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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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