty	Importance
1 (Shel don 1993)	randomise d trials	very serious 1	no serious inconsistenc y	no serious indirectnes s	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)	VER Y LOW	IMPORTAN T
Emerg	ence of resis	stant orga	nisms - isolati	on of resista	nt strains of	S aureus (follow	w-up 12 month	s)				
1 (Shel don 1993)	randomise d trials	very serious 1	no serious inconsistenc y	no serious indirectnes s	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)	VER Y LOW	IMPORTAN T

Abbreviations: CI: confidence interval; FEV₁: 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)

Quality							Nelef		Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisi on	Other consideratio ns	Colis tin	Place bo	Relati ve (95% CI)	Absolu te	Quality	Importa nce
Lung fu	unction: change	e in FEV ₁ °	% predicted (Fo	llow-up: 3 mor	nths; range c	of scores: 0-100;	Better i	ndicated	by highe	r values)		
1 (Jens en 1987)	randomised trials	serious 1	no serious inconsistency	no serious indirectness	serious imprecisio n ²	none	18	11		MD 6.00 (1.07 lower to 13.07 higher)	LOW	CRITICA L
Numbe	r of patients wi	th 1 or mo	ore exacerbatior	າຣ								
ΝΜΑ οι	utcome											
Suppre	ssion of the or	ganism: e	radication of P	aeruginosa fro	m the sputu	m, at 3 months						
1 (Jens en 1987)	randomised trials	serious 1	no serious inconsistency	no serious indirectness	Not calculable ³	none	0/20 (0%)	0/20 (0%)	-	-	MODER ATE	IMPORT ANT
Emerge	ence of resistar	nt organis	ms - superinfec	tion with other	[·] colistin-res	istant organisms	s, during	the 3 m	onths tria	ıl		
1 (Jens en 1987)	randomised trials	serious 1	no serious inconsistency	no serious indirectness	Not calculable ³	none	0/20 (0%)	0/20 (0%)	-	-	MODER ATE	IMPORT ANT
Emerge	ence of resistar	nt organis	ms - resistance	to colistin, du	ring the 3 mo	onths trial						
1 (Jens en 1987)	randomised trials	serious 1	no serious inconsistency	no serious indirectness	Not calculable ³	none	0/20 (0%)	0/20 (0%)	-	-	MODER ATE	IMPORT ANT
Emerge	ence of resistar	nt organis	ms - resistance	to other comm	nonly used a	nti-pseudomona	as txt, dı	uring the	3 months	s trial		

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

Quality	assessment						No of J	patients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc Y	Indirectnes s	Imprecisi on	Other consideratio ns	Colis tin	Place bo	Relati ve (95% Cl)	Absolu te	Quality	Importa nce
1 (Jens en 1987)	randomised trials	serious	no serious inconsistency	no serious indirectness	Not calculable ³	none	0/20 (0%)	0/20 (0%)	-	-	MODER ATE	IMPORT ANT

Abbreviations: CI: confidence interval; FEV₁: 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 asse	essment						No of pat	ients	Effect			
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Other considerat ions	Colistin inhalati on powder (COLI DPI)	Colisti n inhalati on solutio n (COLI neb)	Relati ve (95% CI)	Absolute	Qual ity	Importa nce
Lung function	on: % mean	change in	FEV ₁ % predic	cted (follow-	up: 4 weeks;	range of scor	res: 0-100;	Better inc	licated by	/ lower values)	
1 COLO/DPI/ 02/05	randomis ed trials	serious ¹	no serious inconsisten cy	no serious indirectne ss	very serious ²	none	16	15	-	MD 3.01 lower (18.71 lower to 12.69 higher)	VER Y LOW	CRITICA L
Number of p	atients with	1 or more	exacerbation	าร								
NMA outcom	е											

Quality asse	essment						No of pat	ients	Effect			
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Other considerat ions	Colistin inhalati on powder (COLI DPI)	Colisti n inhalati on solutio n (COLI neb)	Relati ve (95% CI)	Absolute	Qual ity	Importa nce
Minor adver	se events: v	omiting (fo	ollow-up 8 we	eks)								
1 COLO/DPI/ 02/05	randomis ed trials	serious ¹	no serious inconsisten cy	no serious indirectne ss	very serious ³	none	2/16 (12.5%)	0/15 (0%)	RR 4.71 (0.24 to 90.69)	-	VER Y LOW	IMPORT ANT
Minor adver	se events: p	oroductive	cough (follow	-up 8 weeks	5)							
1 COLO/DPI/ 02/05	randomis ed trials	serious ¹	no serious inconsisten cy	no serious indirectne ss	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)	VER Y LOW	IMPORT ANT
Minor adver	se events: c	hest disco	omfort (follow	-up 8 weeks)							
1 COLO/DPI/ 02/05	randomis ed trials	serious ¹	no serious inconsisten cy	no serious indirectne ss	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)	VER Y LOW	IMPORT ANT
Serious adv	erse events	- AE: dysp	onoea (follow-	up 8 weeks								
1 COLO/DPI/ 02/05	randomis ed trials	serious ¹	no serious inconsisten cy	no serious indirectne ss	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)	VER Y LOW	IMPORT ANT

Abbreviations: CI: confidence interval; FEV₁: 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 ass	sessment						No of pa	atients	Effect			
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Other consideratio ns	Colisti n	Tobram ycin	Relative (95% CI)	Absolute	Qualit y	Importan ce
Lung funct nebulised	tion: mean versus TO	% change Bl nebulise	in FEV₁ % pre ed]	edicted (follo	ow-up: 1 to 3	months; range	of score	s: 0-100; E	Better indic	ated by hig	ner values	s) [COLI
1 (Hodson 2002)	randomi sed trials	very serious ¹	no serious inconsisten cy	no serious indirectne ss	serious ²	none	59	50	-	MD 6.33 lower (12.7 lower to 0.04 higher)	VERY LOW	CRITICA L
Lung function: mean % change in FEV ₁ % predicted (follow-up: 4 weeks; range of scores: 0-100; Better indicated by higher values) [versus TOBI nebulised]											lues) [CO	LI DPI
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	serious ²	none	183	191	-	MD 1.67 lower (5.43 lower to 2.09 higher)	LOW	CRITICA L
Lung funct versus TO	tion: mean Bl nebulise	% change ed]	in FEV₁ % pre	edicted (follo	ow-up: 12 we	eks; range of s	cores: 0-	100; Bette	r indicated	by higher v	alues) [C	OLI DPI
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	serious ²	none	183	191	-	MD 2.63 lower (6.67 lower to 1.41 higher)	LOW	CRITICA L
Lung funct versus TO	ion: mean BI]	% change	in FEV₁ % pre	edicted (follo	ow-up: 24 we	eks; range of s	cores: 0-	100; Bette	r indicated	by higher v	alues) [C	OLI

Quality ass	sessment						No of pa	atients	Effect			
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Other consideratio ns	Colisti n	Tobram ycin	Relative (95% CI)	Absolute	Qualit y	Importan ce
2 (COLO/D PI/02/06, Schuster 2013)	randomi sed trials	very serious ⁴	no serious inconsisten cy	no serious indirectne ss	No serious imprecisio n	none	306	352	-	MD 0.99 lower (0.95 to 1.03 higher)	LOW	CRITICA L
Number of	patients w	ith 1 or mo	ore exacerbati	ons								
NMA outco	me											
Time to ne TOBI nebu	xt pulmona lised)	ary exacerl	oation: time to	first additio	onal anti-pse	eudomal treatm	ent (Bette	er indicate	d by highe	r values) [C(DLI DPI v	ersus
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	very serious ⁵	none	183	191	-	MD 3.49 higher (5.14 lower to 12.12 higher)	VERY LOW	CRITICA L
Suppressio	on of the o	rganism: c	hange in sput	um PA dens	sity Log10 C	FU/ml (follow-u	p 4 week	s; Better ir	ndicated by	/ higher valu	ies) [COL	.I
1 (Hodson 2002)	randomi sed trials	very serious1	no serious inconsisten cy	no serious indirectne ss	no serious imprecisio n	none	37	42	-	MD 0.32 higher (0.32 lower to 0.96 higher)	LOW	IMPORT ANT
Nutritional	status: BN	/II change (follow-up 24	weeks; meas	sured with: k	cg; Better indica	ated by h	igher value	es)			
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	serious ⁶	none	183	191	-	MD 0.09 lower (0.26 lower to 0.88 higher)	LOW	IMPORT ANT

Quality ass	sessment						No of pa	atients	Effect			
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Other consideratio ns	Colisti n	Tobram ycin	Relative (95% Cl)	Absolute	Qualit y	Importan ce
Quality of I nebulised)	ife: change	e in CFQ-R	physical (foll	ow-up 24 we	eeks; range	of scores: 0-10	0; Better	indicated I	by higher v	alues) [COL	I DPI vers	sus TOBI
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	Not calculable 7	none	183	191	P=0.353	MD 1.82 higher (0 to 0 higher)	MODE RATE	IMPORT ANT
Quality of I nebulised)	ife: change	e in CFQ-R	vitality (follo	w-up 24 wee	eks; range o	f scores: 0-100	; Better ir	ndicated by	/ higher va	lues) [COLI	DPI versu	us TOBI
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	Not calculable 7	none	183	191	P=0.293	MD 2.27 higher (0 to 0 higher)	MODE RATE	IMPORT ANT
Quality of I nebulised)	ife: change	e in CFQ-R	emotion (foll	ow-up 24 we	eks; range o	of scores: 0-10); Better i	indicated k	oy higher v	alues) [COL	I DPI vers	us TOBI
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	Not calculable 7	none	183	191	P=0.244	MD 1.75 higher (0 to 0 higher)	MODE RATE	IMPORT ANT
Quality of I nebulised)	ife: change	e in CFQ-R	eating (follov	v-up 24 weel	ks; range of	scores: 0-100;	Better in	dicated by	higher val	ues) [COLI D	PI versus	s TOBI
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	Not calculable 7	none	181	191	P=0.925	MD 0.19 lower (0 to 0 higher)	MODE RATE	IMPORT ANT
Quality of I	ife: change	e in CFQ-R	treatment bu	rden (follow	-up 24 week	s; range of sco	res: 0-10	0; Better in	dicated by	higher valu	es) [COL	I DPI
versus TO	BI nebulise	ed)										
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	Not calculable 7	none	183	191	P=0.091	MD 2.87 higher (0 to 0 higher)	MODE RATE	IMPORT ANT

Quality ass	sessment						No of pa	atients	Effect			
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Other consideratio ns	Colisti n	Tobram ycin	Relative (95% Cl)	Absolute	Qualit y	Importan ce
Quality of I versus TO	ife: change Bl nebulise	e in CFQ-R d)	health perce	otion (follow	-up 24 week	s; range of sco	res: 0-10	0; Better ir	ndicated by	/ higher valu	ies) [COL	I DPI
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	Not calculable 7	none	183	191	P=0.159	MD 2.96 higher (0 to 0 higher)	MODE RATE	IMPORT ANT
Quality of I	ife: change	in CFQ-R	social (follow	/-up 24 weel	s; range of	scores: 0-100; I	Better inc	dicated by	higher valu	ues) [COLI D	PI versus	5 ТОВІ
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	Not calculable 7	none	183	191	P=0.153	MD 0.92 higher (0 to 0 higher)	MODE RATE	IMPORT ANT
Quality of I TOBI nebu	ife: change lised)	e in CFQ-R	body image	(follow-up 2	4 weeks; rar	nge of scores: 0)-100; Be	tter indicat	ed by high	er values) [(COLI DPI	versus
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	Not calculable 7	none	183	191	P=0.385	MD 1.85 higher (0 to 0 higher)	MODE RATE	IMPORT ANT
Quality of I	ife: change	e in CFQ-R	role (follow-u	ıp 24 weeks;	range of sc	ores: 0-100; Be	tter indic	ated by high	gher value	s) [COLI DP	versus T	OBI
nebulised)												
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	Not calculable 7	none	183	191	P=0.607	MD 1.22 lower (0 to 0 higher)	MODE RATE	IMPORT ANT
Quality of I nebulised)	ife: change	e in CFQ-R	weight (follow	w-up 24 wee	ks; range of	scores: 0-100;	Better in	dicated by	higher val	ues) [COLI I	DPI versu	s TOBI
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	Not calculable 7	none	183	191	P=0.461	MD 2.81 higher (0 to 0 higher)	MODE RATE	IMPORT ANT

Quality ass	essment						No of pa	atients	Effect			
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Other consideratio ns	Colisti n	Tobram ycin	Relative (95% Cl)	Absolute	Qualit y	Importan ce
Quality of I TOBI nebu	ife: change lised)	e in CFQ-R	respiratory (f	ollow-up 24	weeks; rang	je of scores: 0-	100; Bett	er indicate	d by highe	r values) [C	OLI DPI v	ersus
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	Not calculable 7	none	183	191	P=0.756	MD 0.53 lower (0 to 0 higher)	MODE RATE	IMPORT ANT
Quality of I nebulised)	ife: change	e in CFQ-R	digestion (fo	llow-up 24 w	veeks; range	of scores: 0-10	00; Better	[·] indicated	by higher	values) [CO	LI DPI vei	rsus TOBI
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	Not calculable 7	none	183	191	P=0.077	MD 3.22 higher (0 to 0 higher)	MODE RATE	IMPORT ANT
Minor adve	erse events	: sputum (follow-up 4 w	eeks) [COLI	nebulised v	ersus TOBI net	oulised]					
1 (Hodson 2002)	randomi sed trials	very serious ¹	no serious inconsisten cy	no serious indirectne ss	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	IMPORT ANT
Minor adve	rse events	: pharyngi	tis (follow-up	4 weeks) [C	OLI nebulise	ed versus TOBI	nebulise	d]				
1 (Hodson 2002)	randomi sed trials	very serious ¹	no serious inconsisten cy	no serious indirectne ss	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	IMPORT ANT
Minor adve	erse events	: cough (fe	ollow-up 4 we	eks) [COLI n	ebulised ve	rsus TOBI nebu	lised]					
1 (Hodson 2002)	randomi sed trials	very serious ¹	no serious inconsisten cy	no serious indirectne ss	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	IMPORT ANT

Quality ass	sessment						No of pa	atients	Effect			
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Other consideratio ns	Colisti n	Tobram ycin	Relative (95% CI)	Absolute	Qualit y	Importan ce
Minor adve	erse events	: producti	ve cough (foll	ow-up 24 we	eks) [COLI	DPI versus TOE	BI nebulis	ed)				
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	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	IMPORT ANT
Minor adve	erse events	: chest dis	comfort (follo	w-up 24 we	eks) [COLI D	PI versus TOB	l nebulise	ed)				
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	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	import Ant
Minor adve	erse events	: vomiting	(follow-up 24	weeks) [CO	LI DPI versu	is TOBI nebulis	ed)					
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	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	IMPORT ANT
Serious ad	verse ever	nts: patient	s with >1 seri	ous AE (foll	ow-up 4 wee	eks) [COLI nebu	lised ver	sus TOBI r	nebulised]			
1 (Hodson 2002)	randomi sed trials	very serious ¹	no serious inconsisten cy	no serious indirectne ss	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	import Ant
Serious ad	verse ever	nts: patient	s withdrawn (follow-up 24	weeks) [CC	DLI DPI versus	FOBI neb	ulised)				
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	no serious imprecisio n	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)	MODE RATE	import Ant

Quality ass	sessment						No of pa	atients	Effect			
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Other consideratio ns	Colisti n	Tobram ycin	Relative (95% Cl)	Absolute	Qualit y	Importan ce
Serious ad	verse ever	nts: haemo	ptysis (follow	-up 24 week	s) [COLI net	oulised versus ⁻	ГОВI neb	ulised]				
1 (Hodson 2002)	randomi sed trials	very serious ¹	no serious inconsisten cy	no serious indirectne ss	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	import Ant
Serious ad	verse ever	nts: dyspno	oea (follow-up	4 weeks) [C	OLI nebulis	ed versus TOB	nebulise	ed]				
1 (Hodson 2002)	randomi sed trials	very serious ¹	no serious inconsisten cy	no serious indirectne ss	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	import Ant
Serious ad	verse ever	nts: dyspno	oea (follow-up	24 weeks) [COLI DPI ve	rsus TOBI nebi	ulised)					
1 (COLO/D PI/02/06)	randomi sed trials	serious ³	no serious inconsisten cy	no serious indirectne ss	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	import Ant
Emergence nebulised]	e of resista	nt organis	ms: emergeno	ce of highly	tobramycin-	resistant <i>P aer</i> t	ıginosa (follow-up 2	24 weeks)	COLI nebuli	sed vers	us TOBI
1 (Hodson 2002)	randomi sed trials	very serious ¹	no serious inconsisten cy	no serious indirectne ss	Not calculable	none	0/62 (0%)	0/53 (0%)	-	-	LOW	IMPORT ANT

Abbreviations: CFQ-R: cystic fibrosis questionnaire revised; CI: confidence interval; COLI: colistin; DPI: dry powder for inhalation; FEV₁: 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 as	ssessmer	ıt					No of patie	nts	Effect			
No of studies	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Tobramy cin	Place bo	Relati ve (95% CI)	Absolute	Quality	Importance
Lung fun	ction: mea	an % ch	ange in FEV ₁ %	% predicted (follow-up: 1	to 3 months; ra	nge of score	es 1-100;	Better in	dicated by h	igher valu	es)
4 (Galeva 2013, Konstan 2011/ EVOLV E trial, Lenoir 2007, Ramsey 1993)	rando mised trials	serio us ¹	serious ²	No serious indirectnes s	no serious imprecisio n	none	257	259		MD 9.36 higher (5.01 to 13.70 higher)	LOW	CRITICAL
Number of	of patients	s with 1	or more exace	rbations								
NMA outc	ome											CRITICAL
Suppress	ion of the	organi	sm: eradicatio	n of the orga	nism (negati	ve culture) (fol	low-up 4 wee	eks)				
3 (Chucha lin 2007, Galeva 2013, Lenoir 2007)	rando mised trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	71/217 (32.7%)	17/14 0 (12.1 %) 14.3%	RR 2.46 (1.20 to 5.04)	177 more per 1000 (from 24 more to 491 more) 209 more per 1000 (from 92 more to 465 more)	HIGH	IMPORTAN T

© NICE 2017. All rights reserved. Subject to Notice of rights.

Quality as	ssessmen	t					No of patie	nts	Effect			
No of studies	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Tobramy cin	Place bo	Relati ve (95% Cl)	Absolute	Quality	Importance
Suppress	ion of the	organi	sm: eradicatio	n of the orga	nism (negati	ve culture) (fol	ow-up 6 wee	eks)				
1 (Lenoir 2007)	rando mised trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	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)	MODE RATE	IMPORTAN T
Suppress	ion of the	organi	sm: eradicatio	n of the orga	nism (negati	ve culture) (fol	low-up 8 wee	eks)				
1 (Chucha lin 2007)	rando mised trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	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)	MODE RATE	IMPORTAN T
Suppress	ion of the	organi	sm: eradicatio	n of the orga	nism (negati	ve culture) (fol	low-up 20 we	eks)				
1 (Chucha lin 2007)	rando mised trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	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	IMPORTAN T
Suppress	ion of the	organi	sm: eradicatio	n of the orga	nism (negati	ive culture) (fol	low-up 24 we	eks)				
1 (Chucha lin 2007)	rando mised trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	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)	MODE RATE	IMPORTAN T
Suppress	ion of the	organi	sm: change in	P aeruginos	a sputum de	nsity log10 CFL	J/G (follow-u	p 4 week	s: Better	indicated by	higher va	alues)

 $\ensuremath{\textcircled{\sc online 0.5ex}}$ NICE 2017. All rights reserved. Subject to Notice of rights.

Quality as	ssassman	.+					No of natio	nte	Effect			
No of studies	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Tobramy	Place bo	Relati ve (95% Cl)	Absolute	Quality	Importance
1 (Galeva 2013)	rando mised trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ⁴	none	29	26	-	MD 1.2 lower (2.03 to 0.37 lower)	MODE RATE	IMPORTAN T
Suppress values)	ion of the	organi	sm: change in	non-mucoid	P aeruginos	a sputum dens	ity log10 CF	U/G (follo	ow-up 4 v	veeks; Better	indicated	by higher
1 (Konsta n 2011/ EVOLV E trial)	rando mised trials	very serio us ⁵	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	46	49	-	MD 1.76 lower (2.52 to 1 lower)	LOW	IMPORTAN T
Suppress values)	ion of the	organi	sm: change in	mucoid <i>P a</i> e	ruginosa sp	utum density lo	g10 CFU/G ((follow-u	p 4 weeks	s; Better indi	cated by h	igher
1 (Konsta n 2011/ EVOLV E trial)	rando mised trials	very serio us ⁵	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	46	49	-	MD 2.18 (2.97 to 1.39 lower)	LOW	IMPORTAN T
Nutritiona	al status:	body we	eight change (f	ollow-up 12	weeks; meas	sured with: kg;	Better indica	ated by h	igher val	ues)		
1 (Lenoir 2007)	rando mised trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	29	30	-	MD 0.23 higher (0.23 lower to 0.69 higher)	HIGH	IMPORTAN T
Nutritiona	al status:	body we	eight change (f	ollow-up 24	weeks; meas	sured with: kg;	Better indica	ated by h	igher val	ues)		

Quality as	ssessmer	nt					No of patie	nts	Effect			
No of studies	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Tobramy cin	Place bo	ve (95% Cl)	Absolute	Quality	Importance
1 (Chucha lin 2007)	rando mised trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ⁴	none	161	84	-	MD 0.75 higher (0.22 to 1.28 higher)	MODE RATE	IMPORTAN T
Minor adv	verse eve	nts: min	or adverse eve	ents (any) (fo	llow-up 4 we	eeks)						
2 r. (Galeva n 2013, tr Konstan 2011/ EVOLV	rando mised trials	very serio us ⁶	no serious inconsistenc y	no serious indirectnes s	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	IMPORTAN T
E trial)								42.3%		144 fewer per 1000 (from 47 fewer to 216 more)		
Minor adv	verse eve	nts: min	or adverse eve	ents (any) (fo	llow-up 24 w	veeks)						
1 (Chucha lin 2007)	rando mised trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	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	IMPORTAN T
Minor adv	verse eve	nts: aud	itory impairme	ent (follow-up	o 4 weeks)							
1 (Galeva 2013)	rando mised trials	no serio us risk	no serious inconsistenc y	no serious indirectnes s	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	IMPORTAN T

Quality as	ssessmer	nt					No of patie	nts	Effect			
No of studies	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Tobramy cin	Place bo	Relati ve (95% CI)	Absolute	Quality	Importance
		of bias										
Minor adv	verse eve	nts: aud	litory impairme	ent (follow-up	24 weeks)							
1 (Ramse y 1999)	rando mised trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	0/152 (0%)	0/148 (0%)	-	-	HIGH	IMPORTAN T
Minor adv	verse eve	nts: aud	litory impairme	ent (follow-up	42 weeks)							
1 (Ramse y 1993)	rando mised trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	0/36 (0%)	0/35 (0%)	-	-	HIGH	IMPORTAN T
Minor adv	verse eve	nts: cou	igh (follow-up	4 weeks)								
2 (Galeva 2013, Konstan 2011/ EVOLV	rando mised trials	very serio us ⁶	very serious ⁸	no serious indirectnes s	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	IMPORTAN T
								-		-		
Minor adv	verse eve	nts: tinn	nitus (follow-up	o 24 weeks)								
1 (Ramse y 1999)	rando mised trials	no serio us	no serious inconsistenc y	no serious indirectnes s	serious ⁴	none	8/258 (3.1%)	0/262 (0%)	RR 17.26 (1 to	-	MODE RATE	IMPORTAN T

 $\ensuremath{\textcircled{\sc online 0.5ex}}$ NICE 2017. All rights reserved. Subject to Notice of rights.

Quality as	ssessmen	t					No of patie	nts	Effect Relati			
No of studies	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Tobramy cin	Place bo	ve (95% CI)	Absolute	Quality	Importance
		risk of bias							297.5 4)			
Minor adv	verse evei	nts: hea	daches (follow	/-up 4 weeks)								
1 (Konsta n 2011/ EVOLV E trial)	rando mised trials	very serio us ⁵	no serious inconsistenc y	no serious indirectnes s	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	IMPORTAN T
Major adv	verse ever	nts: any	(follow-up 4 w	veeks)								
E trial) Major advers 2 ra (Galeva m 2013, tri Konstan 2011/ EVOLV	rando mised trials	very serio us ⁶	no serious inconsistenc y	no serious indirectnes s	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	IMPORTAN T
EVOLV E trial)								3.9%		19 fewer per 1000 (from 33 fewer to 25 more)		
Major adv	verse ever	nts: any	(follow-up 24	weeks)								
1 (Chucha lin 2007)	rando mised trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	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	IMPORTAN T
Major adv	verse ever	nts: hae	moptysis (follo	ow-up 4 week	(S)							

Quality as	ssessmer	it					No of patie	nts	Effect			
No of studies	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Tobramy cin	Place bo	Relati ve (95% CI)	Absolute	Quality	Importance
1 (Konsta n 2011/ EVOLV E trial)	rando mised trials	very serio us⁵	no serious inconsistenc y	no serious indirectnes s	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	IMPORTAN T
Major adv	erse ever	nts: hae	moptysis (follo	ow-up 24 wee	eks)							
1 (Ramse y 1999)	rando mised trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ⁴	none	69/258 (26.7%)	81/26 2 (30.9 %)	RR 0.87 (0.66 to 1.13)	40 fewer per 1000 (from 105 fewer to 40 more)	MODE RATE	IMPORTAN T
Major adv	erse eve	nts: pne	umothorax (fo	llow-up 24 w	eeks)							
1 (Ramse y 1999)	rando mised trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	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	IMPORTAN T
Mortality	(follow-uj	o 4 weeł	ks)									
1 (Konsta n 2011/ EVOLV E trial)	rando mised trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	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	IMPORTAN T
Mortality	(follow-uj	o 3 to 12	2 months)									
2 (Chucha lin 2007,	rando mised trials	no serio us	no serious inconsistenc y	no serious indirectnes s	serious ³	none	1/419 (0.24%)	6/348 (1.7%)	RR 0.17 (0.03	14 fewer per 1000 (from 17	MODE RATE	IMPORTAN T

Quality as	ssessmer	nt					No of patie	nts	Effect			
No of studies	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Tobramy	Place	Relati ve (95% Cl)	Absolute	Quality	Importance
Ramsey 1999)		risk of bias							to 1.09)	fewer to 2 more)		
Emergen	ce of resis	stant or	ganisms: frequ	lency of Tob	ramycin-resi	istant P aerugin	osa (follow-	up 24 we	eks)			
2 (Chucha lin 2007, Ramsey 1999)	rando mised trials	no serio us risk of bias	very serious ¹⁰	no serious indirectnes s	serious ⁴	none	86/376 (22.9%)	31/29 6 (10.5 %)	RR 1.95 (0.86 to 4.42)	99 more per 1000 (from 15 fewer to 385 more)	VERY LOW	IMPORTAN T
Emergen	ce of resis	stant or	ganisms: frequ	lency of new	isolates of o	drug resistant <i>E</i>	<mark>8 cepacia</mark> (fo	llow-up 2	4 weeks)		
1 (Ramse y 1999)	rando mised trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	0/258 (0%)	0/262 (0%)	-	-	HIGH	IMPORTAN T
Emergen	ce of resis	stant or	ganisms: frequ	lency of new	isolates of o	drug resistant S	altophilia maltophilia	(follow-เ	up 24 wee	eks)		
1 (Ramse y 1999)	rando mised trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	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	IMPORTAN T
Emergen	ce of resis	stant or	ganisms: frequ	ency of new	isolates of o	drug resistant A	xylosidans	(follow-u	ip 24 wee	eks)		
1 (Ramse y 1999)	rando mised trials	no serio us risk	no serious inconsistenc y	no serious indirectnes s	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	IMPORTAN T

Quality as	ssessmer	ıt					No of patie	ents	Effect			
No of studies	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Tobramy cin	Place bo	Relati ve (95% Cl)	Absolute	Quality	Importance
		of bias										
Emergen	ce of resis	stant or	ganisms: frequ	lency of new	isolates of	drug resistant a	spergillus (f	follow-up	24 week	s)		
1 (Ramse y 1999)	rando mised trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	4/196 (2%)	20/19 3 (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; FEV₁: 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 bias for bias for the domains randomisation, allocation concealment, and blinding and another trial had unclear risk of bias for bias for bias for bias for the domains randomisation.

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%)

Quality as	ssessmen	it					No of patier	nts	Effect			
No of studies	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Tobramyc in inhalation powder (TOBI DPI)	Tobramyc in inhalation solution (TOBI neb)	Relati ve (95% Cl)	Absolu te	Qual ity	Importance
Lung fund	ction: % n	nean cha	ange in FEV₁%	predicted (fo	ollow-up: 4 w	eeks; range of	scores: 0-10	0; Better indi	cated by	higher va	lues)	
1 (Konsta n 2011a/E AGER trial)	random ised trials	serio us ¹	no serious inconsistenc y	no serious indirectnes s	serious ²	none	308	209	-	MD 0.8 lower (3.90 lower to 2.30 higher)	LOW	IMPORTAN T
Lung fund	ction: % n	nean cha	ange in FEV₁%	predicted (fo	llow-up: 20	weeks; range o	f scores: 0-1	00; Better inc	dicated by	y higher v	alues)	
1 (Konsta n 2011a/E AGER trial)	random ised trials	serio us ¹	no serious inconsistenc y	no serious indirectnes s	serious ²	none	308	209	-	MD 1.10 higher (2.33 lower to 4.53 higher)	LOW	IMPORTAN T
Lung fund	ction: % n	nean cha	ange in FEV₁%	predicted (fo	llow-up: 24	weeks; range o	f scores: 0-1	00; Better inc	dicated by	y higher v	alues)	
1 (Konsta n 2011a/E AGER trial)	random ised trials	serio us ¹	no serious inconsistenc y	no serious indirectnes s	serious ²	none	308	209	-	MD 2.20 lower (1.11 to 5.51 lower)	LOW	IMPORTAN T
Number o	Number of patients with 1 or more exacerbations											
NMA outo	come											
Suppress	ion of the	organis	sm: mean chan	ige in P aerug	<i>ginosa</i> sputu	im density log1	0 CFU (follov	v-up 4 weeks	; Better i	ndicated	by high	er values)

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

Quality as	ssessmen	t					No of patier	nts	Effect			
No of studies	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Tobramyc in inhalation powder (TOBI DPI)	Tobramyc in inhalation solution (TOBI neb)	Relati ve (95% Cl)	Absolu te	Qual ity	Importance
1 (Konsta n 2011a/E AGER trial)	random ised trials	serio us ¹	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	308	209	-	MD 0.44 lower (0.79 to 0.09 lower)	MOD ERA TE	IMPORTAN T
Suppress	sion of the	organis	sm: mean chan	ige in <i>P aeru</i> g	ginosa sputu	im density log1	0 CFU (follov	v-up 20 week	s; Better	indicated	by hig	ner values)
1 (Konsta n 2011a/E AGER trial)	random ised trials	serio us ¹	no serious inconsistenc y	no serious indirectnes s	serious ³	none	308	209	-	MD 0.84 lower (1.17 to 0.51 lower)	LOW	IMPORTAN T
Adverse	events: an	y mild o	or moderate ad	verse (follow	up 24 week	s)						
1 (Konsta n 2011a/E AGER trial)	random ised trials	serio us ¹	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	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)	MOD ERA TE	IMPORTAN T
Adverse	events: an	y seriou	us adverse (fol	low-up 24 we	eks)							
1 (Konsta n 2011a/E	random ised trials	serio us ¹	no serious inconsistenc y	no serious indirectnes s	serious ³	none	84/308 (27.3%)	61/209 (29.2%)	RR 0.93 (0.71	20 fewer per 1000	LOW	IMPORTAN T

Quality as	ssessmen	t					No of patier	nts	Effect			
No of studies	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Tobramyc in inhalation powder (TOBI DPI)	Tobramyc in inhalation solution (TOBI neb)	Relati ve (95% CI)	Absolu te	Qual ity	Importance
AGER trial)									to 1.24)	(from 85 fewer to 70 more)		
Mild adve	erse event	s: produ	ctive cough (f	ollow-up 24 v	veeks)							
1 (Konsta n 2011a/E AGER trial)	random ised trials	serio us ¹	no serious inconsistenc y	no serious indirectnes s	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)	VER Y LOW	IMPORTAN T
Mild adve	erse event	s: heada	ache (follow-up	o 24 weeks)								
1 (Konsta n 2011a/E AGER trial)	random ised trials	serio us ¹	no serious inconsistenc y	no serious indirectnes s	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)	VER Y LOW	IMPORTAN T
Mild adve	erse event	s: vomit	ing (follow-up	24 weeks)								
1 (Konsta n 2011a/E	random ised trials	serio us¹	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	19/308 (6.2%)	12/209 (5.7%)	RR 1.07 (0.53	4 more per 1000 (from	VER Y LOW	IMPORTAN T

Quality as	ssessmen	ıt					No of patier	nts	Effect			
No of studies	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Tobramyc in inhalation powder (TOBI DPI)	Tobramyc in inhalation solution (TOBI neb)	Relati ve (95% Cl)	Absolu te	Qual ity	Importance
AGER trial)									to 2.17)	27 fewer to 67 more)		
Serious a	dverse ev	vents: dy	/spnoea (follov	v-up 24 week	s)							
1 (Konsta n 2011a/E AGER trial)	random ised trials	serio us ¹	no serious inconsistenc y	no serious indirectnes s	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)	VER Y LOW	IMPORTAN T
Serious a	idverse ev	vents: ha	emoptysis (fo	llow-up 24 we	eeks)							
1 (Konsta n 2011a/E AGER trial)	random ised trials	serio us ¹	no serious inconsistenc y	no serious indirectnes s	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)	VER Y LOW	IMPORTAN T

Abbreviations: CFU: colony forming units; CI: confidence interval; FEV₁: 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. Chinical evidence prome. Companyon 4.5 robraniyoni versus Azireonani iyani	Table 45: Clinical evidence	profile: Compari	son 4.3 Tobramycir	າ versus Aztreonam lysi
--	-----------------------------	------------------	--------------------	-------------------------

Quality ass	sessment	t					No of patie	ents	Effect			
No of studies	Desig n	Risk of bias	Inconsist ency	Indirect ness	Impreci sion	Other considerati ons	Tobramy cin	Aztreon am lysine	Relati ve (95% Cl)	Absolute	Qualit y	Importa nce
Lung funct versus AZI	tion: % cl _l inhalec	nange in FE\ I]	/1 % predicte	ed (follow-	up: 3 mont	hs; range of s	cores: 0-100	; Better ind	icated by	v higher values) [TOBI neb	ulised
1 (Assael 2013)	rando mised trials	serious ¹	no serious inconsiste ncy	no serious indirectn ess	no serious imprecis ion	none	132	136	-	MD 2.71 lower (2.88 to 2.54 lower)	MODE RATE	CRITIC AL
Number of	patients	with 1 or mo	ore exacerba	tions								
NMA outco	me											
Suppression nebulised	on of the versus A	organism: a ZLI inhaled]	dj mean cha	inge sputu	m density	log10 PA CFU/	G (follow-up	20 weeks;	Better in	dicated by highe	er values)	[ТОВІ
1 (Assael 2013)	rando mised trials	serious ¹	no serious inconsiste ncy	no serious indirectn ess	serious ²	none	97	97	-	MD 0.23 higher (0.3 lower to 0.76 higher)	LOW	IMPOR TANT
Nutritional	status: %	∕₀ adj mean v	veight chang	ge (follow-u	up 24 week	s; Better indic	ated by high	er values)	[TOBI ne	bulised versus A	ZLI inhal	ed]
1 (Assael 2013)	rando mised trials	serious ¹	no serious inconsiste ncy	no serious indirectn ess	serious ²	none	132	136	-	MD 0.52 lower (1.68 lower to 0.64 higher)	LOW	IMPOR TANT
Quality of I	ife: CFQ	-R respirator	y, adj mean	change (fo	ollow-up 20	weeks; Better	indicated b	y higher va	lues) [TC	BI nebulised ver	rsus AZLI	inhaled]
1 (Assael 2013)	rando mised trials	serious ¹	no serious inconsiste ncy	no serious indirectn ess	serious ³	none	131	131	-	MD 4.1 lower (8.59 lower to 0.39 higher)	LOW	IMPOR TANT
Minor adve	erse even	ts: chest dis	comfort (fol	low-up 3 n	nonths) [T(OBI nebulised	versus AZLI	inhaled]				
1 (Assael 2013)	rando mised 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	IMPOR TANT

Quality ass	sessment	:					No of patie	nts	Effect			
No of studies	Desig n	Risk of bias	Inconsist ency	Indirect ness	Impreci sion	Other considerati ons	Tobramy cin	Aztreon am lysine	Relati ve (95% CI)	Absolute	Qualit y	Importa nce
			inconsiste ncy	indirectn ess					to 1.96)	fewer to 99 more)		
Minor adve	erse even	ts: cough (fe	ollow-up 3 m	onths) [TC	BI nebulis	ed versus AZL	I inhaled]					
1 (Assael 2013)	rando mised trials	serious ¹	no serious inconsiste ncy	no serious indirectn ess	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	IMPOR TANT
Minor adve	erse even	ts: headach	e (follow-up	3 months)	[TOBI neb	ulised <i>versus</i> /	AZLI inhaled	IJ				
1 (Assael 2013)	rando mised trials	serious ¹	no serious inconsiste ncy	no serious indirectn ess	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	IMPOR TANT
Minor adve	erse even	ts: vomiting	(follow-up 3	8 months) [TOBI nebu	lised versus A	ZLI inhaled]					
1 (Assael 2013)	rando mised trials	serious ¹	no serious inconsiste ncy	no serious indirectn ess	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	IMPOR TANT
Major adve	erse even	ts: dyspnoe	a (follow-up	3 months)	[TOBI neb	ulised <i>versus</i> /	AZLI inhaled	IJ				
1 (Assael 2013)	rando mised trials	serious ¹	no serious inconsiste ncy	no serious indirectn ess	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	IMPOR TANT
Major adve	erse even	ts: haemopt	ysis (follow-	up 3 mont	hs) <mark>[TOBI</mark> r	nebulised vers	us AZLI inha	led]				
1 (Assael 2013)	rando mised 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	IMPOR TANT

Quality ass	sessment						No of patie	nts	Effect			
No of studies	Desig n	Risk of bias	Inconsist ency	Indirect ness	Impreci sion	Other considerati ons	Tobramy cin	Aztreon am Iysine	Relati ve (95% Cl)	Absolute	Qualit y	Importa nce
			inconsiste ncy	indirectn ess					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; FEV1: 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

Qualit No of studi es	y assessmer Design	nt Risk of bias	Inconsistenc y	Indirectne ss	Imprecisi on	Other consideration s	No of patier Combinatio n of fosfomacy n +	its Place bo	Effect Relati ve (95% Cl)	Absolu te	Quality	Importanc
Lung	function: rela	ative cha	nge in FEV₁%	predicted (fo	llow-up 4 w	eeks; range of	scores: 0-100	: Better	indicated	l by highe	er values) [FT	e 80/20 mg]
1 (Trap nell 2012)	randomise d trials	seriou s ¹	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	38	32	-	MD 7.5 higher (3.6 to 11.4 higher)	MODERAT E	CRITICAL
Lung f	function: rela	ative cha	nge in FEV₁%	predicted (fo	llow-up 4 w	eeks; range of	scores: 0-100	; Better i	indicated	l by highe	er values) [FT	l 160/40 mg]
1 (Trap nell 2012)	randomise d trials	seriou s ¹	no serious inconsistenc y	no serious indirectnes s	serious ²	none	41	32	-	MD 6.2 higher (2.42 to 9.98 higher)	LOW	CRITICAL

© NICE 2017. All rights reserved. Subject to Notice of rights.

Quality	y assessmer	nt					No of patien	Its	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectne ss	Imprecisi on	Other consideration s	Combinatio n of fosfomacy n + tobramycin	Place bo	Relati ve (95% CI)	Absolu te	Quality	Importanc
Suppre 80/20 r	ession of the ng]	e organis	m: sputum <i>P a</i>	eruginosa d	/20 mg (follow	v-up 4 w	eeks; Be	tter indic	ated by lower	values) [FTI		
1 (Trap nell 2012)	randomise d trials	seriou S ¹	no serious inconsistenc y	no serious indirectnes s	serious ³	none	38	32	-	MD 1.04 lower (1.82 to 0.26 lower)	LOW	IMPORTAN T
Suppro	ession of the 60/40 mg]	e organis	m: sputum <i>P a</i>	eruginosa d	ensity, log 1	0 CFU/g FTI 16	0/40 mg (follo	ow-up 4 \	weeks; B	etter indi	cated by lowe	er values)
1 (Trap nell 2012)	randomise d trials	seriou s ¹	no serious inconsistenc y	no serious indirectnes s	serious ³	none	41	32	-	MD 0.28 lower (1.06 lower to 0.5 higher)	LOW	IMPORTAN T

Abbreviations: CFU: colony forming units; CI: confidence interval; FEV₁: 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

	,	•		,								
Qualit	y assessme	nt					No of patie	ents	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Continuo us alternatin g therapy: aztreona m lysine + tobramyci n	Intermite nt treatment : placebo + tobramyc in	Relati ve (95% CI)	Absolu te	Quality	Importanc e
Lung	function: %	change ii	n FEV₁% predi	cted (follow-	up 20 week	s ¹ ; range of sc	ores: 0-100;	Better indic	ated by	higher va	alues)	
1 (Flu me 2016)	randomis ed trials	seriou S ²	no serious inconsisten cy	no serious indirectne ss	no serious imprecisi on	none	42	46	-	MD 1.33 higher (1.05 to 1.61 higher)	MODERAT E	CRITICAL
Time t	o next pulm	onary ex	acerbation									
1 (Flu me 2016)	randomis ed trials	seriou s ²	no serious inconsisten cy	no serious indirectne ss	serious ³	none	42	46	HR 0.89 (0.49 to 1.6)	-	LOW	CRITICAL
Qualit	y of life: cha	inge in C	FQ-R (follow-u	up 20 weeks ¹	; range of s	cores: 0-100; B	etter indicat	ted by high	er values	5)		
1 (Flu me 2016)	randomis ed trials	seriou S ²	no serious inconsisten cy	no serious indirectne ss	serious ⁴	none	42	46	-	MD 3.06 higher (2.35 to 3.77 higher)	LOW	
Minor	adverse eve	ents: cou	gh (follow-up	3 months)								

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

© NICE 2017. All rights reserved. Subject to Notice of rights.

Quality assessment							No of patients		Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Continuo us alternatin g therapy: aztreona m lysine + tobramyci n	Intermite nt treatment : placebo + tobramyc in	Relati ve (95% CI)	Absolu te	Quality	Importanc e
1 (Flu 2016)	randomis ed trials	seriou S ²	no serious inconsisten cy	no serious indirectne ss	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	IMPORTAN T
Seriou	is adverse e	vents: dy	vspnoea (follo	w-up 3 mont	hs)							
1 (Flu 2016)	randomis ed trials	seriou S ²	no serious inconsisten cy	no serious indirectne ss	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	IMPORTAN T
Seriou	is adverse e	ot treatment re	elated) (follov									
1 (Flu me 2016)	randomis ed trials	seriou s ²	no serious inconsisten cy	no serious indirectne ss	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	IMPORTAN T

Quality assessment							No of patients		Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Continuo us alternatin g therapy: aztreona m lysine + tobramyci n	Intermite nt treatment : placebo + tobramyc in	Relati ve (95% CI)	Absolu te	Quality	Importanc e
										188 fewer to 230 more)		

Abbreviations: CFQ-R: cystic fibrosis questionnaire reviewed; CI: confidence interval; FEV₁: 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 studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Itraconazo le	Placeb o, 24- week treatme nt	Relativ e (95% Cl)	Absol ute	Quality	Importan ce
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 (Aaro n 2012)	randomise d trials	seriou S ¹	no serious inconsistenc y	serious ²	very serious ³	none	18	17	-	MD 4.94 lower (15.33 lower to 5.45 higher)	VERY LOW	CRITICA L
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 (Aaro n 2012)	randomise d trials	seriou s ¹	no serious inconsistenc y	serious ²	very serious ³	none	18	17	-	MD 3.71 lower (- 13.26 to 20.28)	VERY LOW	CRITICA L
Time to next pulmonary exacerbation (follow-up mean 24 weeks; Better indicated by lower values)												
1 (Aaro n 2012)	randomise d trials	seriou S ¹	no serious inconsistenc y	serious ²	very serious ⁴	none	0/18 (0%)	0/17 (0%)	adjHR 1.34 (0.57 to 3.14)	-	VERY LOW	CRITICA L
proxy:	proxy: number of patients with an exacerbation requiring antibiotics (follow-up mean 24 weeks; Better indicated by lower values)											

© NICE 2017. All rights reserved. Subject to Notice of rights.
Quality No of studi es	y assessmen Design	t Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	No of patier Itraconazo Ie	nts Placeb o, 24- week treatme nt	Effect Relativ e (95% CI)	Absol ute	Quality	Importan
1 (Aaro n 2012)	randomise d trials	seriou s ¹	no serious inconsistenc y	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	IMPORT ANT
proxy:	number of p	oatients w	vith an exacerb	ation requiri	ng AB (follo	w-up mean 48 w	veeks; Better	indicated	by lower v	alues)		
1 (Aaro n 2012)	randomise d trials	seriou s ¹	no serious inconsistenc y	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	IMPORT ANT
proxy:	number of p	oatients w	vith an exacerb	ation admitte	ed to hospita	al (follow-up me	an 24 weeks;	Better inc	licated by	lower val	ues)	
1 (Aaro n 2012)	randomise d trials	seriou s ¹	no serious inconsistenc y	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	IMPORT ANT

 $\ensuremath{\textcircled{\sc 0}}$ NICE 2017. All rights reserved. Subject to Notice of rights.

Quality No of studi es	/ assessmen Design	nt Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	No of patier Itraconazo Ie	nts Placeb o, 24- week treatme nt	Effect Relativ e (95% CI)	Absol ute	Quality	Importan ce
1 (Aaro n 2012)	randomise d trials	seriou S ¹	no serious inconsistenc y	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	IMPORT ANT
Quality	/ of life – CF	Q-R all do	omains (follow	-up mean 24	weeks; rang	e of scores: 0-1	00; Better inc	dicated by	higher val	ues)		
1 (Aaro n 2012)	randomise d trials	seriou s¹	no serious inconsistenc y	serious ²	not calculable 7	none	18	17	-	No signific ant differen ces	VERY LOW	import Ant
Quality	y of life - CFC	Q-R respi	ratory domain	(follow-up m	ean 24 week	s; range of sco	res: 0-100; Be	etter indica	ated by hig	her value	s)	
1 (Aaro n 2012)	randomise d trials	seriou s¹	no serious inconsistenc y	serious ²	not calculable 7	none	18 (mean: 3.76)	17 (mean: 4.77)	MD 1.01	p- value= 0.87	VERY LOW	IMPORT ANT
Minor	adverse evei	nts: incre	ased dyspnoe	a (follow-up r	nean 24 wee	eks; Better indic	ated by lowe	r values)				
1 (Aaro n 2012)	randomise d trials	seriou S ¹	no serious inconsistenc y	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	IMPORT ANT

Quality	/ assessmen	ıt					No of patier	nts	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	ltraconazo le	Placeb o, 24- week treatme nt	Relativ e (95% CI)	Absol ute	Quality	Importan ce
										to 575 more)		
Minor	adverse ever	nts: rash	(follow-up mea	an 24 weeks;	Better indica	ated by lower va	alues)					
1 (Aaro n 2012)	randomise d trials	seriou s ¹	no serious inconsistenc y	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	IMPORT ANT
Minor	adverse evei	nts: hype	rglycaemia (fo	llow-up mear	1 24 weeks; I	Better indicated	by lower val	ues)				
1 (Aaro n 2012)	randomise d trials	seriou s ¹	no serious inconsistenc y	serious ²	very serious ⁶	none	1/18 (5.6%)	0/16 (0%)	RR 2.68 (0.12 to 61.58)	-	VERY LOW	import Ant
Minor	adverse evei	nts: flu-lik	ke illness (follo	w-up mean 2	4 weeks; Be	tter indicated b	y lower value	es)				
1 (Aaro n 2012)	randomise d trials	seriou s ¹	no serious inconsistenc y	serious ²	very serious ⁶	none	3/18 (16.7%)	0/16 (0%)	RR 6.26 (0.35 to 112.7)	-	VERY LOW	IMPORT ANT
Minor	adverse ever	nts: diarr	hoea (follow-uj	o mean 24 we	eks; Better	indicated by lov	wer values)					
1 (Aaro n	randomise d trials	seriou s ¹	no serious inconsistenc y	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	IMPORT ANT

Quality	y assessmer	it		1			No of patier	nts	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	ltraconazo le	Placeb o, 24- week treatme nt	Relativ e (95% Cl)	Absol ute	Quality	Importan ce
2012)										(from 62 fewer to 365 more)		
Minor	adverse eve	nts: conju	unctivitis (follo	w-up mean 2	4 weeks; Be	tter indicated b	y lower value	s)				
1 (Aaro n 2012)	randomise d trials	seriou s ¹	no serious inconsistenc y	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	IMPORT ANT
Major	adverse ever	nts: haem	optysis (follov	v-up mean 24	weeks; Bet	ter indicated by	v lower values	5)				
1 (Aaro n 2012)	randomise d trials	seriou s ¹	no serious inconsistenc y	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	IMPORT ANT
Major	adverse ever	nts: spon	taneous pneur	mothorax (fol	low-up meai	n 24 weeks; Bet	ter indicated	by lower v	values)			
1 (Aaro n	randomise d trials	seriou s ¹	no serious inconsistenc y	serious ²	very serious ⁶	none	1/18 (5.6%)	0/17 (0%)	RR 2.84 (0.12 to 65.34)	-	VERY LOW	IMPORT ANT

Quality	y assessmer	nt					No of patier	nts	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Itraconazo le	Placeb o, 24- week treatme nt	Relativ e (95% Cl)	Absol ute	Quality	Importan ce
2012												

Abbreviations: CFQ-R: cystic fibrosis questionnaire reviewed; CI: confidence interval; FEV1: 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 as	sessment						No of pati	ents	Effect			
No of studies	Design	Risk of bias	Inconsis tency	Indirectn ess	Imprecis ion	Other consider ations	Macrolid e antibioti cs	Placebo	Relative (95% CI)	Absolute	Quality	Importanc e
Rate of ex	acerbations	after short	t-term (1-10	month) trea	atment							
3 (Equi 2002, Robinson 2012, Wolter 2002)	Randomis ed trials	no serious risk of bias	very serious ¹	no serious indirectn ess	very serious ²	none	114	112	Rate Ratio 0.75 (0.38 to 1.49)	Not calculabl e	VERY LOW	IMPORTA NT

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

Quality	/ assessmen	lt Diele	Inconsisten	In dive store	Incomenciai	Other	No of patie	nts	Effect	Abool		
NO Of Studi	Design	of bias	cy	ss	on	consideratio ns	ne	bo	Relati ve (95%	ute	Quality	Importance
Time to	o first exace	rbation	(follow-up 6 m	onths)					01)		Quanty	importance
1 (Balf our- Lynn 2006)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	very serious ¹	none	41/84 (48.8%) ²	40/87 (46%) 2	HR 1.07 (0.68 to 1.683 8)	23 more per 1000 (from 118 fewer to 186 more)	LOW	CRITICAL
Growt	h (change in	height)	(follow-up 12)	months; mea	sured with:	SDS (standard	deviation) so	core; Bet	ter indica	ated by hi	gher values)	
1 (De Boec k 2007)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ³	none	15	15	-	MD 0.37 lower (0.77 lower to 0.03 higher)	MODERAT E	IMPORTAN T
Growt	h (change in	height)	in paediatric p	articipants (f	ollow-up 8 r	nonths; measu	red with: cm	; Better i	ndicated	by highe	r values)	
1 (Balf our- Lynn 2006)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ³	none	42	38	-	MD 0.6 higher (0.46 lower to 1.66 higher)	MODERAT E	IMPORTAN T

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

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.

Quali	ty assessme	nt					No of patients		Effect			
No of stud ies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Impreci sion	Other considerat ions	Prednisolone	Plac ebo	Relat ive (95% Cl)	Absol ute	Quality	Importan ce
Abso	lute change i	in weigh	t (follow-up 12	2 weeks; me	easured wit	th: kg; Better i	ndicated by higher valu	ues) [2 n	ng pred	nisone]		
1 (Gre ally 199 4)	randomise d trials	seriou s ¹	no serious inconsisten cy	no serious indirectn ess	very serious ²	none	13	12	-	MD 0.34 higher (2.32 lower to 3 higher)	VERY LOW	CRITICAL
Weigl	nt at 18 Years	s of Age	- Boys - (mea	sured with:	Kg; Better	indicated by	higher values) [1 mg pr	ednisor	ie]			
1 (Lai 200 0)	observatio nal studies	no seriou s risk of bias	no serious inconsisten cy	no serious indirectn ess	serious ³	none	34	21	-	MD 4.6 lower (9.69 lower to 0.49 higher)	VERY LOW	CRITICAL
Weigl	nt at 18 Years	s of Age	- Boys (meas	ured with: M	Kg; Better i	ndicated by h	igher values) [2 mg pre	dnisone	2]			
1 (Lai 200 0)	observatio nal studies	no seriou s risk of bias	no serious inconsisten cy	no serious indirectn ess	no serious imprecisi on	dose response gradient ⁴	3	21	-	MD 6.7 lower (11.59 lower to 1.81 lower)	MODERA TE	CRITICAL
Weigl	nt at 18 Years	s of Age	- Girls (measu	ured with: K	g; Better i	ndicated by hi	gher values) [1 mg pree	dnisone]			

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

© NICE 2017. All rights reserved. Subject to Notice of rights.

Qualit No of stud ies	ty assessme Design	nt Risk of bias	Inconsiste ncy	Indirectn ess	Impreci sion	Other considerat ions	No of patients Prednisone/ Prednisolone	Plac ebo	Effect Relat ive (95% CI)	Absol ute	Quality	Importan ce
1 (Lai 200 0)	observatio nal studies	no seriou s risk of bias	no serious inconsisten cy	no serious indirectn ess	very serious ²	none	20	23	-	mean 0 higher (7.62 lower to 3.02 higher)	VERY LOW	CRITICAL
Weigh	nt at 18 Years	s of Age	- Girls (measu	ured with: K	g; Better i	ndicated by hi	gher values) [2 mg pre	dnisone]			
1 (Lai 200 0)	observatio nal studies	no seriou s risk of bias	no serious inconsisten cy	no serious indirectn ess	very serious ²	none	23	23	-	MD 1.7 higher (3.37 lower to 6.77 higher)	VERY LOW	CRITICAL
Heigh	it at 18 Years	of Age	- Boys (measi	ured with: c	m; Better i	ndicated by hi	igher values) [1 mg pre	dnisone	e]			
1 (Lai 200 0)	observatio nal studies	no seriou s risk of bias	no serious inconsisten cy	no serious indirectn ess	serious ³	none	34	21	-	MD 3.9 lower (7.77 to 0.03 lower)	VERY LOW	CRITICAL
Heigh	t at 18 Years	of Age	- Boys (measi	ured with: c	m; Better i	ndicated by hi	igher values) [2 mg pre	dnisone]			

Qualit	tv assessme	nt					No of natients		Effect			
No of stud ies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Impreci sion	Other considerat ions	Prednisolone	Plac ebo	Relat ive (95% CI)	Absol ute	Quality	Importan ce
1 (Lai 200 0)	observatio nal studies	no seriou s risk of bias	no serious inconsisten cy	no serious indirectn ess	serious ³	none	31	21	-	MD 4.1 lower (7.82 to 0.38 lower)	VERY LOW	CRITICAL
Heigh	it at 18 Years	of Age	- Girls (measu	ired with: ci	m; Better ir	ndicated by hi	gher values) [1 mg pred	dnisone]			
1 (Lai 200 0)	observatio nal studies	no seriou s risk of bias	no serious inconsisten cy	no serious indirectn ess	very serious ²	none	20	23	-	MD 1 lower (4.54 lower to 2.54 higher)	VERY LOW	CRITICAL
Heigh	t at 18 Years	of Age	- Girls (measu	red with: c	m; Better ir	ndicated by hi	gher values) [2 mg pred	dnisone]			
1 (Lai 200 0)	observatio nal studies	no seriou s risk of bias	no serious inconsisten cy	no serious indirectn ess	very serious ²	none	23	23	-	MD 0.5 lower (4.43 lower to 3.43 higher)	VERY LOW	CRITICAL
Adve	rse effects - (Cataract	s (follow-up 4	years) [1 m	ng predniso	one]						
1 (Eig en	randomise d trials	seriou s ¹	no serious inconsisten cy	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

Qualit	ty assessme	nt					No of patients		Effect			
No of stud ies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Impreci sion	Other considerat ions	Prednisone/ Prednisolone	Plac ebo	Relat ive (95% Cl)	Absol ute	Quality	Importan ce
199 5)				indirectn ess					to 1.61)	1000 (from 66 fewer to 45 more)		
Adve	rse effects - (Cataract	ts (follow-up 3	years) [2 m	ng predniso	one]						
1 (Eig en 199 5)	randomise d trials	seriou s ¹	no serious inconsisten cy	no serious indirectn ess	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
Adve	rse effects - I	Diabetes	s mellitus (foll	ow-up 4 yea	ars) [1 mg p	orednisone]						
1 (Eig en 199 5)	randomise d trials	seriou s ¹	no serious inconsisten cy	no serious indirectn ess	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
Adve	rse effects - I	Diabetes	s mellitus (foll	ow-up 3 yea	ars) [2 mg p	orednisone]						
1 (Eig en	randomise d trials	seriou s ¹	no serious inconsisten cy	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

Qualit	y assessme	nt					No of patients		Effect			
No of stud ies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Impreci sion	Other considerat ions	Prednisone/ Prednisolone	Plac ebo	Relat ive (95% Cl)	Absol ute	Quality	Importan ce
199 5)				indirectn ess					48.89)	(from 3 fewer to 504 more)		
Adver	se effects - (Glycosu	ria (follow-up	4 years) [1 i	mg prednis	one]						
1 (Eig en 199 5)	randomise d trials	seriou s ¹	no serious inconsisten cy	no serious indirectn ess	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
Adver	se events - (Glycosu	ria (follow-up	3 years) [2 ı	mg prednis	one]						
1 (Eig en 199 5)	randomise d trials	seriou s ¹	no serious inconsisten cy	no serious indirectn ess	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
Adver	se effects - l	Hypergly	/caemia (follo	w-up 4 year	s) [1 mg pr	ednisone]						
1 (Eig en	randomise d trials	seriou s ¹	no serious inconsisten cy	no serious indirectn ess	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

Qualit	y assessme	nt Risk	Inconsiste	Indirecto	Impreci	Other	No of patients	Plac	Effect	Absol		
of stud ies	Design	of bias	ncy	ess	sion	considerat ions	Prednisolone	ebo	ive (95% CI)	ute	Quality	Importan ce
199 5)									to 8.78)	16 fewer to 164 more)		
Adver	se effects - l	Hypergly	caemia (follo	w-up 3 year	s) [2 mg pr	ednisone]						
1 (Eig en 199 5)	randomise d trials	seriou s ¹	no serious inconsisten cy	no serious indirectn ess	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
Morta	lity (follow-u	ip 4 year	s)									
1 (Aub erch 198 5)	randomise d trials	no seriou s risk of bias ⁵	no serious inconsisten cy	no serious indirectn ess	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	IMPORTA NT

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%Cl crossed the null effect line, and it is very wide.

Quality No of studi es	y assessmer Design	nt Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	No of patien Azithromy cin <i>versus</i> placebo	its	Effect Relati ve (95% Cl)	Absol ute	Quality	Importance
Time t	o next exace	rbation	(follow-up me	an 6 months	; assessed v	vith: time free o	f exacerbatio	n)				
2 (Sai man 2003, Saim an 2010)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	104/218 (47.7%)1	79/22 7 (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 t	o next exace	rbation	(follow-up 12	months)								
1 (Cle ment 2006)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	14/40 (35%)1	2/42 (4.8%)	HR 0.37 (0.217 to 0.629 9) ¹	30 fewer per 1000 (from 17 fewer to 37 fewer)	HIGH	CRITICAL

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

© NICE 2017. All rights reserved. Subject to Notice of rights.

Quality	v assessmer	nt					No of patier	its	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Azithromy cin <i>versus</i> placebo		Relati ve (95% CI)	Absol ute	Quality	Importance
								3.6%		23 fewer per 1000 (from 13 fewer to 28 fewer)		
Mild ad (Sai man 2003)	dverse effec randomise d trials	ts of and no serio us risk of bias	tibiotic treatme no serious inconsistenc y	ent - Hearing no serious indirectnes s	impairment very serious ²	(follow-up: 6 m none	ionths) 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 a	dverse effect	ts of an	tibiotic treatme	nt – Tinnitus	(follow-up)	6 months)				more)		
1 (Sai man 2003)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	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
Chang	je in BMI z so	core (fo	llow-up 12 mo	nths; Better i	ndicated by	higher values)						
1 (Cle ment	randomise d trials	no serio us risk	no serious inconsistenc y	no serious indirectnes s	serious ³	none	40	42	-	MD 0.15 higher (0.03	MODERAT E	IMPORTAN T

Quality	y assessmen	it					No of patien	ts	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Azithromy cin <i>versus</i> placebo		Relati ve (95% Cl)	Absol ute	Quality	Importance
2006)		of bias								lower to 0.33 higher)		
Chang	e in weight (kg) (Fol	low-up: 6 mon	ths; Better in	ndicated by	higher values)						
2 (Sai man 2003, Saim an 2010)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ³	none	216	224	-	MD 0.62 higher (0.26 to 0.98 higher)	MODERAT E	IMPORTAN T
Quality	y of life: chai	nge in C	FQ-R total (fol	llow-up 6 mo	nths; range	of scores: 0-10	0; Better indi	cated by	higher v	alues)		
1 (Sai man 2003)	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	85	92	-	MD 1.6 higher (0.61 lower to 3.81 higher)	HIGH	IMPORTAN T
Quality	y of life: chai	nge in C	FQ-R physica	l domain sco	re (follow-u	o 6 months; ran	ge of scores:	0-100; E	Better ind	icated by	higher value	s)
1 (Sai man 2003	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	85	92	-	MD 2.7 higher (0.09 to 5.31 higher)	HIGH	IMPORTAN T
Quality	y of life: chai	nge in C	FQ-R psychos	social domain	n score (follo	ow-up 6 months	s; range of sc	ores: 0-1	00; Bette	er indicate	ed by higher v	values)
1 (Sai	randomise d trials	no serio us	no serious inconsistenc y	no serious indirectnes s	no serious	none	85	92	-	MD 0.4 higher (3	HIGH	IMPORTAN T

Quality	y assessmer	nt					No of patien	ts	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Azithromy cin <i>versus</i> placebo		Relati ve (95% Cl)	Absol ute	Quality	Importance
man 2003		risk of bias			imprecisio n					lower to 3.8 higher)		
Quality	y of life: cha	nge in C	FQ-R body im	age domain	score (follov	v-up 6 months;	range of scol	res: 0-10	0; Better	indicated	d by higher va	lues)
1 (Sai man 2003	randomise d trials	no serio us risk of bias	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	85	92	-	MD 3.2 higher (0.24 lower to 6.64 higher)	HIGH	IMPORTAN T

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	assessmen	t					No of pa	tients	Effect			
No of studie s	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	lbuprof en	Place bo	Relativ e (95% Cl)	Absolut e	Quali ty	Importance
Adverse	e effects: in	crease in a	abdominal pain	(follow-up 2	years)							
1 (Lands 2007)	randomis ed trials	no serious risk of bias	no serious inconsistenc y	no serious indirectnes s	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: in	crease in a	abdominal pain	(follow-up 4	years)							

© NICE 2017. All rights reserved. Subject to Notice of rights.

Quality	assessment	t					No of pat	ients	Effect			
No of studie s	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	lbuprof en	Place bo	Relativ e (95% Cl)	Absolut e	Quali ty	Importance
1 (Konst an 1995)	randomis ed trials	serious 2	no serious inconsistenc y	no serious indirectnes s	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)	VER Y LOW	CRITICAL
Adverse	effects: ga	strointest	inal bleeding (f	ollow-up 2 ye	ars)							
1 (Lands 2007)	randomis ed trials	no serious risk of bias	no serious inconsistenc y	no serious indirectnes s	very serious ¹	none	1/70 (1.4%)	0/72 (0%)	RR 3.08 (0.13 to 74.46)	Not calculabl e ²	LOW	CRITICAL
Annual	rate of chan	ige in % id	leal body weigh	nt (follow-up 4	years; Bett	er indicated by I	nigher valu	ues)				
1 (Konst an 1995)	randomis ed trials	serious 3	no serious inconsistenc y	no serious indirectnes s	serious ⁴	none	41	43	-	MD 0.99 higher (0.17 to 1.81 higher)	LOW	IMPORTAN T
Annual	rate of chan	ige in % id	leal body weigh	nt (by age) - U	nder 13 yeai	s at randomisat	ion (follow	v-up 4 ye	ars; Bette	r indicated	by high	er values)
1 (Konst an 1995)	randomis ed trials	serious 3	no serious inconsistenc y	no serious indirectnes s	serious ⁴	none	24	25	-	MD 1.45 higher (0.33 to 2.57 higher)	LOW	IMPORTAN T
Annual	rate of chan	ige in % id	leal body weigh	nt (by age) - 13	3 years or ol	der at randomis	ation (follo	ow-up 4 y	/ears; Bet	ter indicate	d by hig	her values)
1 (Konst an 1995)	randomis ed trials	serious 3	no serious inconsistenc y	no serious indirectnes s	very serious ¹	none	17	18	-	MD 0.34 higher (0.61 lower to	VER Y LOW	IMPORTAN T

Quality	assessmen	t					No of pat	tients	Effect			
No of studie s	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	lbuprof en	Place bo	Relativ e (95% Cl)	Absolut e	Quali ty	Importance
										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

Quality asses	ssment						No of pat	ients	Effect			
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectne ss	Imprecisi on	Other consi derati ons	Oral calorie supplem entation	Usual care	Relative (95% CI)	Absolute	Qualit y	Importan ce
Change in we	eight (kg) (l	Follow-up: 3 i	months; Bette	er indicated								
1 (Poustie 2006)	randomis ed trials	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious ¹	none	48	51	-	MD 0.34 higher (0.07 lower to 0.75 higher)	MODE RATE	CRITICA L
Change in we	eight (kg) (l	Follow-up: 6 i	months; Bette	er indicated	by higher v	alues)						

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

Quality asses	sment						No of pat	ients	Effect			
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectne ss	Imprecisi on	Other consi derati ons	Oral calorie supplem entation	Usual care	Relative (95% CI)	Absolute	Qualit y	Importan ce
2 (Hanning 1993, Poustie 2006)	randomis ed trials	serious ²	no serious inconsiste ncy	no serious indirectne ss ³	serious ¹	none	59	58	-	MD 0.47 higher (0.07 lower to 1.02 higher)	LOW	CRITICA L
Change in we	eight (kg) (F	Follow-up: 1 ງ	vear; Better in	ndicated by I	higher valu	es)						
1 (Poustie 2006)	randomis ed trials	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious ¹	none	50	52	-	MD 0.16 higher (0.68 lower to 1 higher)	MODE RATE	CRITICA L
Change in he	ight (cm) (l	Follow-up: 3 i	nonths; Bett	er indicated	by higher v	values)						
1 (Poustie 2006)	randomis ed trials	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	no serious imprecisi on	none	48	51	-	MD 0.03 lower (0.36 lower to 0.3 higher)	HIGH	CRITICA L
Change in he	ight (cm) (l	Follow-up: 6 i	nonths; Bett	er indicated	by higher v	values)						
1 (Poustie 2006)	randomis ed trials	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	no serious imprecisi on	none	50	51	-	MD 0.47 lower (1.32 lower to 0.38 higher)	HIGH	CRITICA L
Change in he	ight (cm) (l	Follow-up: 1	year; Better i	ndicated by	higher valu	es)						
1 (Poustie 2006)	randomis ed trials	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	no serious	none	50	52	-	MD 0.06 higher (0.5 lower	HIGH	CRITICA L

Quality asses	ssment						No of pat	ients	Effect			
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectne ss	Imprecisi on	Other consi derati ons	Oral calorie supplem entation	Usual care	Relative (95% CI)	Absolute	Qualit y	Importan ce
					imprecisi on					to 0.62 higher)		
Change in we	eight as %	expected for a	age and heig	ht (Follow-uj	p: 6 months	s; Better	indicated	by higher v	values)			
1 (Hanning 1993)	randomis ed trials	serious ²	no serious inconsiste ncy	serious ⁴	very serious⁵	none	9	7	-	MD 3.3 higher (6.27 lower to 12.87 higher)	VERY LOW	CRITICA L
Change in B	VI (kg/m2) ((Follow-up: 3	months; Bet	ter indicated	by higher	values)						
1 (Poustie 2006)	randomis ed trials	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious ¹	none	48	51	-	MD 0.14 higher (0.08 lower to 0.36 higher)	MODE RATE	CRITICA L
Change in B	VI (kg/m2) ((Follow-up: 6	months; Bet	ter indicated	by higher	values)						
1 (Poustie 2006)	randomis ed trials	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious ¹	none	50	51	-	MD 0.24 higher (0.06 lower to 0.54 higher)	MODE RATE	CRITICA L
Change in B	MI (kg/m2) ((Follow-up: 1	year; Better i	indicated by	higher valu	ues)						
1 (Poustie 2006)	randomis ed trials	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious ¹	none	50	52	-	MD 0.08 higher (0.28 lower to 0.44 higher)	MODE RATE	CRITICA L

Quality asses	ssment						No of pat	ients	Effect			
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectne ss	Imprecisi on	Other consi derati ons	Oral calorie supplem entation	Usual care	Relative (95% CI)	Absolute	Qualit y	Importan ce
Change in Bl	MI (centile)	(Follow-up: 3	months; Bet	tter indicated	d by higher	values)						
1 (Poustie 2006)	randomis ed trials	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious ¹	none	48	51	-	MD 3.28 higher (0.7 lower to 7.26 higher)	MODE RATE	CRITICA L
Change in Bl	MI (centile)	(Follow-up: 6	months; Bet	tter indicated	d by highe <mark>r</mark>	values)						
1 (Poustie 2006)	randomis ed trials	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious ¹	none	50	51	-	MD 5.75 higher (0.22 to 11.28 higher)	MODE RATE	CRITICA L
Change in Bl	MI (centile)	(Follow-up: 1	year; Better	indicated by	v higher val	ues)						
1 (Poustie 2006)	randomis ed trials	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious ¹	none	50	52	-	MD 2.99 higher (2.69 lower to 8.67 higher)	MODE RATE	CRITICA L
Change in we	eight (centi	le) (Follow-up	: 3 months;	Better indica	ited by high	ner value	es)					
1 (Poustie 2006)	randomis ed trials	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious ¹	none	48	51	-	MD 1.72 higher (0.59 lower to 4.03 higher)	MODE RATE	CRITICA L
Change in we	eight (centi	le) (Follow-up	: 6 months;	Better indica	ted by high	ner value	es)					

Quality asses	sment						No of pat	ients	Effect			
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectne ss	Imprecisi on	Other consi derati ons	Oral calorie supplem entation	Usual care	Relative (95% CI)	Absolute	Qualit y	Importan ce
1 (Poustie 2006)	randomis ed trials	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious ¹	none	50	51	-	MD 2.12 higher (0.94 lower to 5.18 higher)	MODE RATE	CRITICA L
Change in we	eight (centi	le) (Follow-up	o: 1 year; Bet	ter indicated	by higher	values)						
1 (Poustie 2006)	randomis ed trials	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious ¹	none	50	52	-	MD 1.83 higher (1.77 lower to 5.43 higher)	MODE RATE	CRITICA L
Change in he	ight (centil	e) (Follow-up	: 3 months; I	Better indica	ted by high	er value	s)					
1 (Poustie 2006)	randomis ed trials	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious ¹	none	48	51	-	MD 0.56 lower (2.04 lower to 0.92 higher)	MODE RATE	CRITICA L
Change in he	ight (centil	e) (Follow-up	: 6 months; I	Better indica	ted by high	er value	s)					
1 (Poustie 2006)	randomis ed trials	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	no serious imprecisi on	none	50	51	-	MD 1.74 lower (4.4 lower to 0.92 higher)	HIGH	CRITICA L
Change in he	ight (centil	e) (Follow-up	: 1 year; Bett	ter indicated	by higher	values)						
1(Poustie 2006)	randomis ed trials	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious ¹	none	50	52	-	MD 0.65 lower (3.11	MODE RATE	CRITICA L

Quality asses	ssment						No of pat	ients	Effect			
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectne ss	Imprecisi on	Other consi derati ons	Oral calorie supplem entation	Usual care	Relative (95% CI)	Absolute	Qualit y	Importan ce
										lower to 1.81 higher)		
Change in he	eight as % o	of expected for	or age (Follov	v-up: 6 mont	hs; Better i	ndicated	l by higher	values)				
1 (Hanning 1993)	randomis ed trials	serious ²	no serious inconsiste ncy	serious ⁴	very serious ⁵	none	9	7	-	MD 1.6 lower (21.54 lower to 18.34 higher)	VERY LOW	CRITICA L
Change in FE	EV₁ % predi	cted (Follow-	up: 3 months	s; Better indi	cated by hi	gher val	ues)					
1 (Poustie 2006)	randomis ed trials	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious ⁶	none	31	38	-	MD 7.92 lower (13.89 to 1.95 lower)	MODE RATE	CRITICA L
Change in FE	EV₁ % predi	cted (Follow-	up: 6 months	; Better indi	cated by hi	gher val	ues)					
2 (Hanning 1993, Poustie 2006)	randomis ed trials	serious ²	no serious inconsiste ncy	no serious indirectne ss ³	serious ⁶	none	41	45	-	MD 3.84 lower (9.63 lower to 1.94 higher)	LOW	CRITICA L
Change in FE	EV ₁ % predi	cted (Follow-	up: 1 year; B	etter indicat	ed by highe	er values	;)					
1 (Poustie 2006)	randomis ed trials	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious ⁶	none	32	38	-	MD 1.91 lower (8.57 lower to 4.75 higher)	MODE RATE	CRITICA L

Quality asses	sment						No of pat	ients	Effect			
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectne ss	Imprecisi on	Other consi derati ons	Oral calorie supplem entation	Usual care	Relative (95% CI)	Absolute	Qualit y	Importan ce
Quality of life)											
No evidence a	available											
Adverse effec	cts											
No evidence a	available											
Pulmonary ex	xacerbatio r	າຣ										
No evidence a	available											
Patient or car	rer satisfac	tion										

No evidence available

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; cm: centimetres; FEV₁: 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

		nce prome.	oompansor		alone sup	picifici		Sus nutin				
Quality as a	4						No of rot	: 1 -	Effect.			
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectne SS	Imprecisi on	Other consi derati ons	Oral calorie supplem entation	Nutrition al advice	Relative (95% CI)	Absolute	Qualit y	Importan ce
Change in we	eight (kg) (l	Follow-up: 3 r	nonths; Bett	er indicated	by higher v	values)						
1 (Kalnins 2005)	randomis ed trials	very serious ¹	no serious inconsiste ncy	no serious indirectne ss	very serious ²	none	7	6	-	MD 0.69 lower (3.3 lower to 1.92 higher)	VERY LOW	CRITICA L
Change in wo	eight for he	ight (%) (Foll	ow-up: 3 mo	nths; Better i	indicated b	y higher	values)					
1 (Kalnins 2005)	randomis ed trials	very serious ¹	no serious inconsiste ncy	no serious indirectne ss	very serious ²	none	7	12	-	MD 0.96 lower (5.23 lower to 3.31 higher)	VERY LOW	CRITICA L
Change in wo	eight z scol	re (Follow-up	: 3 months; E	Better indicat	ed by high	er value	s)					
1 (Kalnins 2005)	randomis ed trials	very serious ¹	no serious inconsiste ncy	no serious indirectne ss	very serious ²	none	7	6	-	MD 0 higher (0.59 lower to 0.59 higher)	VERY LOW	CRITICA L
Channa in u	- :		C monthes F	Detter indiced	ad by bigh	o z voluo	- \					
Change in wo	eight z scol	re (Follow-up)	: 6 months; E	setter indicat	ea by nigh	er value	S)					
1 (Kalnins 2005)	randomis ed trials	very serious ¹	no serious inconsiste ncy	no serious indirectne ss	very serious ²	none	7	6	-	MD 0.3 lower (0.98 lower to	VERY LOW	CRITICA L

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

© NICE 2017. All rights reserved. Subject to Notice of rights.

Quality asses	ssment						No of pat	ients	Effect			
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectne ss	Imprecisi on	Other consi derati ons	Oral calorie supplem entation	Nutrition al advice	Relative (95% CI)	Absolute	Qualit y	Importan ce
										0.38 higher)		
Change in %	ideal body	weight (Follo	w-up: 3 mon	ths; Better i	ndicated by	higher	values)					
1 (Kalnins 2005)	randomis ed trials	very serious ¹	no serious inconsiste ncy	no serious indirectne ss	very serious ²	none	7	6	-	MD 2 lower (10.59 lower to 6.59 higher)	VERY LOW	CRITICA L
Change in %	ideal body	weight (Follo	w-up: 6 mon	ths; Better in	ndicated by	higher	values)					
1 (Kalnins 2005)	randomis ed trials	very serious ¹	no serious inconsiste ncy	no serious indirectne ss	very serious ²	none	7	6	-	MD 3 lower (11.59 lower to 5.59 higher)	VERY LOW	CRITICA L
Change in he	eight (cm) (l	Follow-up: 3 r	months; Bett	er indicated	by higher v	values)						
1 (Kalnins 2005)	randomis ed trials	very serious ¹	no serious inconsiste ncy	no serious indirectne ss	very serious ²	none	7	6	-	MD 0.38 lower (3.05 lower to 2.29 higher)	VERY LOW	CRITICA L
Change in he	ight z scor	e (Follow-up:	3 months; B	etter indicat	ed by highe	er values	;)					
1 (Kalnins 2005)	randomis ed trials	very serious ¹	no serious inconsiste ncy	no serious indirectne ss	very serious ²	none	7	6	-	MD 0 higher (0.96	VERY LOW	CRITICA L

© NICE 2017. All rights reserved. Subject to Notice of rights.

Quality asses	ssment						No of pat	ients	Effect			
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectne ss	Imprecisi on	Other consi derati ons	Oral calorie supplem entation	Nutrition al advice	Relative (95% CI)	Absolute	Qualit y	Importan ce
										lower to 0.96 higher)		
Change in he	ight z scor	e (Follow-up:	6 months; B	etter indicate	ed by highe	er values	;)					
1 (Kalnins 2005)	observati onal studies	very serious ¹	no serious inconsiste ncy	no serious indirectne ss	very serious ²	none	7	6	-	MD 0.1 lower (1.07 lower to 0.87 higher)	VERY LOW	CRITICA L
Change in FE	V₁ % predi	cted (Follow-	up: 3 months	; Better indi	cated by hi	gher val	ues)					
1 (Kalnins 2005)	randomis ed trials	very serious ¹	no serious inconsiste ncy	no serious indirectne ss	very serious ³	none	7	6	-	MD 8.2 lower (23.37 lower to 6.97 higher)	VERY LOW	CRITICA L
Change in FE	V₁ % predi	cted (Follow-	up: 6 months	; Better indi	cated by hi	gher val	ues)					
1 (Kalnins 2005)	randomis ed trials	very serious ¹	no serious inconsiste ncy	no serious indirectne ss	very serious ³	none	7	6	-	MD 8 lower (26.96 lower to 10.96 higher)	VERY LOW	CRITICA L
Quality of life)											
No evidence a	available											
Pulmonary ex	xacerbatior	IS										

Quality asses	sment						No of pat	ients	Effect			
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectne ss	Imprecisi on	Other consi derati ons	Oral calorie supplem entation	Nutrition al advice	Relative (95% CI)	Absolute	Qualit y	Importan ce
No evidence a	available											
Adverse effec	cts											
No evidence a	available											
Patient or car	rer satisfac	tion										
No evidence a	vailable											

Abbreviations: confidence interval; CF: cystic fibrosis; cm: centimetres; FEV₁: 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	v assessment						No of patient	S	Effect			
No of studie s	Design	Risk of bias	Inconsistency	Indirectnes s	Imprecisio n	Other consideration s	Enteral tube feeding	Usu al care	Relativ e (95% CI)	Absolute	Quali ty	Importan ce
Change	e in weight (kg) (Follow-	up: 1 year; Bett	er indicated b	y higher valu	ies)						
1 (Whit e 2013)	observationa I studies	very serious	no serious inconsistency	no serious indirectnes s	no serious imprecisio n	none	15	6	-	MD 7.60 higher (4.74 to 10.46 higher)	VER Y LOW	CRITICAL
Change	e in weight (kg) (Follow-	up: 2 years; Be	tter indicated	by higher va	lues)						

Quality No of studie s	assessment Design	Risk of bias	Inconsistency	Indirectnes s	Imprecisio n	Other consideration s	No of patients Enteral tube feeding	s Usu al care	Effect Relativ e (95% CI)	Absolute	Quali	Importan ce
1 (Whit e 2013)	observationa I studies	very serious 1	no serious inconsistency	no serious indirectnes s	no serious imprecisio n	none	15	6	-	MD 9.10 higher (5.43 to 12.77 higher)	VER Y LOW	CRITICAL
Change	e in weight (kg)	(Follow-	up: 3 years; Bet	ter indicated	by higher val	ues)						
1 (Whit e 2013)	observationa I studies	very serious 1	no serious inconsistency	no serious indirectnes s	no serious imprecisio n	none	15	6	-	MD 9.00 higher (5.21 to 12.79 higher)	VER Y LOW	CRITICAL
Change	e in weight z so	ore (Follo	ow-up: 6 month	s; range of sc	ores: -4-4; B	etter indicated b	y higher value	s)				
1 (Bradl ey 2012)	observationa I studies	serious 2	no serious inconsistency	no serious indirectnes s	serious ³	none	20	20	-	MD 0.62 higher (0.27 to 0.97 higher)	VER Y LOW	CRITICAL
Change	e in weight z so	ore (Follo	ow-up: 1 year; r	ange of score	s: -4-4; Bette	r indicated by h	igher values)					
1 (Bradl ey 2012)	observationa I studies	serious 2	no serious inconsistency	no serious indirectnes s	serious ³	none	20	20	-	MD 0.44 higher (0.11 to 0.77 higher)	VER Y LOW	CRITICAL
Change	e in height z-sc	ore (Follo	w-up: 6 month	s; range of sc	ores: -4-4; Be	etter indicated b	y higher value	s)				
1 (Bradl ey 2012)	observationa I studies	serious 2	no serious inconsistency	no serious indirectnes s	serious ³	none	20	20	-	MD 0.2 higher (0.19 lower to 0.59 higher)	VER Y LOW	CRITICAL

 $\ensuremath{\textcircled{\sc online 0.5ex}}$ NICE 2017. All rights reserved. Subject to Notice of rights.

Quality	assessment						No of patients	s	Effect			
No of studie s	Design	Risk of bias	Inconsistency	Indirectnes s	Imprecisio n	Other consideration s	Enteral tube feeding	Usu al care	Relativ e (95% CI)	Absolute	Quali ty	Importan ce
Change	e in height z-sc	ore (Follo	w-up: 1 year; r	ange of score	s: -4-4; Bette	r indicated by h	igher values)					
1 (Bradl ey 2012)	observationa I studies	serious 2	no serious inconsistency	no serious indirectnes s	serious ³	none	20	20	-	MD 0.1 higher (0.29 lower to 0.49 higher)	VER Y LOW	CRITICAL
Change	e in BMI z score	e (Follow-	up: 6 months; i	range of score	es: -4-4; Bette	er indicated by h	igher values)					
1 (Bradl ey 2012)	observationa I studies	serious 2	no serious inconsistency	no serious indirectnes s	no serious imprecisio n	none	20	20	-	MD 0.82 higher (0.48 to 1.16 higher)	VER Y LOW	CRITICAL
Change	e in BMI z score	e (Follow-	up: 1 year; rang	ge of scores:	-4-4; Better in	ndicated by high	er values)					
1 (Bradl ey 2012)	observationa I studies	serious 2	no serious inconsistency	no serious indirectnes s	serious ³	none	20	20	-	MD 0.39 higher (0.09 to 0.69 higher)	VER Y LOW	CRITICAL
Change	e in BMI (kg/m2	2) (Follow-	-up: 1 year; Bet	ter indicated I	oy higher val	ues)						
1 (Whit e 2013)	observationa I studies	very serious	no serious inconsistency	no serious indirectnes s	no serious imprecisio n	none	15	6	-	MD 2.90 higher (2.2 to 3.6 higher)	VER Y LOW	CRITICAL
Change	e in BMI (kg/m2	2) (Follow	-up: 2 years; Be	etter indicated	by higher va	lues)						
1 (Whit e 2013)	observationa I studies	very serious	no serious inconsistency	no serious indirectnes s	no serious imprecisio n	none	15	6	-	MD 3.20 higher (2.33 to	VER Y LOW	CRITICAL

Quality	assessment						No of patients	s	Effect			
No of studie s	Design	Risk of bias	Inconsistency	Indirectnes s	Imprecisio n	Other consideration s	Enteral tube feeding	Usu al care	Relativ e (95% CI)	Absolute	Quali ty	Importan ce
										4.07 higher)		
Change	e in BMI (kg/m2) (Follow	-up: 3 years; Be	tter indicated	by higher va	lues)						
1 (Whit e 2013)	observationa I studies	very serious 1	no serious inconsistency	no serious indirectnes s	no serious imprecisio n	none	15	6	-	MD 2.50 higher (1.55 to 3.45 higher)	VER Y LOW	CRITICAL
Change	e in FEV₁ % pre	dicted (F	ollow-up: 6 mor	nths; range of	scores: 0-10	0; Better indicat	ted by higher v	values)				
1 (Bradl ey 2012)	observationa I studies	serious 2	no serious inconsistency	no serious indirectnes s	very serious ⁴	none	14	13	-	MD 4.5 lower (16.18 lower to 7.18 higher)	VER Y LOW	CRITICAL
Change	e in FEV₁ % pre	dicted (F	ollow-up: 1 yea	r; range of sc	ores: 0-100; E	Better indicated	by higher valu	es)				
1 (Bradl ey 2012)	observationa I studies	serious 2	no serious inconsistency	no serious indirectnes s	serious ⁵	none	14	13	-	MD 8.2 lower (20.5 lower to 4.1 higher)	VER Y LOW	CRITICAL
1 (Whit e 2013)	observationa I studies	very serious 1	no serious inconsistency	no serious indirectnes s	very serious ⁴	none	15	6	-	MD 10.60 higher (10.34 lower to 31.54 higher)	VER Y LOW	CRITICAL
Change	e in FEV1 % pre	aicted (Fe	ollow-up: 2 yea	rs; Better Indi	cated by high	ner values)						

Quality	assessment						No of natient	c	Effect			
No of studie s	Design	Risk of bias	Inconsistency	Indirectnes s	Imprecisio n	Other consideration s	Enteral tube feeding	Usu al care	Relativ e (95% CI)	Absolute	Quali ty	Importan ce
1 (Whit e 2013)	observationa I studies	very serious	no serious inconsistency	no serious indirectnes s	serious ⁵	none	15	6	-	MD 12.20 higher (2.57 lower to 26.97 higher)	VER Y LOW	CRITICAL
Change	e in FEV₁ % pre	dicted (F	ollow-up: 3 yea	rs; Better indi	cated by hig	her values)						
1 (Whit e 2013)	observationa I studies	very serious 1	no serious inconsistency	no serious indirectnes s	serious⁵	none	15	6	-	MD 12.20 higher (1.84 lower to 26.24 higher)	VER Y LOW	CRITICAL
Change	e in IV treatmer	nt days (F	ollow-up: 1 yea	r; Better indic	ated by lowe	r values)						
1 (Whit e 2013)	observationa I studies	very serious	no serious inconsistency	no serious indirectnes s	serious ³	none	15	6	-	MD 17.90 higher (5.96 lower to 41.76 higher)	VER Y LOW	IMPORTA NT
Change	e in IV treatmer	nt days (F	ollow-up: 2 yea	rs; Better indi	icated by low	ver values)						
1 (Whit e 2013)	observationa I studies	very serious 1	no serious inconsistency	no serious indirectnes s	serious ³	none	15	6	-	MD 36.00 higher (5.06 to 66.94 higher)	VER Y LOW	IMPORTA NT
Change	e in IV treatmer	nt days (F	ollow-up: 3 yea	rs; Better indi	icated by low	er values)						
1 (Whit	observationa I studies	very serious	no serious inconsistency	no serious indirectnes s	serious ³	none	15	6	-	MD 36.20 higher (6.29	VER Y LOW	IMPORTA NT

 $\ensuremath{\textcircled{\sc online 0.5ex}}$ NICE 2017. All rights reserved. Subject to Notice of rights.

Quality assessment								No of patients		Effect		
No of studie s	Design	Risk of bias	Inconsistency	Indirectnes s	Imprecisio n	Other consideration s	Enteral tube feeding	Usu al care	Relativ e (95% CI)	Absolute	Quali ty	Importan ce
e 2013)										lower to 78.69 higher)		
Quality of life												
No evidence available												
Patient	Patient or carer satisfaction											
No evid	lence available											
Advers	e events											

No evidence available

Abbreviations: BMI: body mass index; confidence interval; CF: cystic fibrosis; FEV₁: 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		
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Appetite stimulants	Place bo	Relativ e (95% CI)	Absolute	Quali ty	Importance
Chang	Change in weight in kg. (follow-up 3 months: range of scores: 3-120: Better indicated by higher values)											

Quality No of studi es	assessment Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	No of patien Appetite stimulants	ts Place bo	Effect Relativ e (95%	Absolute	Quali	Importance
1 (Eub anks 2002, Hom nick 2004)	randomised trials	very serious 1	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	18	15	-	MD 2.97 higher (0.94 to 4.99 higher)	LOW	CRITICAL
Chang	e in weight in	kg. (follov	w-up 6 months;	; range of sco	ores: 1-120; E	Setter indicated	by higher valu	ues)				
1 (Eub anks 2002)	randomised trials	very serious 2	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	10	7	-	MD 3.8 higher (1.27 to 6.33 higher)	LOW	CRITICAL
Chang	e in weight z s	core (foll	ow-up 3 month	s; range of s	cores: -4-4; E	Better indicated	by higher val	ues)				
3 (Eub anks 2002, Hom nick 2004, Marc hand 2000)	randomised trials	very serious 3	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	20	20	-	MD 0.61 higher (0.29 to 0.93 higher)	LOW	CRITICAL
Chang	e in weight z s	core (foll	ow-up 6 month	s; range of s	cores: -4-4; E	Better indicated	by higher valu	ues)				
1 (Eub anks 2002)	randomised trials	very serious 2	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	10	7	-	MD 0.74 higher (0.26 to 1.22 higher)	LOW	CRITICAL

Quality assessment								No of patients		Effect		
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Appetite stimulants	Place bo	Relativ e (95% CI)	Absolute	Quali ty	Importance
Chang	e in height (cn	n) (follow	-up 3 months; I	Better indicat	ed by higher	values)						
1 (Hom nick 2004)	randomised trials	serious 4	no serious inconsistenc y	serious ⁵	very serious ⁶	none	8	8	-	MD 0.2 higher (11.88 lower to 12.28 higher)	VER Y LOW	CRITICAL
Chang	Change in BMI (kg/m2) (follow-up 3 months; Better indicated by higher values)											
1 (Hom nick 2004)	randomised trials	serious 4	no serious inconsistenc y	serious⁵	serious ⁷	none	8	8	-	MD 0.88 higher (0.76 lower to 2.52 higher)	VER Y LOW	CRITICAL
Chang	e in BMI centil	e (follow-	up 3 months; E	Better indicate	ed by higher	values)						
1 (Hom nick 2004)	randomised trials	serious 4	no serious inconsistenc y	serious⁵	serious ⁷	none	8	8	-	MD 11.1 higher (0.15 to 22.05 higher)	VER Y LOW	CRITICAL
Change	e in % ideal bo	ody weigh	it (follow-up 3 r	nonths; Bette	er indicated b	y higher values	;)					
1 (Hom nick 2004)	randomised trials	serious 4	no serious inconsistenc y	serious⁵	serious7	none	8	8	-	MD 5.14 higher (0.2 to 10.08 higher)	VER Y LOW	CRITICAL
Chang	e in FEV ₁ % pr	edicted (f	follow-up 3 mo	nths; range o	f scores: 0-1	00; Better indica	ated by highe	r values)				

								4-				
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Appetite stimulants	Place bo	Relativ e (95% CI)	Absolute	Quali ty	Importance
1 (Eub anks 2002)	randomised trials	very serious 2	no serious inconsistenc y	no serious indirectnes s	serious ⁸	none	10	7	-	MD 13.55 higher (1.88 lower to 28.98 higher)	VER Y LOW	CRITICAL
Chang	e in FEV₁ % pr	redicted (f	follow-up 6 mo	nths; range o	f scores: 0-1	00; Better indic	ated by highe	r values)				
1 (Eub anks 2002)	randomised trials	very serious 2	no serious inconsistenc y	no serious indirectnes s	serious ⁸	none	10	7	-	MD 5.64 higher (4.43 lower to 15.71 higher)	VER Y LOW	CRITICAL
Quality	of life											
No evic	lence available											
Numbe	er of pulmonar	y exacert	oations (follow-	up: 3 months	; Better indi	cated by lower	values)					
1 (Marc hand 2000)	randomised trials	very serious 9	no serious inconsistenc y	no serious indirectnes s	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)	VER Y LOW	IMPORTAN T
Advers	e effects: con	stipation	(follow-up: 6 m	nonths; Better	r indicated b	y lower values)						
1 (Eub anks 2002)	randomised trials	very serious	no serious inconsistenc y	no serious indirectnes s	very serious ⁶	none	1/10 (10%)	0/7 (0%)	RR 2.18 (0.1 to 46.92)	-	VER Y LOW	IMPORTAN T
Quality	assessment						No of patient	ts	Effect			
-----------------------------	----------------------	----------------------------------	---------------------------------	--------------------------------	-------------------	-----------------------------	---	--	---	--	-------------	---------------
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Appetite stimulants	Place bo	Relativ e (95% CI)	Absolute	Quali ty	Importance
Advers	e effects: hig	h blood g	lucose levels (f	ollow-up: 3 m	nonths; Bette	er indicated by I	ower values)					
1 (Marc hand 2000)	randomised trials	very serious ¹⁰	no serious inconsistenc y	no serious indirectnes s	Not calculable	none	6 participants . Values not reported	6 partici pants. Value s not report er	Fasting blood glucos e levels remain ed unchan ged in both groups		LOW	IMPORTAN T
Advers	e effects: dec	reased m	orning cortisol	levels <0.6m	cg/dl (follow	-up: 3 months; I	Better indicate	ed by hig	her value	s)		
1 (Marc hand 2000)	randomised trials	very serious ¹⁰	no serious inconsistenc y	no serious indirectnes s	Not calculable	none	4/6	Not report ed	-	All participa nts in the intervent ion group had normal morning cortisol levels at baseline ; at follow- up 4 out of the 6	LOW	IMPORTAN T

 $\ensuremath{\textcircled{\sc online \sc on$

Quality	y assessment						No of patien	ts	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Appetite stimulants	Place bo	Relativ e (95% CI)	Absolute	Quali ty	Importance
										participa nts in the intervent ion group had morning cortisol levels decreas ed to <0.6mcg /dl		
Advers	se effects: dec	reased m	orning cortisol	levels <30 nr	mol/L at 6 mo	onths						
1 (Eub anks 2002)	randomised trials	very serious 2	no serious inconsistenc y	no serious indirectnes s	very serious ⁶	none	7/10 (70%) ^a Baseline levels not reported	0/7 (0%) Baseli ne levels not report er	RR 10.91 (0.72 to 164.61)	-	VER Y LOW	IMPORTAN T
Patien	t or carer satis	faction (E	Better indicated	l by higher va	lues)							

No evidence available

Abbreviations: BMI: body mass index; confidence interval; CF: cystic fibrosis; FEV₁: 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 No of studi es	y assessmen t Design	t Risk of bias	Inconsistenc y	Indirectne ss	Imprecisio n	Other consideration s	No of patie Nutrition education	nts Standar d treatme nt	Effect Relati ve (95% Cl)	Absolu te	Quality	Importan ce
Chang	je in weight (k	(g) (follow-	up 6 months; r	ange of scor	es: 1-120; B	etter indicated	by higher va	lues)				
1 (Wat son 2008)	randomised trials	no serious risk of bias ¹	no serious inconsistenc y	serious indirectnes s ²	very serious ³	none	23	25	-	MD 0.4 lower (4.85 lower to 4.05 higher)	VERY LOW	CRITICA L
Chang	je in weight (k	(follow-	up 1 years; rar	nge of scores	: 1-120; Bet	ter indicated by	v higher valu	es)				
1 (Wat son 2008)	randomised trials	no serious risk of bias ¹	no serious inconsistenc y	serious indirectnes s ²	serious ⁴	none	23	25	-	MD 0.4 lower (4.87 lower to 4.07 higher)	LOW	CRITICA L

Quality	vassessment						No of patie	nts	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectne ss	Imprecisio n	Other consideration s	Nutrition education	Standar d treatme nt	Relati ve (95% CI)	Absolu te	Quality	Importan ce
Chang	<mark>e in FEV</mark> ₁ % p	redicted (f	ollow-up 6 mo	nths; range o	of scores: 0-	100; Better indi	cated by hig	her values	;)			
1 (Wat son 2008)	randomised trials	no serious risk of bias ¹	no serious inconsistenc y	serious indirectnes s ²	very serious⁵	none	23	25	-	MD 1.49 higher (8.84 lower to 11.82 higher)	VERY LOW	CRITICA L
Chang	<mark>e in FEV</mark> ₁ % p	redicted (f	ollow-up 1 yea	rs; range of	scores: 0-10	0; Better indica	ited by highe	r values)				
1 (Wat son 2008)	randomised trials	no serious risk of bias ¹	no serious inconsistenc y	serious indirectnes s ²	very serious⁵	none	23	25	-	MD 0.99 higher (9.29 lower to 11.27 higher)	VERY LOW	CRITICA L
Quality	y of life: CFQ	OL, physica	al functioning	(follow-up 6 i	months; ran	ge of scores: 0	-100; Better i	ndicated k	by higher	values)		
1 (Wat son 2008)	randomised trials	serious ⁶	no serious inconsistenc y	serious indirectnes s ²	Not calculable	none	23	25	-	p- value: 0.05	LOW	CRITICA L
Quality	y of life: CFQ	OL, physica	al functioning	(follow-up 12	months; ra	nge of scores: (0-100; Better	indicated	by highe	er values)		
1 (Wat son 2008)	randomised trials	serious ⁶	no serious inconsistenc y	serious indirectnes s ²	Not calculable	none	23	25	-	p- value: 0.61	LOW	CRITICA L

Quality	/ assessment	:					No of patier	nts	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectne ss	Imprecisio n	Other consideration s	Nutrition education	Standar d treatme nt	Relati ve (95% CI)	Absolu te	Quality	Importan ce
Quality	of life: CFQ	DL, social f	unctioning (fo	llow-up 6 mo	nths; range	of scores: 0-10	0; Better ind	icated by	higher va	lues)		
1 (Wat son 2008)	randomised trials	serious ⁶	no serious inconsistenc y	serious indirectnes s ²	Not calculable	none	23	25	-	p- value: 0.85	LOW	CRITICA L
Quality	of life: CFQ	DL, social f	unctioning at ^a	12 months (fe	ollow-up 12	months; range	of scores: 0-	100; Bette	r indicat	ed by hig	her values)	
1 (Wat son 2008)	randomised trials	serious ⁶	no serious inconsistenc y	serious indirectnes s ²	Not calculable	none	23	25	-	p- value: 0.54	LOW	CRITICA L
Quality	of life: CFQ	OL, treatme	ent issues (follo	ow-up 6 mon	ths; range o	of scores: 0-100	; Better indic	ated by hi	igher val	ues)		
1 (Wat son 2008)	randomised trials	serious ⁶	no serious inconsistenc y	serious indirectnes s ²	Not calculable	none	23	25	-	p- value: 0.74	LOW	CRITICA L
Quality	of life: CFQ	OL, treatme	ent issues (foll	ow-up 12 mo	nths; range	of scores: 0-10	0; Better ind	icated by I	higher va	lues)		
1 (Wat son 2008)	randomised trials	serious ⁶	no serious inconsistenc y	serious indirectnes s ²	Not calculable	none	23	25	-	p- value: 0.68	LOW	CRITICA L
Quality	of life: CFQ	OL, chest s	ymptoms (follo	ow-up 6 mon	ths; range o	f scores: 0-100	; Better indic	ated by hi	gher val	ues)		
1 (Wat son	randomised trials	serious ⁶	no serious inconsistenc y	serious indirectnes s ²	Not calculable	none	23	25	-	p- value: 0.59	LOW	CRITICA L

Quality	y assessment						No of patie	nts	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectne ss	Imprecisio n	Other consideration s	Nutrition education	Standar d treatme nt	Relati ve (95% CI)	Absolu te	Quality	Importan ce
2008)											Ē	
Quality	y of life: CFQ0	OL, chest s	ymptoms (follo	ow-up 12 mo	nths; range	of scores: 0-10	0; Better ind	icated by I	higher va	lues)		
1 (Wat son 2008)	randomised trials	serious ⁶	no serious inconsistenc y	serious indirectnes s ²	Not calculable	none	23	25	-	p- value: 0.62	LOW	CRITICA L
Quality	y of life: CFQ0	OL, emotio	nal responses	(follow-up 6	months; ran	ige of scores: 0	-100; Better	indicated	by highe	r values)		
1 (Wat son 2008)	randomised trials	serious ⁶	no serious inconsistenc y	serious indirectnes s ²	Not calculable	none	23	25	-	p- value: 0.45	LOW	CRITICA L
Quality	y of life: CFQ	OL, emotio	nal responses	(follow-up 12	2 months; ra	inge of scores:	0-100; Bette	r indicated	l by high	er values))	
1 (Wat son 2008)	randomised trials	serious ⁶	no serious inconsistenc y	serious indirectnes s ²	Not calculable	none	23	25	-	p- value: 0.07	LOW	CRITICA L
Quality	y of life: CFQ0	OL, conceri	ns for the futu	re (follow-up	6 months; r	ange of scores	: 0-100; Bette	er indicate	d by higł	ner values	5)	
1 (Wat son 2008)	randomised trials	serious ⁶	no serious inconsistenc y	serious indirectnes s ²	Not calculable	none	23	25	-	p- value: 0.46	LOW	CRITICA L
Quality	y of life: CFQ0	OL, conceri	ns for the futu	re (follow-up	12 months;	range of scores	s: 0-100; Bet	ter indicat	ed by hig	gher value	es)	

Quality	y assessment						No of patie	nts	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectne ss	Imprecisio n	Other consideration s	Nutrition education	Standar d treatme nt	Relati ve (95% CI)	Absolu te	Quality	Importan ce
1 (Wat son 2008)	randomised trials	serious ⁶	no serious inconsistenc y	serious indirectnes s ²	Not calculable	none	23	25	-	p- value 0.03:	LOW	CRITICA L
Quality	y of life: CFQ0	OL, interpe	rsonal relation	ship (follow-	up 6 months	s; range of scor	res: 0-100; B	etter indica	ated by h	igher val	ues)	
1 (Wat son 2008)	randomised trials	serious ⁶	no serious inconsistenc y	serious indirectnes s ²	Not calculable	none	23	25	-	p- value: 0.75	LOW	CRITICA L
Quality	y of life: CFQ0	DL, interpe	rsonal relation	ship (follow-	up 12 month	ns; range of sco	ores: 0-100; E	Better indi	cated by	higher va	alues)	
1 (Wat son 2008	randomised trials	serious ⁶	no serious inconsistenc y	serious indirectnes s ²	Not calculable	none	23	25	-	p- value: 0.64	LOW	CRITICA L
)												
) Quality	y of life: CFQ0	DL, body in	nage (follow-u	p 6 months; I	range of sco	res: 0-100; Bet	ter indicated	by higher	values)			
) Quality 1 (Wat son 2008)	<mark>y of life: CFQ(</mark> randomised trials	<mark>DL, body in</mark> serious ⁶	nage (follow-u no serious inconsistenc y	p 6 months; i serious indirectnes s ²	r <mark>ange of sco</mark> Not calculable	<mark>res: 0-100; Bet</mark> none	<mark>ter indicated</mark> 23	<mark>by higher</mark> 25	values) -	p- value: 0.24	LOW	CRITICA L
) Quality 1 (Wat son 2008) Quality	y of life: CFQC randomised trials y of life: CFQC	DL, body in serious ⁶ DL, body in	nage (follow-u no serious inconsistenc y nage (follow-u	p 6 months; i serious indirectnes s ² p 12 months;	range of sco Not calculable range of sc	res: 0-100; Bet none ores: 0-100; Be	ter indicated 23 etter indicate	by higher 25 d by highe	values) - r values)	p- value: 0.24	LOW	CRITICA L

Quality	v accordence						No of potio	nto	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectne ss	Imprecisio n	Other consideration s	No of patie Nutrition education	Standar d treatme nt	Relati ve (95% Cl)	Absolu te	Quality	Importan ce
Quality	y of life: CFQ	OL, career	issues (follow-	up 6 months	; range of so	cores: 0-100; B	etter indicate	d by high	er values	;)		
1 (Wat son 2008)	randomised trials	serious ⁶	no serious inconsistenc y	serious indirectnes s ²	Not calculable	none	23	25	-	p- value: 0.15	LOW	CRITICA L
Quality	y of life: CFQ	OL, career	issues (follow-	up 12 month	s; range of s	scores: 0-100; I	Better indicat	ted by hig	her value	es)		
1 (Wat son 2008)	randomised trials	serious ⁶	no serious inconsistenc y	serious indirectnes s ²	Not calculable	none	23	25	-	p- value: 0.28	LOW	CRITICA L
Pulmo	nary exacerb	ations										
No evi	dence availabl	е										
Adver	se effects											
No evi	dence availabl	е										
Patien	t or carer sati	sfaction										
No evia Abbreviati mean diffe 1 The qua influenced 2 The qua representa 3 The qua	dence available ons: CI: confider rence lity of the evider by the lack of b lity of the evider ative of people w lity of the evider	e nce interval; nce was not c linding. nce was dow. rho would red nce was dow.	CF: cystic fibrosis downgraded desp ngraded by 1 bec ceive this interver ngraded by 2 bec	s; CFQOL: cyst ite unclear risk ause there was ttion in clinical ause the 95%	ic fibrosis qual of bias in relat no inclusion c practice Cl crossed 2 d	ity of life question. ion to blinding and criteria related to u efault MIDs	naire; FEV1: for d selective repo underweight, the	rced expirato orting, becau erefore the s	ory volume Ise objecti study popu	in 1 secon ve measure lation is un	d; kg: kilogramr es are unlikely to likely to be	nes; MD: o be

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	s	Effect			
No of studie s	Design	Risk of bias	Inconsistency	Indirectness	Imprecisio n	Other consideration s	Behavioural intervention	Usu al care	Relativ e (95% CI)	Absolute	Quali ty	Importan ce
Change	e in weight (k	g) (follow	-up 6 weeks; Be	etter indicated	by higher va	alues)						
1 (Stark 1996)	randomise d 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)	VER Y LOW	CRITICAL
Change	e in height (cr	m) (follow	-up 6 weeks; B	etter indicated	l by higher v	alues)						
1 (Stark 1996)	randomise d 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)	VER Y LOW	CRITICAL
Change	e in weight z	score (fol	low-up 6 weeks	; Better indica	ted by highe	er values)						
1 (Stark 1996)	randomise d 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)	VER Y LOW	CRITICAL
Change	e in FEV1 <mark>% p</mark>	redicted (follow-up 6 wee	eks; Better ind	icated by high	gher values)						
1 (Stark 1996)	randomise d trials	serious	no serious inconsistency	serious indirectness 2	very serious⁵	none	5	4	-	MD 6.5 lower (28.09 lower to	VER Y LOW	CRITICAL

Quality	assessment						No of patients		Effect			
No of studie s	Design	Risk of bias	Inconsistency	Indirectness	Imprecisio n	Other consideration s	Behavioural intervention	Usu al care	Relativ e (95% CI)	Absolute	Quali ty	Importan ce
										15.09 higher)		
Quality	of life											
No evid	lence available	e										
Pulmo	nary exacerba	tions										
No evid	lence available	;										
Advers	e effects											
No evid	lence available	9										
Patient	or carer satis	sfaction										
No evid	lence available	; ; ; ; ; ;	05									

Abbreviations: CI: confidence interval; CF: cystic fibrosis; cm: centimetres; FEV1: 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	y assessment	t					No of patie	nts	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideration s	Behaviour al interventio n	Education al interventio n	Relati ve (95% CI)	Absolu te	Quality	Importanc e
Chang	e in weight z	score (follow-up 6 mg	onths: Better	indicated by	v higher values)					

Change in weight z score (follow-up 6 months; Better indicated by higher values

Quality	y assessment	t					No of patie	nts	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideration s	Behaviour al interventio n	Education al interventio n	Relati ve (95% CI)	Absolu te	Quality	Importanc e
1 (Pow ers 2015)	randomise d trials	no serio us risk of bias ¹	no serious inconsistenc y	no serious indirectnes s	serious ²	none	36	42	-	MD 0.06 higher (0.1 lower to 0.22 higher)	MODERAT E	CRITICAL
Chang	e in weight z	score (f	follow-up 18 m	onths; Bette	r indicated b	oy higher value	s)					
1 (Pow ers 2015)	randomise d trials	no serio us risk of bias ¹	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	36	42	-	MD 0.04 higher (0.2 lower to 0.28 higher)	HIGH	CRITICAL
Chang	je in height z	score (f	ollow-up 18 m	onths; Better	r indicated b	y higher values	s)					
1 (Pow ers 2015)	randomise d trials	no serio us risk of bias ¹	no serious inconsistenc y	no serious indirectnes s	serious ²	none	36	42	-	MD 0.11 higher (0.02 lower to 0.24 higher)	MODERAT E	CRITICAL
Quality	y of life											
No evi	dence availabl	е										
Pulmo	nary exacerb	ations										
No evi	dence availabl	е										
Adver	se effects: dig	gestive	system (follow	-up 6 months	s Better indi	cated by lower	values)					

Quality No of studi es	y assessmen t Design	t Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideration s	No of patie Behaviour al interventio n	nts Education al interventio n	Effect Relati ve (95% Cl)	Absolu te	Quality	Importanc e
1	randomise d trials	no serio us risk of bias ¹	no serious inconsistenc y	no serious indirectnes s	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)	MODERAT	IMPORTAN T
Patien	t or carer sati	sfaction	า									

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	y assessment	t					No of patien	ts	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideration s	Behavioural manageme nt training + nutritional intervention	Education al interventi on alone	Relati ve (95% CI)	Absolu te	Quality	Importan ce
Chang	e in weight (k	(follov	w-up: 2 month	s; Better indi	icated by hig	gher values)						

Quality No of studi es	y assessment Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideration s	No of patien Behavioural manageme nt training + nutritional intervention	ts Education al interventi on alone	Effect Relati ve (95% CI)	Absolu te	Quality	Importan ce
1 (Star k 2009)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectne ss	serious ¹	none	33	34	-	MD 0.55 higher (0 to 1.1 higher)	MODERAT E	CRITICA L
Chang	e in weight (k	(follov	w-up: 1 year; B	letter indicat	ed by highe	r values)						
1 (Pow ers 2003)	randomise d trials	seriou s ²	no serious inconsistenc y	no serious indirectne ss	very serious ³	none	4	4	-	MD 0.43 lower (1.27 lower to 0.41 higher)	VERY LOW	CRITICA L
Chang	e in weight (k	(follow	w-up: 2 years;	Better indica	ted by high	er values)						
1 (Star k 2009)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectne ss	serious ¹	none	28	31	-	MD 0.52 higher (1.34 lower to 2.38 higher)	MODERAT E	CRITICA L
Chang	e in BMI z sco	ore (follo	w-up: 2 month	s; Better ind	icated by hi	gher values)						
1 (Star k 2009)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectne ss	serious ¹	none	33	34	-	MD 0.2 higher (0.02 lower to 0.42 higher)	MODERAT E	CRITICA L

Quality	y assessment	t					No of patien	ts	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideration s	Behavioural manageme nt training + nutritional intervention	Education al interventi on alone	Relati ve (95% CI)	Absolu te	Quality	Importan ce
Chang	e in BMI z sc	ore (follo	w-up: 2 years;	Better indic	ated by high	er values)						
1 (Star k 2009)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectne ss	serious ¹	none	28	31	-	MD 0.35 higher (0 to 0.7 higher)	MODERAT E	CRITICA L
Chang	e in % ideal b	ody weig	ght (follow-up:	1 years; Bet	ter indicated	d by higher valu	les)					
1 (Pow ers 2003)	randomise d trials	seriou s2	no serious inconsistenc y	no serious indirectne ss	very serious ³	none	4	3	-	MD 0.91 lower (37.52 lower to 35.7 higher)	VERY LOW	CRITICA L
Chang	e in weight %	for age	(follow-up: 1 y	ears; Better	indicated by	higher values						
1 (Pow ers 2003)	randomise d trials	seriou S ²	no serious inconsistenc y	no serious indirectne ss	very serious ³	none	4	4	-	MD 0.6 lower (17.25 lower to 16.05 higher)	VERY LOW	CRITICA L
Chang	e in height (c	m) (follo	w-up: 1 years;	Better indic	ated by high	ner values)						
1 (Pow ers 2003)	randomise d trials	seriou s ²	no serious inconsistenc y	no serious indirectne ss	very serious ³	none	3	4	-	MD 2.03 lower (4.87 lower	VERY LOW	CRITICA L

Quality	y assessment	t					No of patien	ts	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideration s	Behavioural manageme nt training + nutritional intervention	Education al interventi on alone	Relati ve (95% Cl)	Absolu te	Quality	Importan ce
										to 0.81 higher)		
Chang	e in height (c	m) (follow	w-up: 2 years;	Better indica	ated by high	er values)						
1 (Star k 2009)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectne ss	no serious imprecisio n	none	28	31	-	MD 0.2 lower (1.45 lower to 1.05 higher)	HIGH	CRITICA L
Chang	e in height z	score (fo	llow-up: 2 yea	rs; Better inc	licated by h	igher values)						
1 (Star k 2009)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectne ss	serious ¹	none	28	31	-	MD 0.01 lower (0.17 lower to 0.15 higher)	MODERAT E	CRITICA L
Chang	<mark>e in</mark> FEV₁ <mark>% p</mark>	oredicted	(follow-up: 2 y	/ears; Better	indicated b	y higher values	;)					
1 (Star k 2009)	randomise d trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectne ss	very serious ⁴	none	13	15	-	MD 5.16 higher (8.49 lower to 18.81 higher)	LOW	CRITICA L
Quality	y of life											
No evi	dence availabl	е										

Quality	y assessment	t					No of patien	ts	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideration s	Behavioural manageme nt training + nutritional intervention	Education al interventi on alone	Relati ve (95% CI)	Absolu te	Quality	Importan ce
Advers	se effects											
No evi	dence availabl	е										
Time t	o next exacer	bation										
No evi	dence availabl	е										
Patien	t or carer sati	sfaction	(follow-up: 2 r	nonths; Bett	er indicated	by higher valu	es)					
1 (Star k 2009)	randomise d trials	seriou s risk of bias⁵	no serious inconsistenc y	no serious indirectne ss	Not calculable	none	33	34	Parents groups high rat satisfac treatme a 7 poir	in both reported ings of tion with nt (>6 in t scale)	MODERAT E	IMPORT ANT

Abbreviations: BMI: body mass index; CI: confidence interval; FEV1: 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 No of studi es	y assessmen Design	it Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	No of pat PERT + Cimetidi ne	tients PERT alone	Effect Relati ve (95% CI)	Absolute	Quality	Importan ce
Faecal	fat excretio	n (FFE) (fo	ollow-up 14 da	ys; measured	l as: % of int	take, or consun	ned fat that	t is excre	ted ; Bet	ter indicate	ed by lower va	alues)
1 (Duri e 1980) 2	randomise d trials ¹	very serious 3	no serious inconsistenc y	no serious indirectnes s	Not assessed ⁴	none	2 ⁻ Mean: 17.8±9.	1 Mean: 27.6±1	-	-	LOW	CRITICA L
Facal	fot overetion		allow up 14 do		l agy g/ 24bg	uro*: Dottor ind	74	J.J				
Faeca	Tal excretion	(FFE) (IC	Show-up 14 da	ys; measured	i as: g/ 2410	urs"; Detter ma	icated by i	ower vai	ues)			
1 (Duri e 1980) ²	randomise d trials ¹	serious ⁵	no serious inconsistenc y	very serious indirectnes s ⁶	serious imprecisio n ⁷	none	2	1	-	MD 11 lower (18.577 to 3.423 lower)	LOW	CRITICA L

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

Quality a	ssessment						No of pat	tients	Effect			
No of studies	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other considerati ons	PERT + Ranitidi ne	PERT alone	Relativ e (95% CI)	Absolute	Quality	Importan ce
Fat absor low-dose	rption (CFA) ranitidine]	(follow-	up 12 days; m	easured as:	% of intake	e, or consume	d fat that i	s absorb	ed; Bette	r indicated by hig	her values) [PERT +
1 (Francis co 2002) ²	randomis ed trials ¹	no seriou s risk of bias	no serious inconsisten Cy	no serious indirectne ss	Not calculable ³	none ⁴	12 Median: 83.60 (74.10 to 89.67) <i>versus</i> . 80.37 (72.43 to 89.44)		-	p=0.87*	HIGH	CRITICAL
Fat absor high-dos	rption (CFA) e ranitidine]	(follow-	up 12 days; m	easured as:	% of intake	e, or consume	d fat that i	s absorb	ed; Bette	r indicated by hig	her values) [PERT +
1 (Francis co 2002) ⁵	randomis ed trials ¹	no seriou s risk of bias	no serious inconsisten cy	no serious indirectne ss	Not calculable ³	none ⁴	12 Median 8 (74.15 to <i>versus</i> . 8 (72.43 to	2 0.91 88.21) 0.37 89.44)	-	p=1*	HIGH	CRITICAL

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

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 dailv.

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.

Quality as	sessment						No of patier	nts	Effect			
No of studies	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	PERT + Omeprazo le	PER T alone	Relati ve (95% CI)	Absolu te	Quality	Importan ce
Fat absorp	otion (CFA) (follow-up	o 12 days; mea	sured with:	% of intake	or consumed fa	at that is abso	orbed; E	Better ind	dicated by	y higher value	es)
1 (Francisc o 2002) ²	randomis ed trials ¹	no serious risk of bias	no serious inconsistenc y	no serious indirectne ss	Not calculable ³	Other ⁴	9 Median: 87.40 (84.72 to 90.88) <i>versus</i> . 88.59 (79.01 to 93.46) umed fat that is excre		-	p≤0.05 *	MODERAT E	CRITICA L
Faecal fat [low-dose	excretion (F PERT + ome	FE) (follo eprazole o	w-up 4 weeks or placebo]	; measured v	vith: % of in	take, or consur	ned fat that i	s excret	ted; Bett	er indicat	ed by lower v	alues)
1 (Heijerm an 1991) ⁵	randomis ed trials ¹	serious 6	no serious inconsistenc y	very serious ⁷	Not calculable ⁸	Other ⁹	9 Median: 14 (6 to 32) <i>versus</i> . 20 (12 to 44)		-	p>0.05	VERY LOW	CRITICA L
Faecal fat [high-dose	excretion (F PERT + orr	FE) (follo eprazole	ow-up 4 weeks or placebo]	; measured	with: % of ir	itake, or consu	med fat that	is excre	ted; Bett	ter indica	ted by lower	values)
1 (Heijerm an 1991) ¹⁰	randomis ed trials ¹	serious ⁶	no serious inconsistenc y	very serious ⁷	Not calculable ⁸	Other ⁹	9 Median: 9 (4 to 25) <i>versus</i> . 18 (10 to 34)		-	p<0.01	VERY LOW	CRITICA L
Faecal fat	excretion (F	FE) (follo	w-up 4 weeks	; measured v	vith: % of in	take, or consur	ned fat that i	s excret	ted; Bett	er indicat	ed by lower v	alues)
1 (Heijerm an 1993) ¹¹	randomis ed trials ¹	no serious risk of bias	no serious inconsistenc y	very serious ¹²	Not calculable	none	11 Median: 17 45) <i>versus</i> . 2 to 44)	(4 to 20 (12	-	p>0.05	LOW	CRITICA L

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

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 a No of studies	ssessment Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other considerati ons	No of pat PERT + Ranitidi ne	ients PERT alone	Effect Relativ e (95% CI)	Absolute	Quality	Importan ce
Fat abso low-dose	rption (CFA) ranitidine]	(follow-up 1	2 days; meas	ured with: %	of intake or	r consumed fa	at that is al	osorbed;	Better in	dicated by high	gher values)) [PERT +
1 (Francis co 2002) ²	randomise d trials ¹	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	Not calculable ³	none ⁴	10 Median: 93.06 (84.90 to 96.11) <i>versus</i> . 89.20 (79.38 to 93.04)		-	p=0.01*	HIGH	CRITICA L
Fat absorbight	rption (CFA) e ranitidine]	(follow-up 1	2 days; meas	ured with: %	of intake or	r consumed fa	at that is al	osorbed;	Better in	dicated by hi	gher values)) [PERT +
1 (Francis co 2002)⁵	randomise d trials ¹	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	Not calculable ³	Other ^{4,6}	9 Median: 8 (81.89 to <i>versus</i> . 88 (79.01 to	8.92 91.87) 3.59 93.76)	-	p≤0.05*	MODERA TE	CRITICA L

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).

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

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

Quality	assessmen	t					No of patie	ents	Effect			
No of studie s	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	High dose PERT	Low dose PER T	Relati ve (95% CI)	Absolute	Quality	Importan ce
Faecal	fat excretior	n (FFE) (fo	llow-up 14 day	ys; measure	d with: g/kg	/day; Better inc	dicated by Ic	wer val	ues)			
1 (Brady 1991) ¹	randomis ed trials ²	serious ³	no serious inconsisten cy	very serious ^{4,a}	not calculabl e⁵	Other ⁶	9		-	MD 0.141 lower (0.253 to 0.029 lower)	VERY LOW	CRITICAL
Faecal	fat excretior	n (FFE) (fo	llow-up 14 day	ys; measure	d with: % of	intake, or con	sumed fat t	hat is ex	creted;	Better indicat	ed by lower	values)
1 (Brady 1991) ¹	randomis ed trials ²	serious ³	no serious inconsisten cy	very serious ⁴	not calculabl e⁵	Other ⁶	9 Mean±SEM ⁵ 8.7±2.2 versus 13+3 06		-	-	VERY LOW	CRITICAL
Faecal	fat excretior	n (FFE) (fo	llow-up 9 days	s; measured	with: g/day	; Better indicat	ed by lower	values)				
2 (Brady 1991 ¹ , Beker 1994 ³)	randomis ed trials ²	serious ⁷	no serious inconsisten cy	very serious ^{4,a}	Not calculabl e⁵	none	<mark>ited by lower values</mark>) 30		-	MD 5 lower (8.877 to 1.123 lower)	VERY LOW	CRITICAL
Faecal	fat excretior	n (FFE) (fo	llow-up 4 wee	ks; measure	d with: g/da	y; Better indica	ated by lowe	er value	s)			
1	randomis ed trials ²	serious ⁹	no serious inconsisten cy	very serious ^{4,a}	serious ¹⁰	none ¹¹	12 Mean±SD ⁹		-	ns	VERY LOW	CRITICAL

Quality	assessmen	t					No of patie	ents	Effect			
No of studie s	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	High dose PERT	Low dose PER T	Relati ve (95% CI)	Absolute	Quality	Importan ce
(Mitch ell 1982) ⁸							8.7±4.1 <i>ver</i> 11.5±6.9	sus.				
Fat abs	orption (CF	A) (follow-	up 4 weeks; m	neasured wit	h: % of inta	ke or consume	d fat that is	absorbe	ed; Bette	r indicated by	y higher valu	ues)
1 (Mitch el 1982) ⁸	randomis ed trials ²	serious ⁹	no serious inconsisten cy	very serious ⁴	very serious ¹²	none ¹¹	12 Mean±SEM ¹¹ 89.5±4.2 <i>versus</i> . 85.4±11.26 ted by higher value		-	-	VERY LOW	CRITICAL
Fat abs	orption (CF)	A) (follow-	up 9 days; me	asured with	: % of intake	e; Better indica	ted by highe	er value	s)			
1 (Beker 1984) ³	randomis ed trials ²	serious ¹ 3	no serious inconsisten cy	very serious⁴	very serious ¹²	none ¹⁴	ted by higher value 21 Mean±SEM ¹¹ 91.2±1.6 <i>versus</i> . 86.2±3.2		-		VERY LOW	CRITICAL
Stool fr	equency (fo	llow-up 4	weeks; measu	red with: bo	wel movem	ents/ day, self-	report; Bette	er indica	ated by l	ower values)		
1 (Mitch el 1982) ⁸	randomis ed trials ²	serious ⁹	no serious inconsisten cy	very serious ⁴	no serious imprecisi on	none ¹¹	86.2±3.2 - report; Better indic 12			MD 0.1 lower (0.189 lower to 0.011 higher)	VERY LOW	CRITICAL
Abdom	inal pain (fo	llow-up 4 v	weeks; assess	sed with: sel	f-report; Be	tter indicated b	y lower valu	ies)				
1 (Mitch ell 1982) ⁸	randomis ed trials ²	serious ⁹	no serious inconsisten cy	very serious ⁴	Not calculabl e ¹⁵	none ¹¹	-	-	-	The study reports that there were no differences between the groups ¹⁵	VERY LOW	CRITICAL

Quality	assessmen	t				No of patio	ents	Effect				
No of studie s	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	High dose PERT	Low dose PER T	Relati ve (95% CI)	Absolute	Quality	Importan ce
Advers	e events (co	nstipation	, elevation in	serum uric a	cid levels) (follow-up 9 da	ys; assesse	d with:	self-repo	rt; Better indi	icated by lov	ver values)
1 (Beker 1994) ³	randomis ed trials ²	serious ¹ 3	no serious inconsisten cy	very serious ⁴	Not calculabl e 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: Compa	rison 2.2. High dose	PERT versus low dose	PERT in adults
-----------------------------	----------------	----------------------	----------------------	----------------

Quality ass	sessment						No of pati	ents	Effect			
No of studies	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	High dose PERT	Low dose PERT	Relati ve (95% CI)	Absolu te	Qualit y	Importan ce
Faecal fat	excretion (FF	E) (follov	v-up 14 days; n	neasured wit	h: % of intak	e, or consumed	fat that is o	excreted;	Better in	ndicated b	by lower v	values)
1 (Heijerma n 1991) ²	randomise d trials ¹	serious 3	no serious inconsistenc y	very serious ⁴	Not calculable ⁵	other ⁶	9 Median: 18 34) <i>versus</i> to 44)	3 (10 to 5. 20 (12	-	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 desig n	N	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Sensitivi ty % (95% CI)	Specific ity % (95% Cl)	Positiv e likeliho od ratio (95% Cl)	Negativ e Likeliho od ratio (95% Cl)	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 inconsisten cy	no serious indirectne ss	no serious imprecisio n	52.7 (95% Cl: 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. Subgro	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 inconsisten cy	no serious indirectne ss	no serious imprecisio n	55.2 (95% Cl: 40.7- 66.8)*	78.1 (95% CI: 65.0- 88.7)*	2.52 (95% CI: 1.16- 5.89)*	0.57 (95% Cl: 0.38- 0.91)*	0.69 (95% CI: 0.56- 0.81)	HIGH	
Test 16. Subgro	up analy:	sis:Tra	ansient elas	tography usir	ng Fibroscar	n @ 5.5kPa c	ut off in a po	opulation o	f children				
1 (Rath 2012)	Cohort study	75	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	no serious imprecisio n	53.3 (95% Cl: 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 desig n	N	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Sensitivi ty % (95% Cl)	Specific ity % (95% Cl)	Positiv e likeliho od ratio (95% Cl)	Negativ e Likeliho od ratio (95% Cl)	AUR OC	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 inconsisten cy	no serious indirectne ss	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 inconsisten cy	no serious indirectne ss	very serious imprecision a	83.3 (95% CI: 38.7- 99.1)*	85.0 (95% CI: 80.5- 86.6)*	5.6 (95% Cl: 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 (Ditrasound and Transient elastography) versus Biochemical CFLDT definition to detect CFLD													
Number of studies (Reference)	Study design	N	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Sensitivi ty % (95% Cl)	Specific ity % (95% Cl)	Positiv e likeliho od ratio (95% Cl)	Negativ e Likeliho od ratio (95% Cl)	AUROC	Quality	
Test 9. Ultrasound (cut off of Williams score ≥ 4) in a population of adults and children													
1 (Witters 2009)	Cohort study	6 6	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	very serious imprecisio n ^a	50.0 (95% Cl: 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	6 6	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	very serious imprecisio n ^a	50.0 (95% Cl: 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 \geq 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	Inconsiste ncy	Indirectn ess	Imprecisi on	Sensitivit y % (95% CI)	Specifi city % 95% CI)	Positive likelihoo d ratio (95% Cl)	Negativ e Likeliho od ratio (95% Cl)	AUROC	Quality	
Test 10. Ultrasound (cut off of Williams score \geq 4) in a population of adults and children													

Number of studies (Reference)	Study design	N	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Sensitivit y % (95% CI)	Specifi city % 95% CI)	Positive likelihoo d ratio (95% Cl)	Negativ e Likeliho od ratio (95% CI)	AUROC	Quality		
1 (Fagundes 2004)ª	Cohort study	7 0	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	serious imprecisi on ^b	50.0 (95% CI: 22.0- 75.1)*	91.7 (95% CI: 87.0- 95.8)*	6.0 (95% Cl: 1.70- 18.07)*	0.55 (95% CI: 0.26- 0.90	Not reported	MODERA TE		
1(Witters 2009) ^c	Cohort study	6 6	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	serious imprecisi on ^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% Cl: 0.51- 0.89)	MODERA TE		
Test 15. Transie of adults and ch	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 Co 2009) ^c stu	Cohort study	6 6	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	serious imprecisi on ^b	63.6 (95% CI: 34.4- 86.0)*	87.3 (95% Cl: 81.4- 91.8)*	5.0 (95% Cl: 1.86- 10.43)*	0.42 (95% CI: 0.15- 0.81)*	0.86 (95% CI: 0.74- 0.98)	MODERA TE
---	-----------------	--------	----------------------------------	---------------------------------	--------------------------------	---	-------------------------------------	--	----------------------------------	-------------------------------------	---------------------------------------	--------------

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

		(-		,									
Number of studies (Reference)	Study design	N	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Sensitivi ty % (95% CI)	Specific ity % 95% CI)	Positive likelihoo d ratio (95% CI)	Negative Likelihoo d ratio (95% CI)	AURO C	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 inconsistenc y	no serious indirectne ss	no serious imprecisio n	63.2 (95% CI: 48.0- 76.3)*	79.0 (95% CI: 75.3- 82.2)*	3.0 (95% Cl: 1.95- 4.28)*	0.47 (95% CI: 0.29- 0.69)*	Not report ed	HIGH	
Test 2. AST usin	ig an unsp	ecified	d cutoff in a	a population of	children								
1 (Patriquin 1999)	Cohort study	195	no serious risk of bias	no serious inconsistenc y	no serious indirectne ss	no serious imprecisio n	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 report ed	HIGH	
Test 2. GGT usir	ng an unsp	oecifie	d cutoff in a	a population o	f children								
1 (Patriquin 1999)	Cohort study	195	no serious risk of bias	no serious inconsistenc y	no serious indirectne ss	no serious imprecisio n	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 report ed	HIGH	

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

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	Inconsist ency	Indirectn ess	Imprecisi on	Sensitivit y % (95% Cl)	Specific ity % (95% Cl)	Positiv e likeliho od ratio (95% Cl)	Negativ e Likeliho od ratio (95% Cl)	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 inconsiste ncy	no serious indirectne ss	serious imprecisio n ^b	70.6 (95% Cl: 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)	MODER ATE	
Test 6. APRI usi	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 inconsiste ncy	no serious indirectne ss	no serious imprecisio n	47.1 (95% Cl: 28.2- 56.7)*	93.1 (95% CI: 82.0- 98.7)*	6.82 (95% Cl: 1.57- 44.7)*	0.57 (95% CI: 0.44- 0.88)*	0.75 (95% CI: 0.58- 0.91)	HIGH	
Test 6. APRI usi	ng a cut of	ff of 0	.231 in a po	pulation of a	dults								
1 (Karlas 2012) ^c	Cohort study	55	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious imprecisio n ^b	85.7 (95% Cl: 60- 97.4)*	70.7 (95% CI: 62.0- 74.7)*	2.93 (95% Cl: 1.58- 3.86)*	0.20 (95% CI: 0.04- 0.65)*	0.82 (95% CI: 0.69- 0.91)	MODER ATE	
Test 6. APRI usi	ng a cut of	ff of 0	.4 in a popu	lation of adu	ults								
1(Sadler 2015) ^d	Cohort study	122	serious ^e	no serious inconsiste ncy	no serious indirectne ss	serious imprecisio n ^b	50 (95% CI: 29- 69)*	92 (95% Cl: 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	Inconsist ency	Indirectn ess	Imprecisi on	Sensitivit y % (95% CI)	Specific ity % (95% Cl)	Positiv e likeliho od ratio (95% Cl) 2.48- 13.50)*	Negativ e Likeliho od ratio (95% Cl) 0.33- 0.80)*	AUROC 0.54- 0.86)	Quality	
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 inconsiste ncy	no serious indirectne ss	serious imprecisio n ^b	50 (95% Cl: 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)⁰	Cohort study	55	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious imprecisio n ^b	92.9 (95% Cl: 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)	MODER ATE	
Test 17. Transie	nt elastog	raphy	using Fibro	scan at a cu	t off of 3.7kF	Pa in a popul	ation of adu	lts					
1(Sadler 2015) ^d	Cohort study	127	serious ^e	no serious inconsiste ncy	no serious indirectne ss	serious imprecisio n ^b	89 (95% Cl: 66- 98)*	37 (95% CI: 33- 38)*	1.40 (95% Cl: 0.98- 1.59)*	0.30 (95% CI: 0.05- 1.04)*	Not reported	LOW	
Test 17. Transie	nt elastog	raphy	using Fibro	scan at a cu	toff of 5.3kP	a in a popula	ation of adul	ts					
1(Sadler 2015) ^d	Cohort study	127	serious ^e	no serious inconsiste ncy	no serious indirectne ss	serious imprecisio n ^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	

 $\ensuremath{\textcircled{\sc online \sc on$

Number of studies (Reference)	Study design	N	Risk of bias	Inconsist ency	Indirectn ess	Imprecisi on	Sensitivit y % (95% CI)	Specific ity % (95% Cl)	Positiv e likeliho od ratio (95% Cl) 2.04- 5.87)*	Negativ e Likeliho od ratio (95% Cl)	AUROC	Quality
Test 17. Transie	nt elastog	raphy	using Fibro	scan at a cu	toff of 5.9kP	a in a popula	ation of adul	ts				
1 (Karlas 2012)⁰	Cohort study	49	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious imprecisio n ^b	42.9 (95% Cl: 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)	MODER ATE
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 inconsiste ncy	no serious indirectne ss	serious imprecisio n ^b	56 (95% Cl: 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. Transie	nt elastog	raphy	using Fibro	scan at a cu	toff of 6.3kP	a in a popula	ation of child	Iren and ad	ults			
1 (Rath 2013)ª	Cohort study	45	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	no serious imprecisio n	82.4 (95% Cl: 64.2- 85.3)*	98.2 (95% CI: 87.4- 100)*	46.9 (95% CI: 5.1- 254896 47)*	0.18 (95% CI: 0.15- 0.41)*	0.91 (95% CI: 0.78- 1.00)	HIGH
Test 17. Transie	nt elastog	raphy	using Fibro	scan at a cu	toff of 6.8kP	a in a popula	ation of adul	ts				
1 (Kitson 2013) ^f	Case Control study	50	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	no serious imprecisio n	76 (95% CI: 61.6- 82.5)*	92 (95% CI: 77.6- 98.5)*	9.5 (95% Cl:	0.26 (95% CI: 0.18- 0.50)*	0.87 (95% CI: 0.77- 0.98)	LOW

 $\ensuremath{\textcircled{\sc online \sc on$

Number of studies (Reference)	Study design	N	Risk of bias	Inconsist ency	Indirectn ess	Imprecisi on	Sensitivit y % (95% Cl)	Specific ity % (95% Cl)	Positiv e likeliho od ratio (95% Cl)	Negativ e Likeliho od 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, biochemica	I testing and/or ultrasound)	versus Biopsy CLFD
definitions† to detect CFLD		-	

Number of studies (Reference)	Study design	N	Risk of bias	Inconsist ency	Indirectn ess	Imprecisi on	Sensitivit y % (95% Cl)	Specific ity % (95% CI)	Positive likelihoo d ratio (95% Cl)	Negativ e Likeliho od ratio (95% Cl)	AUROC	Quality
Test 4 Oliviasia												

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	Inconsist ency	Indirectn ess	Imprecisi on	Sensitivit y % (95% Cl)	Specific ity % (95% Cl)	Positive likelihoo d ratio (95% Cl)	Negativ e Likeliho od ratio (95% Cl)	AUROC	Quality
1 (Lewindon 2011)	Cohort study	40	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	no serious imprecisio n	68 (95% Cl: 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 inconsiste ncy	no serious indirectne ss	serious imprecisio n°	30 (95% Cl: 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)	MODER ATE
Test 3. Liver fun and adults	ction tests	^d to de	etect mode	rate or sever	e fibrosis an	d cirrhosis a	and/or mode	rate to seve	ere steatosi	s in a popu	lation of c	hildren
1 (Lindblad 1999)	Cohort study	41	serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	no serious imprecisio n	83 (95% Cl: 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	MODER ATE
Test 3. Liver fun	ction tests	^d to de	etect mode	rate or sever	e fibrosis an	d cirrhosis i	n a populati	on of childr	en and adu	lts		
1 (Lindblad 1999)	Cohort study	41	serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious imprecisio n ^c	100 (95% CI: 78- 100)*	44 (95% Cl: 33- 44)*	1.8 (95% CI: 1.17- 1.8)*	0 (95% CI: 0- 0.67)*	not reported	LOW
Test 11. Ultrasou	und ^e to det	tect F1	-F4 fibrosis	s in a popula	tion of child	ren						
1 (Lewindon 2011)	Cohort study	40	no serious	no serious inconsiste ncy	no serious indirectne ss	no serious imprecisio n	81 (95% CI: 73- 89)*	44 (95% Cl: 17- 73)*	1.45 (95% CI:	0.44 (95% CI:	0.63 (95% CI: not	HIGH

 $\ensuremath{\textcircled{\sc online \sc on$

Number of studies (Reference)	Study design	N	Risk of bias	Inconsist ency	Indirectn ess	Imprecisi on	Sensitivit y % (95% CI)	Specific ity % (95% Cl)	Positive likelihoo d ratio (95% Cl)	Negativ e Likeliho od ratio (95% Cl) 0.15	AUROC	Quality
			bias						3.3)*	1.64)*)	
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 inconsiste ncy	no serious indirectne ss	no serious imprecisio n	65 (95% Cl: 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 ⁹ 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 inconsiste ncy	no serious indirectne ss	no serious imprecisio n	70 (95% Cl: 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	MODER ATE
Test 11. Ultraso	und ^g t dete	ect mo	derate or se	evere fibrosis	s and cirrho	sis in a popu	lation of chi	ldren and a	dults			
1 (Lindblad 1999)	Cohort study	41	serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious imprecisio n ^c	86 (95% Cl: 61- 97)*	70 (95% CI: 58- 76)*	2.9 (95% Cl: 1.45- 4.13)*	0.2 (95% CI: 0.03- 0.67)*	not reported	LOW
Test 19. Liver fu population of ch	nction tes ildren and	ts ^d and I adults	t ultrasoun s	d ^f to detect m	noderate or s	severe fibros	is and cirrh	osis and/or	moderate t	o severe s	teatosis in	a
1 (Lindblad 1999)	Cohort study	41	serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	no serious imprecisio n	65 (95% CI: 50- 76)*	78 (95% Cl: 58- 92)*	2.94 (95% CI:	0.45 (95% Cl:	not reported	MODER ATE

 $\ensuremath{\textcircled{\sc online \sc on$

Number of studies (Reference)	Study design	N	Risk of bias	Inconsist ency	Indirectn ess	Imprecisi on	Sensitivit y % (95% CI)	Specific ity % (95% CI)	Positive likelihoo d ratio (95% CI) 1.18-	Negativ e Likeliho od ratio (95% CI) 0.26-	AUROC	Quality
									9.1)*	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 inconsiste ncy	no serious indirectne ss	serious imprecisio n ^c	86 (95% CI: 62- 97)*	74 (95% Cl: 62- 80)*	3.31 (95% CI: 1.6-4.9)*	0.19 (95% CI: 0.03- 0.63)*	not reported	LOW
Test 20. Clinical	examinati	onª, li	ver functio	n tests ^b and	ultrasound ^e	to detect F1	-F4 fibrosis i	n a populat	tion of child	ren		
1 (Lewindon 2011)	Cohort study	40	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	no serious imprecisio n	97 (95% Cl: 85- 100)*	13 (95% Cl: 4- 15)*	1.12 (95% CI: 0.89- 1.18)*	0.22 (95% Cl: 0- 3.6)*	0.69 (95% CI: not reported)	HIGH
Test 20. Clinical	examinati	onª, li	ver functio	n tests ^b and	ultrasound ^e	to detect F2	-F4 significa	nt fibrosis i	n a populat	ion of chile	dren	
1 (Lewindon 2011)	Cohort study	40	no serious risk of bias	no serious inconsiste ncy	no serious indirectne ss	serious imprecisio n°	82 (95% Cl: 62- 95)*	48 (95% Cl: 33- 57)*	1.58 (95% Cl: 0.93- 2.22)*	0.37 (95% CI: 0.09- 1.15)*	0.68 (95% CI: not reported)	MODER ATE

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 desig n	N	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Sensitivit y % (95% CI)	Specificit y % (95% Cl)	Positive likelihoo d ratio (95% Cl)	Negative Likeliho od ratio (95% Cl)	AUROC	Quality
Test 12. Transie	nt elastog	grap	hy to detect	F2-F4 ^ª in a p	opulation of	adults						
1 (Lemaitre 2016)	Cohort study	2 3	serious risk of bias ^ь	no serious inconsisten cy	no serious indirectne ss	very serious imprecisio n ^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 d	detect at I	least	1 abnormal	l sign ^d in a po	pulation of	adults						
1 (Lemaitre 2016)	Cohort study	2 3	serious risk of bias ^b	no serious inconsisten cy	no serious indirectne ss	very serious imprecisio n ^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	MODER ATE

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 desig n	N	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Sensitivit y % (95% Cl)	Specificit y % (95% Cl)	Positive likelihoo d ratio (95% CI)	Negative Likeliho od ratio (95% CI)	AUROC	Quality
Test 1. APRI usi	ng a cut	off o	f 0.344 in a	population of	f adults with	CFLD						
1 (Karlas 2012)	Cohort study	1 4	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	very serious imprecisio n ^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 so	ore usin	aad	ut off of 4.0	59 in a popul	ation of adu	Its with CFL	D					
1 (Karlas 2012)	Cohort study	1 4	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	very serious imprecisio n ^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. Transien	t elastog	raph	y using a cu	ut off of 4.4kP	a in a popul	ation of adu	Its with CFL	.D				
1 (Karlas 2012)	Cohort study	1 4	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	very serious imprecisio n ^a	92.3 (95% CI: 56.2- 100)*	75 (95% Cl: 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)

Number of studies (Reference)	Study desig n	N	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Sensitivit y % (95% Cl)	Specificity % (95% Cl)	Positiv e likeliho od ratio (95% Cl)	Negativ e Likeliho od ratio (95% CI)	AUROC	Quality
Test 3. Ultrasou	nd ^a to de	tect	F1-F4 fibros	is in a popula	tion of child	dren						
1 (Mueller-Abt 2008)	Cohort study	3 0	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	serious imprecisio n ^b	0.57 (95% Cl: 0.36- 0.64)*	0.94 (95% Cl: 0.75- 1.00)*	9.14 (95% CI: 1.47- 192.8)*	0.46 (95% CI: 0.36- 0.85)*	Not reported	MODER ATE

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

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)

Target condition: portal hypertension J.16.1.3

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 desig n	N	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Sensitivit y % (95% CI)	Specificit y % (95% Cl)	Positive likelihoo d ratio (95% Cl)	Negative Likelihoo d ratio (95% Cl)	AUROC	Quality
Test 1. APRI at a	a cut off	of ≥	0.49 in a po	pulation of a	dults							
1(Kitson 2013)	Case control study	5 0	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	no serious imprecisio n	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 desig n	N	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Sensitivit y % (95% CI)	Specificit y % (95% CI)	Positive likelihoo d ratio (95% CI)	Negative Likelihoo d ratio (95% CI)	AUROC	Quality
Test 1. Subgrou	p analysi	is: Al	PRI at a cut	off of ≥ 0.49 ir	n a populatio	on of adults	with CFLD					
1(Kitson 2013)	Case control study	2 5	no serious risk of bias of bias	no serious inconsisten cy	no serious indirectne ss	no serious imprecisio n	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	ⁱ of ≥	0.68 in a po	pulation of a	dults							
1(Kitson 2013)	Case control study	5 0	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	no serious imprecisio n	87.5 (95% Cl: 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. Subgrou	p analysi	is: Fo	orn's score a	at a cut off of	≥ 0.68 in a p	opulation of	f adults with	CFLD				
1(Kitson 2013)	Case control study	2 5	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	no serious imprecisio n	87.5 (95% Cl: 53.2- 99.3)*	82.4 (95% CI: 66.2- 87.9)*	5.0 (95% Cl: 1.6- 8.2)*	0.15 (95% CI: 0.01- 0.71)*	0.93 (95% CI: 0.82- 1.00)	LOW
Test 3. Transien	t elastog	raph	y at a cut of	f of ≥ 8.9 kPa	in a populat	ion of adult	S					
1(Kitson 2013)	Case control study	5 0	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	no serious imprecisio n	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. Subgrou	p analysi	is: Tr	ransient elas	stography at a	n cut off of ≥	8.9 kPa in a	population	of adults wi	ith CFLD			

Number of studies (Reference)	Study desig n	N	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Sensitivit y % (95% CI)	Specificit y % (95% Cl)	Positive likelihoo d ratio (95% Cl)	Negative Likelihoo d ratio (95% Cl)	AUROC	Quality
1(Kitson 2013)	Case control study	2 5	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	no serious imprecisio n	87.5 (95% CI: 52.9- 99.3)*	76.5 (95% CI: 60.2- 82.0)*	3.7 (95% Cl: 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 imag	ing defined portal hypertension †
--	------------------------------	--------------------------	-----------------------------	-----------------------------------

Number of studies (Reference)	Stud y desi gn	N	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Sensitivit y % (95% Cl)	Specificit y % (95% Cl)	Positive likelihoo d ratio (95% Cl)	Negative Likelihoo d ratio (95% Cl)	AUROC	Quality
Transient elastog	raphy a	tac	ut off of 11.	5 kPA in an ac	dult populati	ion						
1(Rath 2012)	Coho rt study	7 0	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	no serious imprecisio n	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 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). 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 desig n	N	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Sensitivit y % (95% CI)	Specificit y % (95% CI)	Positive likelihoo d ratio (95% Cl)	Negative Likelihoo d ratio (95% Cl)	AUROC	Quality
Test 1. APRI usi	ing a cut	off o	of ≥ 0.49 in a	population of	f adults			_				
1(Kitson 2013)	Case control study	2 3	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	no serious imprecisio n	100 (95% CI: 60.0- 100)*	94.1(95% CI: 80.0- 94.1)*	17.0 (95% Cl: 3.0-17.0)*	0 (95% CI: 0- 0.50)*	0.99 (95% Cl: 0.96- 1.00)	LOW
Test 1. Subgrou	p analysi	is: A	PRI using a	cut off of ≥ 0 .	49 in a popu	lation of ad	ults with CF	LD				
1(Kitson 2013)	Case control study	1 3	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	serious imprecisio n ^a	100 (95% Cl: 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 s	core usin	ga	cut off of ≥ 0	.68 in a popul	lation of adu	ılts						
1(Kitson 2013)	Case control study	2 3	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	no serious imprecisio n	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% Cl: 0.93- 1.00)	LOW
Test 2. Subgrou	ıp analysı	is: F	orn's score	using a cut of	ff of ≥ 0.68 ir	n a populatio	on of adults	with CFLD				
1(Kitson 2013)	Case control study	1 3	no serious	no serious inconsisten cy	no serious	very serious	100 (95% CI: 62.9- 100)*	85.7 (95% CI:	7.0 (95% Cl: 1.37- 7.0)*	0 (95% Cl: 0- 0.69)*	0.98 (95% CI:	VERY LOW

Number of studies (Reference)	Study desig n	N	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Sensitivit y % (95% CI)	Specificit y % (95% Cl)	Positive likelihoo d ratio (95% Cl)	Negative Likelihoo d ratio (95% Cl)	AUROC	Quality
			risk of bias		indirectne ss	imprecisio n ^a		53.9- 85.7)*			0.91- 1.00)	
Test 3. Transien	t elastog	raph	y using a cu	It off of ≥ 8.9 I	kPa in a pop	ulation of a	dults					
1(Kitson 2013)	Case control study	2 3	no serious risk of bias	no serious inconsisten cy	no serious indirectne ss	no serious imprecisio n ^a	100 (95% Cl: 57.8- 100)*	76.5 (95% CI: 61.6- 76.5)*	4.25 (95% CI: 1.51- 4.25)*	0 (95% Cl: 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 (transi	ient elastography and b	iopsy) for prognosis of CFLI	D and portal hypertension

Index Prognostic factors	Included studies	Study design	Setting	N	Adjusted OR/HRs	Quality	Notes
CFLD (includes cir	rhosis)						
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 Hypertensio	on						
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,

 $\ensuremath{\textcircled{\sc online 0.5ex}}$ NICE 2017. All rights reserved. Subject to Notice of rights.

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 e	evidence profile:	Comparison 1	. UDCA versus	placebo or control
----------------------	-------------------	--------------	---------------	--------------------

Quality assessment								patients	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideration s	UDC A	Placebo/contr ol	Relati ve (95% Cl)	Absolu te	Quality	Importan ce
Lack c	of normalisat	tion of AS	ST (follow-up (6 months)								
2 (Merl i 1994 , O'Bri en	randomis ed trials ¹	no seriou s risk of bias	no serious inconsistenc y	no serious indirectne ss	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	MODERAT E	CRITICA L

Quality assessment Inconsisten cy Indirectne ss Imprecisi on Other consideration							No of patientsUDC APlacebo/contr ol		Effect Relati Absolu ve te			
es						S			(95% CI)		Quality	Importan ce
1992)										1000 more)	Ē	
								75%		382 more per 1000 (from 128 fewer to 1000 more)		
Lack c	of normalisa	tion of AL	T (follow-up 6	6 months)								
2 (Merl i 1994 , O'Bri en 1992)	randomis ed trials ¹	no seriou s risk of bias	no serious inconsistenc y	no serious indirectne ss	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)	MODERAT E	CRITICA L
								83.3%		258 fewer per 1000 (from 608 fewer to 616 more)		

Quality No of studi es	/ assessme i Design	nt Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideration s	No of p UDC A	oatients Placebo/contr ol	Effect Relati ve (95% CI)	Absolu te	Quality	Importan ce
Lack o	of normalisat	tion of G	GT (follow-up	6 months)								
2 (Merl i 1994 , O'Bri en 1992)	randomis ed trials1	no seriou s risk of bias	no serious inconsistenc y	no serious indirectne ss	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	CRITICA L
								33.3%		133 fewer per 1000 (from 280 fewer to 430 more)		
Final b	oilirubin valu	ie (umol/l	l) (follow-up 6	months; Bet	ter indicated	l by lower value	es)					
1 (O'Br ien 1992)	randomis ed trials	no seriou s risk of bias	no serious inconsistenc y	no serious indirectne ss	very serious ³	none	6	6	-	MD 4 higher (3.72 lower to 11.72 higher)	LOW	CRITICA L
Percer	ntage chang	e in AST	(follow-up 12)	months: Bett	er indicated	by lower value	es)					

Quality	Quality assessment							oatients	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideration s	UDC A	Placebo/contr ol	Relati ve (95% CI)	Absolu te	Quality	Importan ce
1 (Colo mbo 1996)	randomis ed trials	seriou s ⁷	no serious inconsistenc y	no serious indirectne ss	serious ²	none	15	12	-	MD - 14 (- 39.93 to 11.93)	LOW	CRITICA L
Percer	ntage chang	e in ALT	(follow-up 12 ເ	months; Bett	er indicated	by lower value	es)					
1 (Colo mbo 1996)	randomis ed trials	seriou s ⁴	no serious inconsistenc y	no serious indirectne ss	serious ²	none	15	12	-	MD - 13 (- 29.35 to 3.35)	LOW	CRITICA L
Percer	ntage chang	e in GGT	(follow-up 12	months; Bet	ter indicated	d by lower valu	es)	-				
1 (Colo mbo 1996)	randomis ed trials	seriou s ⁴	no serious inconsistenc y	no serious indirectne ss	serious ²	none	15	12	-	MD - 11.00 (-36.74 to 14.74)	LOW	
No dev	elopment o	f liver dis	ease (follow-u	ip 6 months)								
1 (Merl i 1994)	randomis ed trials1	no seriou s risk of bias	no serious inconsistenc y	no serious indirectne ss	no serious imprecisio n	none	11/11 (100 %)	11/11 (100%)	Not calcul able⁵	-	HIGH	CRITICA L
Liver f	ailure (jauno	dice) (foll	ow-up 12 mon	ths)								
1 (Colo mbo 1996)	randomis ed trials	seriou s ⁴	no serious inconsistenc y	no serious indirectne ss	no serious imprecisio n	none	1/15	0/13	RR 2.62 (0.12 to 59.40)	Not calcula ble ⁶	MODERAT E	CRITICA L

Quality	y assessme	nt					No of p	oatients	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideration s	UDC A	Placebo/contr ol	Relati ve (95% CI)	Absolu te	Quality	Importan ce
Liver t	ransplantati	on (follo	w-up 12 month	is)								
1 (Colo mbo 1996)	randomis ed trials	seriou s ⁴	no serious inconsistenc y	no serious indirectne ss	Not applicable		15 1 patien t in the treat ment group was withdr awn to receiv e transp lantati on	13	Not applic able	Not applica ble	MODERAT	CRITICA

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

т,	able 92 Clinical avidence profile. Comparison 1	Acrobic eversion training programme		
Ič	able 62: Chinical evidence profile: Comparison 1.	Aerobic exercise training programme	versus no exercise program	nme

Qualit	y assessmen	it					No of patie	nts	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Aerobic exercise training programm e	No exercise program me	Relati ve (95% CI)	Absol ute	Quality	Importance
Chang by hig	je in FEV₁ % her values)	predicte	d at hospital d	lischarge - S	Supervised	orogramme (fo	llow-up mea	n 18.7 days	; range (of scores	s: 0-100; Bett	er indicated
1 (Selv adur ai 2002)	randomise d trials	seriou s ¹	no serious inconsisten cy	no serious indirectne ss	serious ²	none	22	22	-	MD 2.03 higher (2.31 lower to 6.37 higher)	LOW	CRITICAL
Chang	ge in FEV ₁ %	predicte	d - Unsupervis	sed program	me (follow-	up 3 months;	range of sco	res: 0-100;	Better in	dicated	by higher val	ues)
2 (Ho mme rding 2015 , Krie	randomise d trials	very seriou s ³	very serious ⁴	no serious indirectne ss	very serious ⁵	none	31	27	-	MD 5.23 higher (10.06 lower to 20.52	VERY LOW	CRITICAL

Qualit	y assessmen	t					No of patie	nts	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Aerobic exercise training programm e	No exercise program me	Relati ve (95% Cl)	Absol ute	Quality	Importance
mler 2013)										higher)		
Chang	e in FEV ₁ %	predicted	d - Unsupervis	sed program	me (follow-	up 6 months; r	ange of sco	res: 0-100;	Better in	dicated I	oy higher val	ues)
1 (Krie mler 2013)	randomise d trials	very seriou s ⁶	no serious inconsisten cy	no serious indirectne ss	no serious imprecisi on	none	15	10	-	MD 17.17 higher (8.59 to 25.75 higher)	LOW	CRITICAL
Chang	e in FEV ₁ %	predicted	d - Unsupervis	sed program	me (follow-	up 3 years; rar	nge of score	s: 0-100; Be	etter indi	cated by	higher value	s)
1 (Sch neid erma n- Walk er 2000)	randomise d trials	seriou s ⁷	no serious inconsisten cy	no serious indirectne ss	no serious imprecisi on	none	30	35	-	MD 2.01 higher (0.06 lower to 4.08 higher)	MODERA TE	CRITICAL
Chang by hig	je in FVC % p her values)	predicted	at hospital di	ischarge - Si	upervised p	rogramme (fol	low-up meai	n 18.7 days	; range o	of scores:	: 0-100; Bette	er indicated
1 (Selv adur ai	randomise d trials	seriou s ¹	no serious inconsisten cy	no serious indirectne ss	very serious ⁸	none	22	22	-	MD 0.06 higher (2.55 lower to	VERY LOW	IMPORTANT

Qualit	y assessmer	nt					No of patie	nts	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Aerobic exercise training programm e	No exercise program me	Relati ve (95% CI)	Absol ute	Quality	Importance
2002)										2.67 higher)		
Chang	je in FVC % p	oredicted	- Unsupervis	ed program	me (follow-	up 3 months; r	ange of scor	es: 0-100; I	Better in	dicated b	y higher valu	ues)
2 (Ho mme rding 2015 , Krie mler 2013)	randomise d trials	very seriou s ³	very serious ⁹	no serious indirectne ss	very serious ⁸	none	31	27	-	MD 3.99 higher (6.62 lower to 14.61 higher)	VERY LOW	IMPORTANT
Chang	je in FVC % p	oredicted	- Unsupervis	ed program	me (follow-	up 6 months; r	ange of scor	es: 0-100; I	Better in	dicated b	y higher valu	les)
1 (Krie mler 2013)	randomise d trials	very seriou s ⁶	no serious inconsisten cy	no serious indirectne ss	no serious imprecisi on	none	15	10	-	MD 12.51 higher (5.9 to 19.12 higher)	LOW	IMPORTANT
Chang	je in FVC % p	oredicted	- Unsupervis	ed program	me (follow-i	up 3 years; ran	ige of scores	s: 0-100; Be	tter indi	cated by	higher value	s)
1 (Sch neid erma n- Walk er	randomise d trials	seriou s ⁷	no serious inconsisten cy	no serious indirectne ss	serious ¹⁰	none	30	35	-	MD 2.17 higher (0.47 to 3.87	LOW	IMPORTANT

Qualit	y assessmen	ıt					No of patie	ents	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Aerobic exercise training programm e	No exercise program me	Relati ve (95% Cl)	Absol ute	Quality	Importance
2000)										higher)		
Chang values	<mark>je in FEV</mark> ₁ pe s)	ak - Unsi	upervised pro	gramme (fol	low-up 3 m	onths; measur	ed with: ml/ı	min per kg l	oody wei	ght; Bett	er indicated	by higher
2 (Ho mme rding 2015 , Krie mler 2013)	randomise d trials	very seriou s ¹¹	very serious ¹²	no serious indirectne ss	very serious ⁸	none	32	27	-	MD 3.76 higher (6.89 lower to 14.41 higher)	VERY LOW	IMPORTANT
Chang values	ge in FEV₁ pe s)	ak - Unsi	upervised pro	gramme (fol	low-up 6 m	onths; measur	ed with: ml/ı	min per kg l	oody we	ght; Bett	er indicated	by higher
1 (Krie mler 2013)	randomise d trials	very seriou s ⁶	no serious inconsisten cy	no serious indirectne ss	no serious imprecisi on	none	15	10	-	MD 18.33 higher (8.95 to 27.71 higher)	LOW	IMPORTANT
Chang Better	ge in FEV₁ pe r indicated by	ak at hos higher v	spital discharg values)	ge - Supervis	sed program	nme (follow-up	mean 18.7 (days; meas	ured wit	h: ml/min	per kg body	vweight;
1 (Selv adur ai	randomise d trials	seriou s ¹	no serious inconsisten cy	no serious indirectne ss	no serious	none	22	22	-	MD 8.53 higher (4.85	MODERA TE	IMPORTANT

Qualit							No. of working		E fferet			
No of studi es	y assessmer Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Aerobic exercise training programm e	No exercise program me	Relati ve (95% CI)	Absol ute	Quality	Importance
2002)					imprecisi on					to 12.21 higher)		
Time t	o next exace	rbation										
No evi	dence availab	le										
Chang	ge in BMI - <i>Ui</i>	nsupervis	sed programn	ne (follow-up	o 3 months;	measured with	h: <mark>kg/m2; Be</mark>	tter indicate	ed by hig	gher valu	es)	
1 (Krie mler 2013)	randomise d trials	very seriou s ⁶	no serious inconsisten cy	no serious indirectne ss	serious ¹⁰	none	15	10	-	MD 0.3 higher (0.13 lower to 0.73 higher)	VERY LOW	IMPORTANT
Chang	ge in BMI - <i>Ui</i>	nsupervis	sed programn	ne (follow-up	6 months;	Better indicate	ed by higher	values)				
1 (Krie mler 2013)	randomise d trials	very seriou s ⁶	no serious inconsisten cy	no serious indirectne ss	serious ¹⁰	none	15	10	-	MD 0.4 higher (0 to 0.8 higher)	VERY LOW	IMPORTANT
Chang	ge in BMI - Sι	ipervised	d programme									
No evi	dence availab	le										
Qualit	y of life											
No evi	dence availab	le										

Qualit	y assessmen	t					No of patie	nts	Effect			
No of studi es	Design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns	Aerobic exercise training programm	No exercise program me	Relati ve (95% CI)	Absol ute	Quality	Importance
Prefer	ence for train	ning prog	ramme				0				Quality	importanoo

No evidence available

Adverse events

No evidence available

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; kg: kilogrammes MD: mean difference; min: minute; ml: millilitres; FEV₁ 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 FEV₁ 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	y assessment						No of patie	nts	Effect	1	-	
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Strength resistance/ anaerobic training programm e	No exercise programm e	Relati ve (95% CI)	Absolu te	Qual ity	Importance
Chang by hig	le in FEV₁ % p her values)	oredicted	at hospital dis	charge - Sup	ervised pro	gramme (follow	up mean 18	.7 days; ran	ge of sco	ores: 0-10	0; Bette	r indicated
1 (Selv adur ai 2002)	randomised trials	seriou s ¹	no serious inconsistenc y	no serious indirectnes s	serious ²	none	22	22	-	MD 5.58 higher (1.34 to 9.82 higher)	LOW	CRITICAL
Chang	<mark>e in FEV</mark> ₁ % p	redicted	- Unsupervise	d programme	e (follow-up	3 months; rang	e of scores:	0-100; Bette	r indicate	ed by higl	ner valu	es)
1 (Krie mler 2013)	randomised trials	very seriou s ³	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	11	10	-	MD 11.11 higher (5.16 to 17.06 higher)	LOW	CRITICAL
Chang	e in FEV₁ % p	redicted	- Unsupervise	d programme	e (follow-up	6 months; rang	e of scores:	0-100; Bette	r indicate	ed by higl	her valu	es)
1 (Krie mler 2013)	randomised trials	very seriou s ³	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	11	10	-	MD 19.51 higher (10.57 to 28.45 higher)	LOW	CRITICAL

Quality	y assessment						No of patier	nts	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Strength resistance/ anaerobic training programm e	No exercise programm e	Relati ve (95% CI)	Absolu te	Qual ity	Importance
Chang by hig	e in FVC % pr her values)	edicted a	t hospital disc	harge - Supe	ervised prog	ramme (follow-	up mean 18.7	/ days; rang	e of scor	es: 0-100	; Better	indicated
1 (Selv adur ai 2002)	randomised trials	seriou s ¹	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	22	22	-	MD 0.17 higher (2.31 lower to 2.65 higher)	VER Y LOW	IMPORTAN T
Chang	e in FVC % pr	edicted -	Unsupervised	l programme	(follow-up 3	months; range	e of scores: 0	-100; Better	indicate	d by high	er value	es)
1 (Krie mler 2013)	randomised trials	very seriou s ³	no serious inconsistenc y	no serious indirectnes s	serious ⁵	none	11	10	-	MD 7.37 higher (1.89 to 12.85 higher)	VER Y LOW	IMPORTAN T
Chang	e in FVC % pr	edicted -	Unsupervised	l programme	(follow-up 6	months; range	e of scores: 0	-100; Better	indicate	d by high	er value	es)
1 (Krie mler 2013)	randomised trials	very seriou s ³	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	11	10	-	MD 14.05 higher (7.16 to 20.94 higher)	LOW	IMPORTAN T
Chang Better	e in FEV₁ pea indicated by	k at hosp higher va	ital discharge lues)	- Supervised	l programme	e (follow-up mea	an 18.7 days;	measured v	vith: ml/r	nin per ko	g body v	weight;

Quality	v assessment						No of patier	nts	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Strength resistance/ anaerobic training programm e	No exercise programm e	Relati ve (95% CI)	Absolu te	Qual ity	Importance
1 (Selv adur ai 2002)	randomised trials	seriou s ¹	no serious inconsistenc y	no serious indirectnes s	serious⁵	none	22	22	-	MD 1.95 higher (1.61 lower to 5.51 higher)	LOW	IMPORTAN T
Chang body v	e in FEV₁ pea veight; Better	k – Poole indicated	ed results from I by higher val	<i>both superv</i> ues)	ised and un	supervised pro	grammes (fo	ollow-up 3 m	onths; m	easured	with: m	l/min per kg
2 (Krie mler 2013, Klijn 2004)	randomised trials	very seriou s ⁶	no serious inconsistenc y	no serious indirectnes s	serious ⁵	none	22	19	-	MD 6.36 higher (1.22 to 11.49 higher)	VER Y LOW	IMPORTAN T
Chang values	e in FEV₁ pea)	k - Unsup	pervised progr	amme (follov	v-up 3 montl	ns; measured w	vith: ml/min p	er kg body v	weight; B	letter indi	cated b	y higher
1 (Krie mler 2013)	randomised trials	very seriou s ³	no serious inconsistenc y	no serious indirectnes s	serious⁵	none	11	10	-	MD 9.34 higher (1.66 to 17.02 higher)	VER Y LOW	IMPORTAN T
Chang values	e in FEV₁ pea)	k - Super	vised program	ime (follow-u	p 3 months;	measured with	n: ml/min per	kg body wei	ight; Bett	ter indica	ted by h	nigher

Quality	/ assessment						No of patie	nts	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Strength resistance/ anaerobic training programm e	No exercise programm e	Relati ve (95% CI)	Absolu te	Qual ity	Importance
1 (Klijn 2004)	randomised trials	seriou s ⁷	no serious inconsistenc y	no serious indirectnes s	serious⁵	none	11	9	-	MD 3.95 higher (2.95 lower to 10.85 higher)	LOW	IMPORTAN T
Chang values	e in FEV₁ pea)	k - Unsup	pervised progr	amme (follov	v-up 6 montl	hs; measured w	ith: ml/min p	er kg body v	weight; E	Better indi	cated b	y higher
1 (Krie mler 2013)	randomised trials	very seriou s ³	no serious inconsistenc y	no serious indirectnes s	serious⁵	none	8	10	-	MD 17.7 higher (5.98 to 29.42 higher)	VER Y LOW	IMPORTAN T
Time t	o next exacer	bation										
No evi	dence available	Э										
Chang	e in BMI - Uns	supervise	d programme	(follow-up 3	months; Bet	tter indicated by	y higher valu	es)				
1 (Krie mler 2013)	randomised trials	very seriou s ³	no serious inconsistenc y	no serious indirectnes s	serious ⁵	none	15	10	-	MD 0.5 higher (0.07 to 0.93 higher)	VER Y LOW	IMPORTAN T
Chang	e in BMI - Uns	supervise	d programme	(follow-up 6	months; Bet	tter indicated by	y higher valu	es)				

Quality	y assessment						No of patier	nts	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Strength resistance/ anaerobic training programm e	No exercise programm e	Relati ve (95% CI)	Absolu te	Qual ity	Importance
1 (Krie mler 2013)	randomised trials	very seriou s ³	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	15	10	-	MD 0.7 higher (0.27 to 1.13 higher)	LOW	IMPORTAN T
Chang	e in BMI - Suj	pervised	programme									
No evi	dence available	е										
Chang	e in quality of	f life - Un	supervised pro	ogramme								
No evi	dence available	е										
Chang Better	e in quality of indicated by	f life - <i>Suj</i> higher va	pervised progr lues)	amme (follov	v-up 3 mont	hs; measured w	vith: CFQ - pl	nysical funct	tion dom	ain; rango	e of sco	res: 0-100;
1 (Klijn 2004)	randomised trials	very seriou s ³	no serious inconsistenc y	no serious indirectnes s	very serious ⁸	none	11	9	-	MD 1.3 higher (11.55 lower to 14.15 higher)	VER Y LOW	CRITICAL
Prefer	ence for train	ing progr	amme									
No evi	dence available	e										
Advers	se events											
No evi	dence available	ρ										

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; FEV₁: 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 patien	ts	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Strength/ anaerobic training	Aerob ic trainin g	Relativ e (95% CI)	Absolut e	Quali ty	Importance
Chang by hig	e in FEV₁ % p her values)	redicted a	at hospital disc	harge - <i>Sup</i> e	rvised progi	ramme (Follow-	up: mean 18.7	′ days; ra	ange of s	cores: 0-1	00; Bett	er indicated
1 (Selv adura i 2002)	randomised trials	serious 1	no serious inconsistenc y	no serious indirectnes s	serious ²	none	22	22	-	MD 3.55 higher (0.94 lower to 8.04 higher)	LOW	CRITICAL
Chang	e in FEV₁ % pı	redicted -	Unsupervised	programme	(Follow-up: 3	3 months; range	e of scores: 0-	-100; Bet	ter indica	ated by hig	gher val	ues)
1 (Krie mler 2013)	randomised trials	very serious ³	no serious inconsistenc y	no serious indirectnes s	serious ²	none	11	14	-	MD 1.7 lower (7.67 lower to 4.27 higher)	VER Y LOW	CRITICAL
Chang	e in FEV ₁ % p	redicted-	Unsupervised	programme	(Follow-up: (6 months; range	e of scores: 0	-100; Bet	ter indic	ated by hig	gher val	ues)

Quality No of studi es 1 (Krie mler 2013)	/ assessment Design randomised trials	Risk of bias very serious 3	Inconsistenc y no serious inconsistenc y	Indirectnes s no serious indirectnes s	Imprecisio n very serious ⁴	Other consideration s none	No of patien Strength/ anaerobic training 11	ts Aerob ic trainin g 15	Effect Relativ e (95% CI)	Absolut e MD 2.34 higher (6.33 lower to	Quali ty VER Y LOW	Importance CRITICAL
Chang			Currentiand					O. Detter	. in dia ata	11.01 higher)		
1 (Oren stein 2004)	randomised trials	very serious 5	no serious inconsistenc y	ogramme (Fo no serious indirectnes s	very serious ⁴	none	30	26	-	MD 1.66 lower (11.24 lower to 7.92 higher)	VER Y LOW	s) CRITICAL
Chang higher	e in FEV₁ % pı values)	redicted-	Pooled results	for supervis	ed and unsu	<i>pervised</i> (Follo	w-up: 6 mont	hs; rang	e of scor	es: 0-100;	Better i	ndicated by
2 (Krie mler 2013, Oren stein 2004)	randomised trials	very serious 6	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	41	41	-	MD 0.54 higher (5.89 lower to 6.97 higher)	VER Y LOW	CRITICAL
Chang	e in FEV ₁ % pi	redicted -	Supervised pr	ogramme (Fo	llow-up: 12	months; range	of scores: 0-1	00; Bette	er indicat	ed by higl	ner valu	es)
1 (Oren stein 2004)	randomised trials	very serious 5	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	28	25	-	MD 0.3 higher (9.21 lower to	VER Y LOW	CRITICAL

1 (Selv adura irandomised trialsserious 1no serious inconsistenc yno serious sno serious svery serious?none2222-MD (1VER YIMPO T2002)111	Quality No of studi es Change	e in FVC % pro	Risk of bias	Inconsistenc y Supervised pro	Indirectnes s ogramme (Fo	Imprecisio n Ilow-up: at h	Other consideration s ospital discharg	No of patien Strength/ anaerobic training	ts Aerob ic trainin g	Effect Relativ e (95% CI)	Absolut e 9.81 higher) cores: 0-1	Quali ty 00; Bett	Importance er indicated
Change in FVC % predicted - Unsupervised programme (Follow-up: 3 months; range of scores: 0-100; Better indicated by higher values1randomised trialsvery seriousno serious indirectnesno serious indirectnesSerious ⁸ none1114-MDVER 1.87IMPO T iower LOWIMPO T T2013)3serious ssserious sserious sSerious ⁸ none1114-MDVER SIMPO T iower (7.33 lower to 3.59 higher)IMPO TChange in FVC % predicted - Unsupervised programme (Follow-up: 6 months; range of scores: 0-100; Better indicated by higher)1 (Krie mler 2013)randomised trialsVery seriousno serious indirectnes sNo serious serious ³ None1115-MD ND LOW 1.54 Y Y YMPO T T2013)very seriousno serious sNo serious sNone1115-MD LOW LOW LOWVER T T T T	1 (Selv adura i 2002)	randomised trials	serious 1	no serious inconsistenc y	no serious indirectnes s	very serious ⁷	none	22	22	-	MD 0.11 higher (2.49 lower to 2.71 higher)	VER Y LOW	IMPORTAN T
(Krie mler 2013)trials 3serious yinconsistenc yindirectnes sindirectnes 	Change 1	e in FVC % pro	edicted -	Unsupervised no serious	programme (no serious	Follow-up: 3 Serious ⁸	months; range	of scores: 0- 11	100; Bet 14	ter indica	i ted by hig MD	her valı VER	Jes) IMPORTAN
Change in FVC % predicted - Unsupervised programme (Follow-up: 6 months; range of scores: 0-100; Better indicated by higher values)1randomised trialsvery seriousno serious inconsistenc yno serious seriousvery seriousnone1115-MD trialsVER trialsIMPO T LOW2013)3very seriousno serious svery seriousnone1115-MD trialsVER to the programmeIMPO T to the programme	(Krie mler 2013)	trials	serious 3	inconsistenc y	indirectnes s						1.87 lower (7.33 lower to 3.59 higher)	Y LOW	Т
1randomised (Krie mler 2013)very serious ano serious inconsistenc yno serious serious svery serious serious ano no e1115-MD yVER TIMPO T103ysserious serious sserious serious sserious serious to serious1115-MD to serious to serious to seriousVER to serious to seriousIMPO to serious10 <t< td=""><td>Change</td><td>e in FVC % pro</td><td>edicted -</td><td>Unsupervised</td><td>programme (</td><td>Follow-up: 6</td><td>months; range</td><td>of scores: 0-</td><td>100; Bet</td><td>ter indica</td><td>ted by hig</td><td>her valu</td><td>les)</td></t<>	Change	e in FVC % pro	edicted -	Unsupervised	programme (Follow-up: 6	months; range	of scores: 0-	100; Bet	ter indica	ted by hig	her valu	les)
8.2 higher)	1 (Krie mler 2013)	randomised trials	very serious 3	no serious inconsistenc y	no serious indirectnes s	very serious ⁷	none	11	15	-	MD 1.54 higher (5.12 lower to 8.2 higher)	VER Y LOW	IMPORTAN T

Quality No of studi es	zassessment Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	No of patien Strength/ anaerobic training	ts Aerob ic trainin g	Effect Relativ e (95% CI)	Absolut e	Quali ty	Importance
1 (Selv adura i 2002	randomised trials	serious 1	no serious inconsistenc y	no serious indirectnes s	serious ⁸	none	22	22	-	MD 6.58 lower (10.18 to 2.98 lower)	LOW	IMPORTAN T
Chang	e in FEV₁ peak	(- Unsup	ervised progra	mme (Follow	-up: 3 month	ns; Better indica	ated by higher	r values)				
1 (Krie mler 2013)	randomised trials	very serious ³	no serious inconsistenc y	no serious indirectnes s	very serious ⁷	none	11	15	-	MD 0.24 higher (6.1 lower to 6.58 higher)	VER Y LOW	IMPORTAN T
Chang	e in FEV₁ max	- Unsupe	ervised progra	mme (Follow-	up: 6 month	s; Better indica	ted by higher	values)				
1 (Krie mler 2013)	randomised trials	very serious ³	no serious inconsistenc y	no serious indirectnes s	very serious ⁷	none	11	15	-	MD 0.63 lower (10.94 lower to 9.68 higher)	VER Y LOW	IMPORTAN T
Chang	e in FEV₁ max	- Superv	ised programn	ae (Follow-up	: 6 months;	Better indicated	l by higher va	lues)				
1 (Oren stein 2004)	randomised trials	very serious 5	no serious inconsistenc y	no serious indirectnes s	serious ⁸	none	30	26	-	MD 0.25 lower (3.35 lower to 2.85 higher)	VER Y LOW	IMPORTAN T

Quality	assessment		No of patients Effect									
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Strength/ anaerobic training	Aerob ic trainin g	Relativ e (95% CI)	Absolut e	Quali ty	Importance
Chang	e in FEV₁ max	- Pooled	results for su	pervised and	unsupervise	ed programmes	(Follow-up:	6 months	s; Better	indicated	by high	er values)
2 (Krie mler 2013, Oren stein 2004)	randomised trials	very serious ⁶	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	41	41		MD 0.28 lower (3.25 lower to 2.69 higher)	LOW	IMPORTAN T
Chang	e in FEV₁ max	- Superv	ised programn	ne (Follow-up	: 12 months	; Better indicate	d by higher v	alues)				
1 (Oren stein 2004)	randomised trials	very serious 5	no serious inconsistenc y	no serious indirectnes s	serious ⁸	none	28	25	-	MD 0.82 lower (4.32 lower to 2.68 higher)	VER Y LOW	IMPORTAN T
Chang	e in BMI - <i>Uns</i>	upervise	d programme (Follow-up: 3	months; Bet	ter indicated by	higher value	s)				
1 (Krie mler 2013)	randomised trials	very serious 3	no serious inconsistenc y	no serious indirectnes s	serious ⁸	none	15	15	-	MD 0.2 higher (0.23 lower to 0.63 higher)	VER Y LOW	IMPORTAN T
Chang	e in BMI - <i>Uns</i>	upervise	d programme (Follow-up: 6	months; Bet	ter indicated by	higher value	s)				
1 (Krie mler 2013)	randomised trials	very serious 3	no serious inconsistenc y	no serious indirectnes s	serious ⁸	none	15	15	-	MD 0.3 higher (0.1 lower to 0.7 higher)	VER Y LOW	IMPORTAN T

Quality	/ assessment						No of patier	nts	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Strength/ anaerobic training	Aerob ic trainin g	Relativ e (95% CI)	Absolut e	Quali ty	Importance
Chang	e in BMI - Sup	ervised p	orogramme									
No evid	dence available	9										
Quality	/ of life											
No evid	dence available	9										
Prefer	ence for traini	ng progra	mme									
No evid	dence available	9										
Advers	se events											
No evi	dence available	9										
			01 51	tonial: CE: avat	ic fibrosis: EE\	/: forced expirator	v volume in 1 se	econd: EV	C: forced v	ital canacity	. ka: kilor	rammes MD [.]

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 blinding of participants and personnel 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; high risk of 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	v accomment						No of potio	nto	Effoot			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	High intensity interval training programm e	Standard combined aerobic and anaerobic exercise programm e	Relati ve (95% CI)	Absolu te	Qual	Importance
Chang	<mark>je in FEV₁ - <i>Un</i></mark>	supervis	ed programme)								
No evi	dence available	; 					0.40					
Chang	je in FEV₁% pr	edicted -	Supervised pi	<i>rogramme</i> (fo	ollow-up 6 w	eeks; range of	scores: 0-10); Better ind	icated by	/ higher v	alues)	
1 (Gru ber 2014)	observation al studies	very seriou s ¹	no serious inconsistenc y	no serious indirectnes s	serious ²	none	20	23	-	MD 3.9 lower (7.61 to 0.19 lower) 5	VER Y LOW	CRITICAL
Chang	le in vital capa	city (VC)	% predicted -	Unsupervise	d programn	1e						
No evi	dence available)										
Chang	je in vital capa	city (VC)	% predicted -	Supervised	orogramme	(follow-up 6 we	eks; range o	f scores 0-1	00; Bette	r indicate	d by hig	her values)
1 (Gru ber 2014)	observation al studies	very seriou s ¹	no serious inconsistenc y	no serious indirectnes s	serious ³	none	20	23	-	MD 5.1 lower (11.05 lower to 0.85 higher) 5	VER Y LOW	IMPORTAN T
Chang	le in FEV₁ peal	k										
No evi	dence available	9										

Quality	y assessment						No of patie	nts	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	High intensity interval training programm e	Standard combined aerobic and anaerobic exercise programm e	Relati ve (95% CI)	Absolu te	Qual ity	Importance
Chang	e in FEV₁ peal	k - Super	vised program	<i>m</i> e (follow-u	p 6 weeks; E	Better indicated	by higher va	alues)				
1 (Gru ber 2014)	observation al studies	very seriou s ¹	no serious inconsistenc y	no serious indirectnes s	serious ³	none	20	23	-	MD 0.8 lower (4.59 lower to 2.99 higher) 5	VER Y LOW	IMPORTAN T
Time t	o next exacert	oation										
No evi	dence available	•										
Chang	e in BMI - Uns	upervise	d programme									
No evi	dence available	;										
Chang	e in BMI - Sup	ervised p	orogramme (fo	llow-up 6 we	eks; Better i	ndicated by hig	gher values)					
1 (Gru ber 2014)	observation al studies	very seriou s ¹	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	21	23	-	MD 0 higher (1.34 lower to 1.34 higher) 5	VER Y LOW	IMPORTAN T
Quality	y of life											
No evi	No evidence available											
Prefer	ence for traini	ng progra	amme									
No evi	dence available	•										

Quality	y assessment	No of patients		Effect								
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	High intensity interval training programm e	Standard combined aerobic and anaerobic exercise programm e	Relati ve (95% CI)	Absolu te	Qual ity	Importance
Adver	se events											

No evidence available

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; FEV₁: forced expiratory volume in 1 second; VC: vital capacity; kg: kilogrammes MD: mean difference; min: minute; mI: millilitres; FEV₁ 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: Comp	arison 4. Insp	piratory muscle	e training (80%	6 of maximal effort)	versus usual care

Quality	v assessmen	t			No of patients Effect							
No of studie s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Inspiratory muscle training (80% of maximal effort) programme	Usu al care	Relativ e (95% CI)	Absolute	Quali ty	Importan ce
Chang	e in FEV₁ (litı	es) (Follo	w up: 2-6 mont	ths; Better inc	dicated by high	gher values)						
1 (Enrig	randomise d trials	very serious	no serious inconsistenc v	no serious indirectnes s	no serious imprecisio n	none	9	10	-	MD 0 higher (0.9	LOW	CRITICAL

						No of patients Effect						
Quality	assessment	t in the second s					No of patients		Effect			
No of studie s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Inspiratory muscle training (80% of maximal effort) programme	Usu al care	Relativ e (95% CI)	Absolute	Quali ty	Importan ce
htt 2004)										0.9 higher)		
Chang	e in FVC (litre	es) (Follov	w up: <mark>2-6</mark> montl	hs; Better ind	icated by hig	her values)						
1 (Enrig htt 2004)	randomise d trials	very serious 1	no serious inconsistenc y	no serious indirectnes s	very serious ²	none	9	10	-	MD 0.1 higher (0.9 lower to 1.1 higher)	VER Y LOW	CRITICAL
FEV ₁ p	eak											
No evic	lence availabl	е										
Time to	o next exacer	bation										
No evic	lence availabl	е										
Body o	composition											
No evic	lence availabl	е										
Quality	of life											
No evic	lence availabl	е										
Prefere	ence for train	ing progr	amme									
No evic	lence availabl	е										
Advers	se events											

No evidence available

Abbreviations: CI: confidence interval; CF: cystic fibrosis; FEV₁: 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 ass	sessment	t					No of patie	nts	Effect			
No of studies	Design	Risk of bias	Inconsistenc y	Indirectne ss	Imprecisio n	Other consideration s	Combined aerobic and anaerobic training programm e	No exercise program me	Relati ve (95% CI)	Absolu te	Qual ity	Importance
Change in	FEV₁ % p	oredicted -	Unsupervised	programme	(follow-up 3	8 months; range	e of scores: (0-100; Bette	r indicate	ed by high	ner valu	es)
3 (Beaudoin 2016, Rovedder 2014, Schindel 2015)	rando mised trials	serious ¹	no serious inconsistenc y	no serious indirectnes s	serious ²	none	44	45	-	MD 4.27 lower (9.63 lower to 1.09 higher)	LOW	CRITICAL
Change in	FEV₁ % p	oredicted -	Unsupervised	programme	(follow-up 3	-6 months; ran	ge of scores	: 0-100; Bet	ter indica	ited by hi	gher va	lues)
1 (Hebestre it 2010)	rando mised trials	very serious ³	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	22	13	-	MD 2 higher (5.31 lower to 9.31 higher)	VER Y LOW	CRITICAL
Change in	FEV₁ % p	oredicted -	Supervised pr	ogramme								
No evidence	e availabl	е										
Change in	FVC % p	redicted -	Unsupervised	programme	(follow-up 3	months; range	of score: 0-	100; Better i	ndicated	by highe	r values	5)
3 (Beaudoin 2016.Rov edder	rando mised trials	serious ¹	no serious inconsistenc y	no serious indirectnes s	serious ⁵	none	44	45	-	MD 1.47 lower (6.21	LOW	CRITICAL

Quality ass	essment	t					No of patie	nts	Effect			
No of studies	Design	Risk of bias	Inconsistenc y	Indirectne ss	Imprecisio n	Other consideration s	Combined aerobic and anaerobic training programm e	No exercise program me	Relati ve (95% CI)	Absolu te	Qual	Importance
2014, Schindel 2015)										lower to 3.27 higher)		
Change in values)	FVC % p	redicted at	3-6 months -	Unsupervise	d programm	e (follow-up 3-	6 months; ra	nge of score	es: 0-100	; Better ir	ndicated	l by higher
1 (Hebestre it 2010)	rando mised trials	very serious ³	no serious inconsistenc y	no serious indirectnes s	very serious ₆	none	22	13	-	MD 0.5 higher (4.3 lower to 5.3 higher)	VER Y LOW	IMPORTAN T
Change in	FVC % p	redicted -	Supervised pro	ogramme								
No evidend	e availat	ole										
Change in	FEV₁ pea	ik - Unsup	ervised progra	mme (follow	-up 3 month	s; Better indica	ated by highe	er values)				
1 (Beaudoin 2016)	rando mised trials	very serious ⁷	no serious inconsistenc y	no serious indirectnes s	very serious ⁶	none	8	6	-	MD 2.13 lower (7.06 lower to 2.80 higher)	VER Y LOW	IMPORTAN T
Change in	FEV₁ pea	ık - Unsupe	ervised progra	mme (follow	-up 3-6 mon	ths; Better indi	cated by hig	her values)				
1 (Hebestre it 2010)	rando mised trials	very serious ³	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	23	15	-	MD 2.04 higher (0.08	LOW	IMPORTAN T
Quality ass No of studies	Sessment Design	Risk of bias	Inconsistenc y	Indirectne ss	Imprecisio n	Other consideration s	No of patie Combined aerobic and anaerobic training programm e	nts No exercise program me	Effect Relati ve (95% CI)	Absolu te	Qual ity	Importance
---------------------------------	---------------------------	------------------------------	---------------------------------	--------------------------------	------------------------------	-----------------------------	---	--	---------------------------------------	--	-----------------	---------------
										higher)		
Change in	FEV ₁ pea	ık - Superv	rised program	me								
No evidence	e availabl	e										
Time to ne	xt exacer	bation										
No evidence	e availabl	e		10.11								
Change in	weight (k	(g) - Unsup	pervised progr	amme (follov	v-up 3 mont	ns; Better Indic	ated by high	er values)				
1 (Beaudoin 2016)	rando mised trials	very serious ⁵	no serious inconsistenc y	no serious indirectnes s	very serious ⁶	none	8	6	-	MD 0.27 lower (12.95 lower to 12.41 higher)	VER Y LOW	T
Change in	BMI - Un	supervised	d programme (follow-up 3 r	nonths; Bett	er indicated by	higher valu	es)				
1 (Beaudoin 2016)	rando mised trials	very serious ⁷	no serious inconsistenc y	no serious indirectnes s	very serious ⁶	none	8	6	-	MD 0.06 higher (2.68 lower to 2.80 higher)	VER Y LOW	IMPORTAN T
Change in	BMI - Un	supervised	d programme (follow-up 3-6	6 months; Be	etter indicated	by higher va	lues)				

 $\ensuremath{\textcircled{\sc online 0.5ex}}$ NICE 2017. All rights reserved. Subject to Notice of rights.

Quality ass	essment Design	: Risk of	Inconsistenc	Indirectne	Imprecisio	Other	No of patie	nts No	Effect Relati	Absolu		
studies	J	bias	у	SS	n	consideration s	aerobic and anaerobic training programm e	exercise program me	ve (95% CI)	te	Qual ity	Importance
1 (Hebestre it 2010)	rando mised trials	very serious ³	no serious inconsistenc y	no serious indirectnes s	serious⁵	none	22	13	-	MD 0.4 higher (0.17 lower to 0.97 higher)	VER Y LOW	IMPORTAN T
Change in	BMI - Un	supervised	l programme (follow-up 12	months; Be	tter indicated b	y higher val	ues)				
1 (Moorcroft 2004)	rando mised trials	very serious ⁸	no serious inconsistenc y	no serious indirectnes s	serious⁵	none	30	18	-	MD 0.54 higher (0.09 lower to 1.17 higher)	VER Y LOW	IMPORTAN T
Change in	BMI - Suj	pervised p	rogramme									
No evidence	e availabl	е										
Change in values)	quality of	f life: CFQ-	R physical - U	Insupervised	programme	e (follow-up 3 m	ionths; range	e of scores:	0-100; Bo	etter indic	cated by	higher
1 (Beaudoin 2016)	rando mised trials	very serious ⁷	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	8	6	-	MD 0.60 higher (17.56 lower to 18.76 higher)	VER Y LOW	CRITICAL

Quality ass	sessment						No of patie	nts	Effect			
No of studies	Design	Risk of bias	Inconsistenc y	Indirectne ss	Imprecisio n	Other consideration s	Combined aerobic and anaerobic training programm e	No exercise program me	Relati ve (95% CI)	Absolu te	Qual ity	Importance
1 (Rovedde r 2014)	rando mised trials	serious ⁹	no serious inconsistenc y	no serious indirectnes s	Not calculable 10	none	19 Median (IQR): 6.1 (-4 to 8)	22 Median (IQR): 2.4 (1.0 to 13)	P=0.7 42	Not calcula ble	MOD ERA TE	CRITICAL
Change in values)	quality of	f life: CFQ	R body image	- Unsupervi	sed progran	nme (follow-up	3 months; ra	inge of score	es: 0-100	; Better i	ndicated	l by higher
1 (Beaudoin 2016)	rando mised trials	very serious ⁷	no serious inconsistenc y	no serious indirectnes s	serious ²	none	8	6	-	MD 6.03 lower (18.89 lower to 6.83 higher)	VER Y LOW	CRITICAL
1 (Rovedde r 2014)	rando mised trials	serious ⁹	no serious inconsistenc y	no serious indirectnes s	Not calculable	none	19 Median (IQR): 3.3 (-11 to 22)	22 Median (IQR): 3.0 (-2 to 11)	P=0.9 15	Not calcula ble	MOD ERA TE	CRITICAL
Change in values)	quality of	f life: CFQ·	R digestive - I	Unsupervise	d programm	e (follow-up 3 r	nonths; rang	e of scores:	0-100; B	etter indi	cated b	y higher
1 (Beaudoin 2016)	rando mised trials	very serious ⁷	no serious inconsistenc y	no serious indirectnes s	serious ²	none	8	6	-	MD 14.80 higher (0.43 to 29.17 higher)	VER Y LOW	CRITICAL

Quality ass	essment						No of patie	nts	Effect			
No of studies	Design	Risk of bias	Inconsistenc y	Indirectne ss	Imprecisio n	Other consideration s	Combined aerobic and anaerobic training programm e	No exercise program me	Relati ve (95% CI)	Absolu te	Qual ity	Importance
1 (Rovedde r 2014)	rando mised trials	serious ⁹	no serious inconsistenc y	no serious indirectnes s	Not calculable ¹⁰	none	19 Median (IQR): -1.0 (-4 to 0)	22 Median (IQR): - 0.5 (0 to 0)	P=0.9 53	Not calcula ble	MOD ERA TE	CRITICAL
Change in values)	quality of	f life: CFQ	R respiratory	- Unsupervis	ed program	me (follow-up 3	3 months; ra	nge of score	s: 0-100;	Better in	dicated	by higher
1 (Beaudoin 2016)	rando mised trials	very serious ⁷	no serious inconsistenc y	no serious indirectnes s	serious ²	none	8	6	-	MD 4.63 lower (16.88 lower to 7.62 higher)	VER Y LOW	CRITICAL
1 (Rovedde r 2014)	rando mised trials	serious ⁹	no serious inconsistenc y	no serious indirectnes s	Not calculable ¹⁰	none	19 Median (IQR): 3.8 (0 to 11)	22 Median (IQR): - 4.7 (-1 to 7)	P=0.9 25	Not calcula ble	MOD ERA TE	CRITICAL
Change in values)	quality of	f life: CFQ·	-R emotional -	Unsupervise	ed programn	ne (follow-up 3	months; ran	ge of scores	: 0-100; l	Better ind	licated I	oy higher
1 (Beaudoin 2016)	rando mised trials	very serious ⁷	no serious inconsistenc y	no serious indirectnes s	serious ²	none	8	6	-	MD 7.78 lower (18.65 lower	VER Y LOW	CRITICAL

 $\ensuremath{\textcircled{\sc online 0.5ex}}$ NICE 2017. All rights reserved. Subject to Notice of rights.

Quality ass	sessment						No of patie	nts	Effect			
No of studies	Design	Risk of bias	Inconsistenc y	Indirectne ss	Imprecisio n	Other consideration s	Combined aerobic and anaerobic training programm e	No exercise program me	Relati ve (95% CI)	Absolu te	Qual ity	Importance
										to 3.09 higher)		
1 (Rovedde r 2014)	rando mised trials	serious ⁹	no serious inconsistenc y	no serious indirectnes s	Not calculable	none	19 Median (IQR): 1.2 (-6 to 6)	22 Median (IQR): - 4.3 (-13 to 6)	P=0.4 58	Not calcula ble	MOD ERA TE	CRITICAL
Change in values)	quality o	f life: CFQ	-R social - Uns	upervised pi	rogramme (f	ollow-up 3 mor	nths; range o	f scores: 0-	100; Bett	er indicat	ed by h	igher
1 (Beaudoin 2016)	rando mised trials	very serious ⁷	no serious inconsistenc y	no serious indirectnes s	serious ²	none	8	6	-	MD 5.29 lower (18.10 lower to 7.52 higher)	VER Y LOW	CRITICAL
1 (Rovedde r 2014)	rando mised trials	serious ⁹	no serious inconsistenc y	no serious indirectnes s	Not calculable	none	19 Median (IQR): -1.1 (-11 to 5)	22 Median (IQR): - 1.7 (5 to 11)	P=0.9 53	Not calcula ble	MOD ERA TE	CRITICAL
Change in higher valu	quality o les)	f life: CFQ	-R eating distu	irbances- Un	supervised	<i>programme</i> (fo	llow-up 3 mo	onths; range	of score	s: 0-100;	Better i	ndicated by
1 (Beaudoin 2016)	rando mised trials	very serious ⁷	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	8	6		MD - 1.39 (4.91 lower	LOW	CRITICAL

Quality ass	sessment				-		No of patie	nts	Effect			
No of studies	Design	Risk of bias	Inconsistenc y	Indirectne ss	Imprecisio n	Other consideration s	Combined aerobic and anaerobic training programm e	No exercise program me	Relati ve (95% CI)	Absolu te	Qual ity	Importance
										to 2.13 higher)		
1 (Rovedde r 2014)	rando mised trials	serious ⁹	no serious inconsistenc y	no serious indirectnes s	Not calculable	none	19 Median (IQR): -0.3 (-11 to 6)	22 Median (IQR): - 2.0 (-11 to 0)	P=0.9 13	Not calcula ble	MOD ERA TE	CRITICAL
Change in values)	quality o	f life: CFQ	-R treatment -	Unsupervise	d programm	e (follow-up 3	months; rang	ge of scores	: 0-100; E	Better ind	icated k	y higher
1 (Beaudoin 2016)	rando mised trials	very serious ⁷	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	8	6	-	MD 5.56 lower (26.03 lower to 14.91 higher)	VER Y LOW	CRITICAL
1 (Rovedde r 2014)	rando mised trials	serious ⁹	no serious inconsistenc y	no serious indirectnes s	Not calculable	none	19 Median (IQR): -2.0 (-11 to 0)	22 Median (IQR): - 2.5 (-11 to11)	P=0.8 50	Not calcula ble	MOD ERA TE	CRITICAL
Change in values)	quality o	f life: CFQ	R vitality - Un	supervised p	orogramme (follow-up 3 mo	nths; range	of scores: 0-	100; Bet	ter indica	ted by I	nigher
1 (Beaudoin 2016)	rando mised trials	very serious ⁷	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	8	6	-	MD 3.13 higher	VER Y LOW	CRITICAL

Quality ass	sessment	:					No of patie	nts	Effect			
No of studies	Design	Risk of bias	Inconsistenc y	Indirectne ss	Imprecisio n	Other consideration s	Combined aerobic and anaerobic training programm e	No exercise program me	Relati ve (95% CI)	Absolu te	Qual ity	Importance
										(13.45 lower to 19.71 higher)		
1 (Rovedde r 2014)	rando mised trials	serious ⁹	no serious inconsistenc y	no serious indirectnes s	Not calculable	none	19 Median (IQR): -1.2 (-16 to 8)	22 Median (IQR): 2.6 (-8 to 10)	P=0.5 79	Not calcula ble	MOD ERA TE	CRITICAL
Change in values)	quality o	f life: CFQ·	R health - Uns	supervised p	rogramme (f	ollow-up 3 mor	nths; range o	of scores: 0-	100; Bett	er indicat	ed by h	igher
1 (Beaudoin 2016)	rando mised trials	very serious 7	no serious inconsistenc y	no serious indirectnes s	very serious4	none	8	6	-	MD 5.57 lower (21.75 lower to 10.61 higher)	VER Y LOW	CRITICAL
1 (Rovedde r 2014)	rando mised trials	serious ⁹	no serious inconsistenc y	no serious indirectnes s	Not calculable 10	none	19 Median (IQR): 1.7 (-11 to 16)	22 Median (IQR): - 3.0 (-11 to 0)	P=0.3 82	Not calcula ble	MOD ERA TE	CRITICAL
Change in values)	quality o	f life: CFQ·	R weight - Un	supervised p	orogramme (follow-up 3 mo	nths; range (of scores: 0-	100; Bett	ter indica	ted by h	nigher

Quality ass	sessment						No of patier	nts	Effect			
No of studies	Design	Risk of bias	Inconsistenc y	Indirectne ss	Imprecisio n	Other consideration s	Combined aerobic and anaerobic training programm e	No exercise program me	Relati ve (95% CI)	Absolu te	Qual ity	Importance
1 (Beaudoin 2016)	rando mised trials	very serious ⁷	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	8	6	-	MD 8.34 lower (36.73 lower to 20.05 higher)	VER Y LOW	CRITICAL
1 (Rovedde r 2014)	rando mised trials	serious ⁹	no serious inconsistenc y	no serious indirectnes s	Not calculable	none	19 Median (IQR): 4.6 (0 to 33)	22 Median (IQR): 12.1 (0 to 11)	P=0.4 10	Not calcula ble	MOD ERA TE	CRITICAL
Change in higher valu	quality of les)	f life: CFQ-	R social limita	ations - Unsu	pervised pro	ogramme (follo	w-up 3 mont	hs; range of	scores:	0-100; Be	etter ind	icated by
1 (Beaudoin 2016)	rando mised trials	very serious ⁷	no serious inconsistenc y	no serious indirectnes s	serious2	none	8	6	-	MD 5.29 lower (18.10 lower to 7.52 higher)	VER Y LOW	CRITICAL
1 (Rovedde r 2014)	rando mised trials	serious ⁹	no serious inconsistenc y	no serious indirectnes s	Not calculable	none	19 Median (IQR): 0.8 (-8 to 8)	22 Median (IQR): 1.8 (-2 to 0)	P=0.9 35	Not calcula ble	MOD ERA TE	CRITICAL

Quality ass	sessment						No of patie	nts	Effect			
No of studies	Design	Risk of bias	Inconsistenc y	Indirectne ss	Imprecisio n	Other consideration s	Combined aerobic and anaerobic training programm e	No exercise program me	Relati ve (95% CI)	Absolu te	Qual ity	Importance
Change in higher valu	quality o les)	f life: CFQ·	R role limitatio	ons - Unsupe	ervised prog	ramme (follow-	up 3 months	; range of so	cores: 0-	100; Bette	er indica	ated by
1 (Beaudoin 2016)	rando mised trials	very serious ⁷	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	8	6	-	MD 4.52 higher (13.37 lower to 22.41 higher)	VER Y LOW	CRITICAL
Change in by higher v	quality o [.] /alues)	f life- Supe	ervised progra	mme (follow-	up 2 months	s; measured wi	th: CFQ-R cl	nildren's; rar	nge of sc	ores: 0-1	00; Bett	er indicated
1 (Santana- Sosa 2012)	rando mised trials	very serious ¹	no serious inconsistenc y	no serious indirectnes s	Not calculable ¹⁰	none	11 Median pre- interventio n: 696 (495 to 741) Median post- interventio n: 719 (550 to 734)	11 Median pre- interventi on: 649 (578 to 768) Median post- interventi on: 638 (461 to 791)	p=0.2 57	Not calcula ble	LOW	CRITICAL

Quality ass	sessment	:					No of patie	nts	Effect			
No of studies	Design	Risk of bias	Inconsistenc y	Indirectne SS	Imprecisio n	Other consideration s	Combined aerobic and anaerobic training programm e	No exercise program me	Relati ve (95% CI)	Absolu te	Qual ity	Importance
Change in by higher v	quality o [.] /alues)	f life- Supe	ervised progra	mme (follow-	up 2 month	s; measured wi	th: CFQ-R pa	arents'; rang	e of scol	res: 0-100	; Better	indicated
1 (Santana- Sosa 2012)	rando mised trials	very serious ¹	no serious inconsistenc y	no serious indirectnes s	Not calculable ¹⁰	none	11 Median pre- interventio n: 896 (688 to 1011) Median post- interventio n: 889 (811 to 973)	11 Median pre- interventi on: 911 (842 to 1028) Median post- interventi on: 978 (684 to 1059);	p=0.1 43	Not calcula ble	LOW	CRITICAL
Preference	for train	ing progra	mme				,	<i>,,</i>				
No evidence	e availabl	е										
Adverse ev	vents - Ur	nsupervise	ed programme									
No evidence	e availabl	e										
Adverse ev	ents - Su	pervised	orogramme (fo	bliow-up 2 mo	onths)		4.4	44		Net		
(Santana- Sosa 2012)	rando mised trials	very serious ¹	no serious inconsistenc y	no serious indirectnes s	not calculable	none	No adverse events occurred during	No data reported	-	not calcula ble	LOW	URITICAL

Quality ass	sessment	:					No of patie	nts	Effect			
No of studies	Design	Risk of bias	Inconsistenc y	Indirectne ss	Imprecisio n	Other consideration s	Combined aerobic and anaerobic training programm e	No exercise program me	Relati ve (95% CI)	Absolu te	Qual ity	Importance
							exercise training					

Abbreviations: BMI: body mass index; CI: confidence interval; CF: cystic fibrosis; CFQ-R: cystic fibrosis questionnaire revised; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; kg: kilogrammes MD: mean difference; min: minute; ml: millilitres; FEV₁ 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

Quality a	ssessment						No of patier	nts	Effect			
No of studies	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Combined inspiratory muscle training resistance and aerobic training	No exercise programm e	Relati ve (95% CI)	Absolut e	Qual ity	Importan ce
Change i	n FEV₁ (litre	es) - Unsu	pervised prog	ıramme								
No evider	nce available	9										
Change i	n FEV₁ (litre	es) - Supe	ervised progra	mme (follow-	up 2 months	; Better indicat	ed by higher	values)				
1 (Santan a-Sosa 2014)	randomis ed trials	very serious 1	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	none	10	10	-	MD 0.07 higher (0.54 lower to 0.68 higher)	LOW	CRITICAL
Change i	n FVC (litre	s) - Unsu	pervised prog	ramme								
No evider	nce available	è										
Change i	n FVC (litre	s) - Supe	rvised progran	ກme (follow-ເ	ip 2 months;	Better indicate	d by higher v	values)				
1 (Santan a-Sosa 2014)	randomis ed trials	very serious	no serious inconsistenc y	no serious indirectnes s	very serious ²	none	10	10	-	MD 0.16 higher (0.68 lower to 1 higher)	VER Y LOW	CRITICAL
Change i	n FEV₁ peal	k										
No evider	nce available	9										
Time to n	next exacerl	bation										
No evider	nce available	9										

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

© NICE 2017. All rights reserved. Subject to Notice of rights.

Quality as No of studies	ssessment Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	No of patier Combined inspiratory muscle training resistance and aerobic training	nts No exercise programm e	Effect Relati ve (95% CI)	Absolut e	Qual	Importan ce
Change i	n weight - l	Jnsuperv	ised programn	ne								
No eviden	ice available	e										
Change i	n weight (k	g) - Supe	rvised progran	nme (follow-u	ip 2 months;	Better indicate	d by higher v	alues)				
1 (Santan a-Sosa 2014)	randomis ed trials	very serious 1	no serious inconsistenc y	no serious indirectnes s	very serious ²	none	10	10	-	MD 0.50 higher (10.51 lower to 11.51 higher)	VER Y LOW	CRITICAL
Change i	n QOL (CFC	Q-R) - Uns	supervised pro	gramme								
No evider	ice available	9										
Change i	n QOL (CFC	Q-R) - <i>Sup</i>	pervised progra	a <i>mm</i> e (follow	-up 2 month	ns; range of sco	res: 0-100; B	etter indicate	ed by hig	her value	s)	
1 (Santan a-Sosa 2014)	randomis ed trials	very serious 1	no serious inconsistenc y	no serious indirectnes s	Not calculable ³	none	10 Median pre- interventio n: 629 (505 to 701) Median post- interventio n: 688	10 Median pre- interventio n: 636 (626 to 745) Median post- interventio n: 638	p=0.0 71	Not calcula ble	LOW	CRITICAL

Quality a	ssessment				No of patier	nts	Effect					
No of studies	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Combined inspiratory muscle training resistance and aerobic training	No exercise programm e	Relati ve (95% CI)	Absolut e	Qual	Importan ce
							(609 to 791)	(626 to 737)				
Preference for training programme												
No evider	nce available	•										
Adverse	events - Un	supervis	ed programme	,								
No evider	nce available	9										
Adverse	events - Su	pervised	programme (fo	ollow-up 2 m	onths)							
1 (Santan a-Sosa 2014)	randomis ed trials	very serious 1	no serious inconsistenc y	no serious indirectnes s	Not calculable ³	none	10 No adverse events occurred during exercise training	10 No data reported	-	Not calcula ble	LOW	CRITICAL

Abbreviations: CI: confidence interval; CF: cystic fibrosis; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; kg: kilogrammes MD: mean difference; FEV₁ 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 pat	ients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Physical activity for higher amount or longer duration	Physical activity for lower amount or shorter duration	Relativ e (95% CI)	Absolute	Quali ty	Importan ce
Lung f	unction: FEV ₁ 9	% predicte	ed									
No evic	dence available											
Lung f	unction: FVC%	b predicte	d									
No evic	dence available											
FEV ₁ p	eak											
No evic	dence available											
Body o	composition											
No evic	dence available											
Quality	/ of life											
No evic	dence available											
Prefere	ence for trainir	ng progra	mme									
No evi	dence available)										
Advers	se events											
No evi	dence available)										
Need f	or hospitalizat	ion (follow	w-up: 12 month	ns; better indi	cated by low	ver values) [≥30	minutes da	aily versus	< 30 min	utes]		

Quality	y assessment						No of pat	ients	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Physical activity for higher amount or longer duration	Physical activity for lower amount or shorter duration	Relativ e (95% CI)	Absolute	Quali ty	Importan ce
1 (Cox 2016)	observationa I studies	very serious 1	no serious inconsistenc y	no serious indirectnes s	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)	VER Y LOW	CRITICAL
Need f or sho	or hospitalizat rter duration]	ion (follo	w-up: 12 month	ns; better indi	cated by low	ver values) [≥ 30) minutes f	or ≥ 10 min	utes bou	ts daily ver	sus low	er amount
1 (Cox 2016)	observationa I studies	very serious	no serious inconsistenc y	no serious indirectnes s	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)	VER Y 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 patie	nts	Effect				
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Cohort segregatio n into different pathogens by clinic times	No cohort segregatio n	Relativ e (95% CI)	Absolut e	Qual ity	Importan ce
10-yea	r incidence of	f P aerugi	inosa infection	s (Follow-up	10 years)							
1 (Hay es 2010)	randomised trials	serious 1	no serious inconsistenc y	no serious indirectnes s	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	f MRSA (p	percentages) (f	ollow-up 4 ye	ears)							
1 (McK ay 2009)	observation al studies	very serious 3	no serious inconsistenc y	no serious indirectnes s	Not calculable 2	none	1.3%4	1%4	ns	-	VER Y LOW	CRITICAL
4-year prevalence of non-mucoid <i>P aeruginosa</i> (percentages) (follow-up 4 years)												
1 (McK ay 2009)	observation al studies	very serious 3	no serious inconsistenc y	no serious indirectnes s	Not calculable 2	none	22.7%4	22.3%4	ns	-	VER Y LOW	CRITICAL

© NICE 2017. All rights reserved. Subject to Notice of rights.

Quality No of studi es	/ assessment Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	No of patien Cohort segregatio n into different pathogens by clinic times	nts No cohort segregatio n	Effect Relativ e (95% CI)	Absolut e	Qual ity	Importan ce
4-year 1 (McK ay 2009)	prevalence of observation al studies	f mucoid very serious 3	P aeruginosa (no serious inconsistenc y	percentages no serious indirectnes s) (follow-up Not calculable 2	4 years) none	1.0% ⁴	5.9% ⁴	P=0.0 01	-	VER Y LOW	CRITICAL
Staff c	ompliance (pe	ercentage	s) (follow-up 4	years)								
1 (McK ay 2009)	observation al studies	very serious 3	no serious inconsistenc y	no serious indirectnes s	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	-	-	VER Y LOW	IMPORTA NT

Quality	y assessment	No of patie	nts	Effect								
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Cohort segregatio n into different pathogens by clinic times	No cohort segregatio n	Relativ e (95% CI)	Absolut e	Qual ity	Importan ce
							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	2. Cohort segregation by	location versus no o	ohort segregation

Quality	/ assessment					No of patie	nts	Effect				
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Cohort segregatio n into different pathogens by location	No cohort segregatio n	Relati ve (95% CI)	Absolut e	Qual ity	Importan ce
Annua	l incidence of	new grov	vths of <i>P aerug</i>	<i>ginosa</i> (follow	v-up 9 years))						
1 (Lee 2004)	observation al studies	very serious 1	no serious inconsistenc y	no serious indirectnes s	Not calculable 2	none	The annual incidence of new growths of <i>P</i> <i>aeruginosa</i> , while fluctuating, showed no downward trend, despite segregation. ³ N of patients unclear		ns	-	VER Y LOW	CRITICAL

© NICE 2017. All rights reserved. Subject to Notice of rights.

Quality No of studi es	/ assessment Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	No of patie Cohort segregatio n into different pathogens by location	nts No cohort segregatio n	Effect Relati ve (95% CI)	Absolut e	Qual ity	Importan ce
Maral			D	- f (f - 11	0							
Yearly 1 (Lee 2004)	observation al studies	very serious	P aeruginosa i no serious inconsistenc y	no serious indirectnes s	ow-up 9 year	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)	VER Y LOW	CRITICAL
Yearly	prevalence of	intermitt	ent <i>P aeruginc</i>	sa infection	(follow-up 9	years)						
1 (Lee 2004)	observation al studies	very serious	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	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)	VER Y 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

•												
Quality No of studie s	assessment Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	No of patie Protective equipmen t + individual segregati on	Incomplet e protective equipmen t + incomplet e individual segregati	Effect Relative (95% CI)	Absolut e	Qual	Importan
4-montl	h prevalence	of <i>P aeru</i>	ainosa infectio	ons (percenta	aes) (follow	-up 5 vears)		OII			ity	Ce
1 (Sava nt 2014)	observatio nal studies	very serious	no serious inconsistenc y	no serious indirectnes s	Not calculable	none	21.78% (range: 31.09 to 12.95) ³	29.79% (range: 38.74 to 12.95) ³	p<0.000 1	-	VER Y LOW	CRITICAL
4-montl	h prevalence	of MRSA	infections (pe	rcentages) (fe	ollow-up 5 y	ears)						
1 (Sava nt 2014)	observatio nal studies	very serious	no serious inconsistenc y	no serious indirectnes s	Not calculable 2	none	8.68% (range 12.78 to 5.38) ³	10.76% (12.5 to 7.34) ³	p=0.008	-	VER Y LOW	CRITICAL

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

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 No of studi es	y assessment Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	No of patie Cohort segregatio n into different pathogens by location	nts No cohort segregatio n	Effect Relati ve (95% CI)	Absolut e	Qual ity	Importan ce
Annua	l incidence of	B cepaci	a complex (pei	rcentages) (fo	ollow-up 1 ye	ear)						
1 (Che n 2001)	observation al studies	very serious	no serious inconsistenc y	no serious indirectnes s	Not calculable 2	none	3.7% ³	5.8% ³	-	-		CRITICAL
5-mon	th incidence o	f hospita	I-associated co	olonisation of	f <mark>B cepacia</mark> (follow-up 5 mo	nths)					
1 (Tho mass en 1986)	observation al studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	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)	VER Y 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.

Quality	/ assessment						No of patient	S	Effect			
No of studie s	Design	Risk of bias	Inconsistency	Indirectness	Imprecisio n	Other consideration s	Individual segregation	Usu al care	Relativ e (95% CI)	Absolut e	Qual ity	Importan ce
Patient	t's satisfaction											
1 (Russ o 2006)	observationa I studies	very serious	no serious inconsistency	no serious indirectness	Not calculable 2	none	92% of children supported segregated treatment	-	-	-	VER Y LOW	CRITICAL
Parent	s' satisfaction											
1 (Russ o 2006)	observationa I studies	very serious	no serious inconsistency	no serious indirectness	Not calculable 2	none	91% of parents supported segregated treatment	-	-	-	VER Y LOW	CRITICAL

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

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	y assessment						No of patier	nts	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Cohort segregatio n into pathogens	Contro I	Relativ e (95% CI)	Absolut e	Quali ty	Importance
Month	ly incidence of	f multiply	resistant P aei	ruginosa stra	in (follow-up	1 month)						

Quality	y assessment						No of patier	nts	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Cohort segregatio n into pathogens	Contro I	Relativ e (95% CI)	Absolut e	Quali ty	Importance
1 (Hoib y & Pede rsen 1989)	observation al studies	serious 1	no serious inconsistenc y	no serious indirectnes s	no serious imprecisio n	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)	VER Y LOW	CRITICAL
Annua	l incidence of	intermitte	ent <i>P aeruginos</i>	sa (follow-up	1 year)							
1 (Fred eriks en 1999)	observation al studies	serious 3	no serious inconsistenc y	no serious indirectnes s	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)	VER Y LOW	CRITICAL
Annua	l incidence of	chronic F	<i>aeruginosa</i> (f	ollow-up 1 ye	ar)							
1 (Fred eriks en 1999)	observation al studies	serious 3	no serious inconsistenc y	no serious indirectnes s	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)	VER Y LOW	CRITICAL
6-mon	th incidence B	Cepacia	(follow-up 6 m	onths)								

Quality No of studi	/ assessment Design	Risk of bias	Inconsistenc v	Indirectnes s	Imprecisio n	Other consideration	No of patier Cohort segregatio	n ts Contro	Effect Relativ	Absolut e		
es			,			S	n into pathogens		(95% CI)		Quali ty	Importance
1 (Whit eford 1995)	observation al studies	very serious 7	no serious inconsistenc y	no serious indirectnes s	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)	VER Y LOW	CRITICAL
Annua	l incidence of	Burkhold	eria species in	fection (perc	entages) (fol	low-up 1 year)						
1 (Fran ce 2008)	observation al studies	very serious 9	no serious inconsistenc y	no serious indirectnes s	Not calculable ¹⁰	none	16.3% ¹¹	3-5% ¹¹	-	-	VER Y LOW	CRITICAL
Month	ly prevalence o	of multiple	e resistant <i>P a</i>	e <i>ruginosa</i> str	ain (percent	ages) (follow-up	o 1 month)					
1 (Hoib y 1989)	observation al studies	serious 1	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	37% (44/119) ²	33% (39/11 9) ²	OR 1.02 (0.60 to 1.76)	4 more per 1000 (from 101 fewer to 134 more)	VER Y LOW	CRITICAL
Preval	ence of AES-1	P aerugii	nosa epidemic	strain (follow	/-up: 2 years)						
1 (Griffi ths 2005)	observation al studies	no serious risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ⁶	none	-	-	adjRR 0.64 (0.47 to 0.87) ¹²	-	VER Y LOW	CRITICAL

Quality	/ assessment						No of patier	nts	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Cohort segregatio n into pathogens	Contro I	Relativ e (95% CI)	Absolut e	Quali tv	Importance
Annua	l prevalence o	f chronic	P aeruginosa i	nfection (foll	ow-up 1 yea	r)						
1 (Jone s 2005)	observation al studies	no serious risk of bias	no serious inconsistenc y	no serious indirectnes s	serious ⁶	none	184/228 (80.7%) ¹³	156/21 6 (72.2 %) ¹³	OR 1.61 (1.03 to 2.51)	85 more per 1000 (from 6 more to 145 more)	VER Y LOW	CRITICAL
Annua	l prevalence o	f transmi	ssible <i>P aerugi</i>	nosa infectio	n (follow-up	1 year)						
1 (Jone s 2005)	observation al studies	no serious risk of bias	no serious inconsistenc y	no serious indirectnes s	very serious ⁴	none	35/228 (15.4%) ¹³	28/216 (13%) ¹ 3	OR 1.22 (0.71 to 2.08)	24 more per 1000 (from 34 fewer to 107 more)	VER Y LOW	CRITICAL
Annua	l prevalence o	f chronic	infection with	transmissible	P aerugino	sa strain (perce	ntages) (follo	ow-up 1 y	ear)			
1 (Jone s 2005)	observation al studies	no serious risk of bias	no serious inconsistenc y	no serious indirectnes s	Not calculable	none	15.4% ¹³	13.0% ¹³	-	-	VER Y 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 patie	nts	Effect			
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Complete cohort segregatio n	Incomplet e cohort segregatio n	Relati ve (95% CI)	Absolut e	Qual ity	Importan ce
Annua	l incidence of	Burkhold	leria species (p	percentages)	(follow-up 1	year)						
1 (Fran ce 2008)	observation al studies	very serious	no serious inconsistenc y	no serious indirectnes s	Not calculable 2	none	< 3% (for all but 1 year) ³	16.3% ³	-	-	VER Y 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

C	Quality	assessment						No of patier	nts	Effect			
1 5 5	No of studie s	Design	Risk of bias	Inconsistency	Indirectnes s	Imprecisio n	Other consider ations	Individual segregatio n	Usual care	Relativ e (95% CI)	Abso lute	Qualit y	Importa nce
F	Patient	satisfaction											

Quality No of studie s	assessment Design	Risk of bias	Inconsistency	Indirectnes s	Imprecisio n	Other consider ations	No of patier Individual segregatio n	its Usual care	Effect Relativ e (95%	Abso lute	Qualit	Importa
1 (Wain e 2007)	observationa I 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	CRITICA L

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 patie	nts	Effect			
No of studie s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Cohort segregatio n + individual segregatio n	Cohort segregatio n	Relati ve (95% CI)	Absolut e	Qual ity	Importan ce
Yearly r	prevalence of	f B cepac	ia complex infe	ection (perce	ntages) (follo	ow-up 1 vear)						

Quality	assessment		1			1	No of patie	nts	Effect			
No of studie s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Cohort segregatio n + individual segregatio n	Cohort segregatio n	Relati ve (95% CI)	Absolut e	Qual ity	Importan ce
1 (Chen 2001)	observatio nal studies	very serious	no serious inconsistenc y	no serious indirectnes s	not calculable 2	none	7% ³	15% ³	-	-	VER Y LOW	CRITICAL
Yearly p	orevalence of	Burkhole	deria species (percentages)	(follow-up:	5 years)						
1 (Franc e 2008)	observatio nal studies	very serious 4	no serious inconsistenc y	no serious indirectnes s	not calculable 2	none	9.3%5	31.2%5	-	-	VER Y LOW	CRITICAL

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			
No of studie s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Cohort segregation + individual segregation + protective equipment	Usu al care	Relati ve (95% CI)	Absolut e	Qual ity	Importan ce
Annual	l incidence of l	B cepacia	complex infect	tion (percenta	ages) (follow	-up 1 year)						

© NICE 2017. All rights reserved. Subject to Notice of rights.

Quality	/ assassment						No of patients		Effect			
No of studie s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Cohort segregation + individual segregation + protective equipment	Usu al care	Relati ve (95% CI)	Absolut e	Qual	Importan ce
1 (Che n 2001)	observationa I studies	very serious 1	no serious inconsistenc y	no serious indirectnes s	Not calculable 2	none	< 1% ³	8.8 % ³	-	-	VER Y LOW	CRITICAL

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: Comparis	on 11. Cohort segregatior	n + individual segregation v	ersus usual care

Quality No of studi es	/ assessment Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	No of patien Cohort segregatio n into pathogens	nts Contro I	Effect Relativ e (95% CI)	Absolut e	Quali ty	Importance
Patien	t satisfaction								-			
1 (Griffi ths 2004)	observation al studies	serious 1	no serious inconsistenc y	no serious indirectnes s	Not calculable 2	none	Positive: 63%: Negative: 12%: Unsure: 25% (p<0.001)	-	-	-	VER Y LOW	IMPORTAN T
Carer satisfaction												

© NICE 2017. All rights reserved. Subject to Notice of rights.

Quality assessment						No of patients		Effect				
No of studi es	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other consideration s	Cohort segregatio n into pathogens	Contro I	Relativ e (95% CI)	Absolut e	Quali ty	Importance
1 (Griffi ths 2004)	observation al studies	serious 1	no serious inconsistenc y	no serious indirectnes s	Not calculable 2	none	Positive: 85%: Negative: 4%: Unsure: 11% (p<0.001)	-	-	-	VER Y LOW	IMPORTAN T

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