Effectiveness of Recombinant Human Growth Hormone (rhGH) in the Treatment of Patients With Cystic Fibrosis

Appendixes

Appendix A. Search Strategies

Number of citations in ()
/ after an index term indicates that all subheadings were selected.
* before an index term indicates that that term was focused - i.e. limited to records where major MeSH/Emtree term.
"exp" before an index term indicates that the term was exploded.
.tw. indicates a search for a term in title/abstract.
.mp. indicates a free text search for a term.
.pt. indicates a search for a publication type.
$ at the end of a term indicates that this term has been truncated.
? in the middle of a term indicates the use of a wildcard.
adj indicates a search for two terms where they appear adjacent to one another.
sh indicates a search term for subheading.

Key Questions 1, 2, 4, 6, and 7 Search

MEDLINE (Ovid)

1. Cystic Fibrosis/
2. cystic fibrosis.mp.
3. 1 or 2
4. Human Growth Hormone/
5. human growth hormone.mp.
6. recombinant human growth hormone.mp.
7. rhgh.mp.
8. hgh.mp.
9. somatropin.mp.
10. genotropin.mp.
11. humatrope.mp.
12. hypertropin.mp.
13. jintropin.mp.
14. nordotropin.mp.
15. nutropin.mp.
16. omnitrope.mp
17. saizen.mp.
18. serostim.mp.
19. zomacton.mp.
20. zorbtive.mp.
21. crytropin.mp.
22. Or/ 4 – 21
23. **3 and 22**

Central (Ovid)

1. Cystic Fibrosis/
2. cystic fibrosis.mp.

3. 1 or 2
4. Human Growth Hormone/
5. human growth hormone.mp.
6. recombinant human growth hormone.mp.
7. rhgh.mp.
8. hgh.mp.
9. somatropin.mp.
10. genotropin.mp.
11. humatrope.mp.
12. hypertropin.mp.
13. jintropin.mp.
14. nordotropin.mp.
15. nutropin.mp.
16. omnitrope.mp
17. saizen.mp.
18. serostim.mp.
19. zomacton.mp.
20. zorbtive.mp.
21. crytropin.mp.
22. Or/ 4 – 21
23. **3 and 22**

Key Question 3 Search

MEDLINE (Ovid)

1. Epidemiologic studies/
2. Exp case control studies/
3. Exp Cohort Studies/
4. Case control.tw.
5. (cohort adj (study or studies)).tw.
6. cohort analy$.tw.
7. (follow up adj (study or studies)).tw.
8. (observational adj (study or studies)).tw.
9. longitudinal.tw.
10. retrospective.tw.
11. cross sectional.tw.
12. Cross-Sectional Studies/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. randomized controlled trial.pt.
15. controlled clinical trial.pt.
16. randomized.ab.
17. placebo.ab.
18. drug therapy.fs.
19. randomly.ab.
20. trial.ab.
21. groups.ab.

22. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. animals.sh not (humans.sh. and animals.sh.)
24. 22 not 23
25. 13 or 24
26. Cystic Fibrosis/
27. cystic fibrosis.mp.
28. 26 or 27
29. Mortality/
30. mortality.mp.
31. death.mp.
32. Quality of Life/
33. $quality of life.mp.
34. $qol.mp.
35. Fractures, Bone/
36. bone fracture$.mp.
37. broken bones.mp.
38. Neoplasms/
39. neoplas$.mp.
40. malignan$.mp.
41. cancer.mp.
42. tumor.mp.
43. Or/ 29 – 42
44. **25 and 28 and 43**

Central (Ovid)

1. Cystic Fibrosis/
2. cystic fibrosis.mp.
3. 1 or 2
4. Mortality/
5. mortality.mp.
6. death.mp.
7. Quality of Life/
8. $quality of life.mp.
9. $qol.mp.
10. Fractures, Bone/
11. bone fracture$.mp.
12. broken bones.mp.
13. Neoplasms/
14. neoplas$.mp.
15. malignan$.mp.
16. cancer.mp.
17. tumor.mp.
18. Or/ 4 – 17
19. **3 and 18**

Key Question 5 Search

MEDLINE (Ovid)

1. Epidemiologic studies/
2. Exp case control studies/
3. Exp Cohort Studies/
4. Case control.tw.
5. (cohort adj (study or studies)).tw.
6. cohort analy$.tw.
7. (follow up adj (study or studies)).tw.
8. (observational adj (study or studies)).tw.
9. longitudinal.tw.
10. retrospective.tw.
11. cross sectional.tw.
12. Cross-Sectional Studies/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. randomized controlled trial.pt.
15. controlled clinical trial.pt.
16. randomized.ab.
17. placebo.ab.
18. drug therapy.fs.
19. randomly.ab.
20. trial.ab.
21. groups.ab.
22. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. animals.sh not (humans.sh. and animals.sh.)
24. 22 not 23
25. 13 or 24
26. Human Growth Hormone/
27. human growth hormone.mp.
28. recombinant human growth hormone.mp.
29. rhgh.mp.
30. hgh.mp.
31. somatropin.mp.
32. genotropin.mp.
33. humatrope.mp.
34. hypertropin.mp.
35. jintropin.mp.
36. nordotropin.mp.
37. nutropin.mp.
38. omnitrope.mp
39. saizen.mp.
40. serostim.mp.
41. zomacton.mp.
42. zorbtive.mp.
43. crytropin.mp.

44. Or/ 26 – 43
45. Neoplasms/
46. neoplas$.mp.
47. malignan$.mp.
48. cancer.mp.
49. tumor.mp.
50. Or/ 45 – 49
51. idiopathic short stature.mp.
52. ISS.mp.
53. growth hormone deficiency.mp.
54. GHD.mp.
55. GH deficiency.mp.
56. Or/ 51 – 55
57. **25 and 44 and 50 and 56**

Central (Ovid)

1. Human Growth Hormone/
2. human growth hormone.mp.
3. recombinant human growth hormone.mp.
4. rhgh.mp.
5. hgh.mp.
6. somatropin.mp.
7. genotropin.mp.
8. humatrope.mp.
9. hypertropin.mp.
10. jintropin.mp.
11. nordotropin.mp.
12. nutropin.mp.
13. omnitrope.mp
14. saizen.mp.
15. serostim.mp.
16. zomacton.mp.
17. zorbtive.mp.
18. crytropin.mp.
19. Or/ 1 – 18
20. Neoplasms/
21. neoplas$.mp.
22. malignan$.mp.
23. cancer.mp.
24. tumor.mp.
25. Or/ 20 – 24
26. idiopathic short stature.mp.
27. ISS.mp.
28. growth hormone deficiency.mp.
29. GHD.mp.
30. GH deficiency.mp.

31. Or/ 26 – 30
32. 19 and 25 and 31

Appendix B. Data Extraction Forms

Trials Evaluating rhGH in Patients With Cystic Fibrosis

Study Identification

First Author:	Year:
Language:	Location:
Funding Source Specify: ❑ Industry ❑ Government/Foundation Academia ❑ Other/Unknown	Citation:

Design Characteristics

Study Design

❑ RCT – Parallel	❑ Obs – Registry
❑ RCT – Crossover	❑ Case Report
❑ Obs – Cohort	❑ Other
❑ Obs – Case Control	
❑ Obs – Cross-Sectional	

Study Population

Inclusion Criteria:		
Exclusion Criteria:		
rhGH product name:	Dose/Frequency as given in article:	Total dose/week:
Control product:	Dose/Frequency:	

Run-in period? ❑ Yes ❑ No	Describe Run-in:		Patients removed from run-in, why:	
#enrolled:	#completed:	#Withdrawals:	#rhGH w/d, why:	#Control w/d, why:
Length of Study:		Duration of follow-up:		

Baseline Characteristics

	rhGH group	**Control group**
N		
Age: mean (SD)*		
Males: number (%)		
Tanner Stage		
Height (cm): mean (SD)*		
Height Z-score		
Height percentile		
Weight (kg)		
Weight Z-score		
Weight percentile		
BMI (kg/m^2)		
BMI Z-score		
Lean Body Mass (kg)		
FVC (L)		

FVC % Predicted		
FEV_1 (L)		
FEV_1 % Predicted		

*If not reported as mean and SD, please specify

Concurrent Therapies

Nutrition:
❑ Food
❑ Enteral Nutrition
❑ TPN

	rhGH Group		Control Group	
	# Patients	**Mean Dose (SD)***	**# Patients**	**Mean Dose (SD)***
Pancreatic Enzymes				
Inhaled Tobramycin				
Recombinant Human DNase				
Inhaled Beta-2 Agonists				
Inhaled Anticholinergics				
Inhaled Corticosteroids				
Oral Corticosteroids				
IV Corticosteroids				
Oral NSAIDs				

*If not reported as mean and SD, please specify

Pulmonary Outcomes (Continuous)—Means (Standard Deviations or Standard Errors; please specify)

	rhGH group				Control group					
Sample size (n)										
	Baseline Mean (SD)*	**Endpoint Mean (SD)**	**Mean Change from Baseline (SD)**	**P-value for Change from Baseline**	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Mean Change from Baseline (SD)**	**P-value for Change from Baseline**	**Mean Difference between groups (SD)**	**P-value for Difference Between Groups**
FVC (L)										
FVC % predicted										
FEV_1 (L)										
FEV_1 % predicted										
FEV_1 Z-score										

*If not reported as mean and SD, please specify

Height and Weight Outcomes—Means (Standard Deviations or Standard Errors; please specify)

	rhGH group				Control group					
Sample size (n)										
	Baseline Mean (SD)*	**Endpoint Mean (SD)**	**Mean Change from Baseline (SD)**	**P-value for Change from Baseline**	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Mean Change from Baseline (SD)**	**P-value for Change from Baseline**	**Mean Difference between groups (SD)**	**P-value for Difference Between Groups**
Height (cm)										
Height velocity (cm/y)										
Height Z-score										
Height percentile										

Weight (kg)										
Weight velocity (kg/y)										
Weight Z-score										
Weight percentile										
BMI (kg/m^2)										
BMI Z-score										
%Ideal Body Weight										
Lean Body Mass (kg)										

*If not reported as mean and SD, please specify

Bone Outcomes (Continuous)—Means (Standard Deviations or Standard Errors; please specify)

	rhGH group				**Control group**					
Sample size (n)										
	Baseline Mean (SD)*	**Endpoint Mean (SD)**	**Mean Change from Baseline (SD)**	**P-value for Change from Baseline**	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Mean Change from Baseline (SD)**	**P-value for Change from Baseline**	**Mean Difference between groups (SD)**	**P-value for Difference Between Groups**
Bone age (y)										
Bone mineral content (g)										
Bone mineral content Z-score										

*If not reported as mean and SD, please specify

Exercise Tolerance (Continuous)—Means (Standard Deviations or Standard Errors; please specify)

	rhGH group				Control group					
Sample size (n)										
	Baseline Mean (SD)*	**Endpoint Mean (SD)**	**Mean Change from Baseline (SD)**	**P-value for Change from Baseline**	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Mean Change from Baseline (SD)**	**P-value for Change from Baseline**	**Mean Difference between groups (SD)**	**P-value for Difference Between Groups**
Test used:										
Test duration (min)										
Work Rate/Power (W)										
$Vo_{2\text{-peak}}$ (ml)										
$Vo_{2\text{-max}}$ (ml/kg/min)										
Oxygen $pulse_{peak}$ (ml/beat)										
$Ventilation_{peak}$ (L/min)										

*If not reported as mean and SD, please specify

Protein Turnover (Continuous)—Means (Standard Deviations or Standard Errors; please specify)

	rhGH group				Control group					
Sample size (n)										
	Baseline Mean (SD)*	**Endpoint Mean (SD)**	**Mean Change from Baseline (SD)**	**P-value for Change from Baseline**	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Mean Change from Baseline (SD)**	**P-value for Change from Baseline**	**Mean Difference between groups (SD)**	**P-value for Difference Between Groups**
LeuRa (µmol/kg*h)										
LeuOxidation (µmol/kg*h)										
NOLD (µmol/kg*h)										
Oxidation/NOLD										

(µmol/kg*h)										

*If not reported as mean and SD, please specify

Sexual Maturation (Descriptive Text)

Baseline pubertal status:		
	rhGH group	**Control group**
Follow-up pubertal status:		

Health Outcomes (Continuous)—Means (Standard Deviations or Standard Errors; please specify)

	rhGH group				**Control group**					
Sample size (n)										
	Baseline Mean (SD)*	**Endpoint Mean (SD)**	**Mean Change from Baseline (SD)**	**P-value for Change from Baseline**	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Mean Change from Baseline (SD)**	**P-value for Change from Baseline**	**Mean Difference between groups (SD)**	**P-value for Difference Between Groups**
HRQOL—Scale used:										
HRQOL Overall score										
HRQOL Sub-score 1 **Please specify**										
HRQOL Sub-score 2 **Please specify**										

HRQOL Sub-score 3 **Please specify**										
Antibiotic use—Definition of outcome:										
Antibiotic use										

*If not reported as mean and SD, please specify

	rhGH group	Control group
Sample size (n)		
Categorical outcomes below :		
Hospitalizations (number of events)		
Pulmonary Exacerbation—Definition of outcome:		
Pulmonary Exacerbations (number of events)		
Cancer—Describe type:		
Cancer (number of cases)		
Cancer—Describe type:		
Cancer (number of cases)		
Cancer—Describe type:		
Cancer (number of cases)		

Glucose Parameters—Means (Standard Deviations or Standard Errors; please specify)

	rhGH group				Control group					
Sample size (n)										
	Baseline Mean (SD)*	**Endpoint Mean (SD)**	**Mean Change from**	**P-value for Change from**	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Mean Change from**	**P-value for Change from**	**Mean Difference between**	**P-value for Difference Between**

			Baseline (SD)	Baseline			Baseline (SD)	Baseline	groups (SD)	Groups
HbA1c (%)										
Random BG (mg/dl)										
Fasting BG (mg/dl)										
Stimulated BG (mg/dl)										
Postprandial BG (mg/dl)										

	rhGH group	Control group
Sample size (n)		
Categorical outcomes below :		
Hyperglycemia (number of events)		
Onset of DM (number of events)		

*If not reported as mean and SD, please specify

Biomarkers (Continuous)—Means (Standard Deviations or Standard Errors; please specify)

	rhGH group				Control group					
Sample size (n)										
	Baseline Mean (SD)*	**Endpoint Mean (SD)**	**Mean Change from Baseline (SD)**	**P-value for Change from Baseline**	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Mean Change from Baseline (SD)**	**P-value for Change from Baseline**	**Mean Difference between groups (SD)**	**P-value for Difference Between Groups**
IGF-I (ng/dl)										
IGF-I Z-score										
IGFBP-3 (ng/ml)										
IGFBP-3 Z-score										

*If not reported as mean and SD, please specify

Linkages of Intermediate Outcomes to Important Health Outcomes

Study Identification

First Author:	Year:
Language:	Location:
Funding Source Specify: ❑ Industry ❑ Government/Foundation ❑ Academia ❑ Other/Unknown	Citation (Journal Name. Year;Volume:Page):

Study Population

Inclusion Criteria:
Exclusion Criteria:
Duration of follow-up:

Design Characteristics

Study Design
❑ RCT – Parallel ❑ Obs – Registry
❑ RCT – Crossover ❑ Case Report
❑ Obs – Cohort ❑ Other
❑ Obs – Case Control
❑ Obs – Cross-Sectional

Terminal Outcome

❑ Mortality
❑ Bone Outcomes
❑ Health-Related Quality-of-Life

Predictor 1

List/Define:			
❑ Significantly Related	❑ Not Significant		
Univariate Stats: ❑ p-value ❑ r-value ❑ HR (95%CI) ❑ RR (95%CI) ❑ OR (95%CI) ❑ No stats given - only text	Provide Effect Size:	Multivariate Stats: ❑ p-value ❑ r-value ❑ AHR (95%CI) ❑ ARR (95%CI) ❑ AOR (95%CI) ❑ No stats given - only text	Provide Effect Size:

Predictor 2

List/Define:			
❑ Significantly Related	❑ Not Significant		
Univariate Stats: ❑ p-value ❑ r-value ❑ HR (95%CI) ❑ RR (95%CI) ❑ OR (95%CI)	Provide Effect Size:	Multivariate Stats: ❑ p-value ❑ r-value ❑ AHR (95%CI) ❑ ARR (95%CI) ❑ AOR (95%CI)	Provide Effect Size:

❑ No stats given - only text	❑ No stats given - only text

Predictor 3

List/Define:			
❑ Significantly Related	❑ Not Significant		
Univariate Stats: ❑ p-value ❑ r-value ❑ HR (95%CI) ❑ RR (95%CI) ❑ OR (95%CI) ❑ No stats given - only text	Provide Effect Size:	Multivariate Stats: ❑ p-value ❑ r-value ❑ AHR (95%CI) ❑ ARR (95%CI) ❑ AOR (95%CI) ❑ No stats given - only text	Provide Effect Size:

Predictor 4

List/Define:			
❑ Significantly Related	❑ Not Significant		
Univariate Stats: ❑ p-value ❑ r-value ❑ HR (95%CI) ❑ RR (95%CI) ❑ OR (95%CI) ❑ No stats given - only text	Provide Effect Size:	Multivariate Stats: ❑ p-value ❑ r-value ❑ AHR (95%CI) ❑ ARR (95%CI) ❑ AOR (95%CI) ❑ No stats given - only text	Provide Effect Size:

Predictor 5

List/Define:			
❑ Significantly Related	❑ Not Significant		
Univariate Stats: ❑ p-value ❑ r-value ❑ HR (95%CI) ❑ RR (95%CI) ❑ OR (95%CI) ❑ No stats given - only text	Provide Effect Size:	Multivariate Stats: ❑ p-value ❑ r-value ❑ AHR (95%CI) ❑ ARR (95%CI) ❑ AOR (95%CI) ❑ No stats given - only text	Provide Effect Size:

Predictor 6

List/Define:			
❑ Significantly Related	❑ Not Significant		
Univariate Stats: ❑ p-value ❑ r-value ❑ HR (95%CI) ❑ RR (95%CI) ❑ OR (95%CI)	Provide Effect Size:	Multivariate Stats: ❑ p-value ❑ r-value ❑ AHR (95%CI) ❑ ARR (95%CI) ❑ AOR (95%CI)	Provide Effect Size:

❑ No stats given - only text	❑ No stats given - only text

Malignant Harms

Study Identification

First Author:	Year:
Language:	Location:
Funding Source Specify: ❑ Industry ❑ Government/Foundation ❑ Academia ❑ Other/Unknown	Citation (Journal Name. Year;Volume:Page):

Design Characteristics

Study Design	
❑ RCT – Parallel	❑ Obs – Registry
❑ RCT – Crossover	❑ Case Report
❑ Obs – Cohort	❑ Other
❑ Obs – Case Control	
❑ Obs – Cross-Sectional	

Study Population

Inclusion Criteria: ❑ Idiopathic Short Stature ❑ Growth Hormone Deficiency		
Exclusion Criteria:		
rhGH product name:	Dose/Frequency as given in article:	Total dose/week:
Control product:	Dose/Frequency:	

Run-in period? ❑ Yes ❑ No	Describe Run-in:	Patients removed from run-in, why:

#enrolled:	#completed:	#Withdrawals:	#rhGH w/d, why:	#Control w/d, why:
Length of Study:		Duration of follow-up:		

Biomarkers (Continuous)—Means (Standard Deviations or Standard Errors; please specify)

	rhGH group				**Control group**					
Sample size (n)										
	Baseline Mean (SD)*	**Endpoint Mean (SD)**	**Mean Change from Baseline (SD)**	**P-value for Change from Baseline**	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Mean Change from Baseline (SD)**	**P-value for Change from Baseline**	**Mean Difference between groups (SD)**	**P-value for Difference Between Groups**
IGF-I (ng/dl)										
IGF-I Z-score										
IGFBP-3 (ng/ml)										
IGFBP-3 Z-score										

Cancer Outcomes (Categorical)

	rhGH group	**Control group**
Sample size (n)		
Cancer – Describe type:		
Cancer (number of cases)		
Cancer – Describe type:		
Cancer (number of cases)		
Cancer – Describe type:		
Cancer (number of cases)		

Appendix C. Excluded Studies from Searches

Excluded Studies from Full-Text Review of Key Questions 1, 2, 4, 6, and 7 Search

Reference	Reason for Exclusion
Bucuvalas JC, Chernausek SD. Growth hormone and cystic fibrosis: Good for more than growth? J Pediatr 2001;139:616-618.	Not a report of a new discovery
Colombo C, Battezzati A. Growth failure in cystic fibrosis: A true need for anabolic agents? J Pediatr 2005;146:303-305.	Not a report of a new discovery

Legend: CF=cystic fibrosis; rhGH=recombinant human growth hormone

Excluded Studies from Full-Text Review of Key Question 3 Search

Reference	Reason for Exclusion
Abbott J, Hart A, Morton AM, et al. Can health-related quality of life predict survival in adults with cystic fibrosis? Am J Respir Crit Care Med 2009;179:54-58.	Not evaluating the link between intermediate outcomes and important health outcomes
Abbott J, Morton AM, Musson H, et al. Nutritional status, perceived body image and eating behaviours in adults with cystic fibrosis. Clin Nutr 2007;26:91-99.	Not evaluating the link between intermediate outcomes and important health outcomes
Abman SH, Accurso FJ, Bowman CM. Persistent morbidity and mortality of protein calorie malnutrition in young infants with CF. J Pediatr Gastroenterol Nutr 1986;5:393-396.	Not evaluating the link between intermediate outcomes and important health outcomes
Aebi C, Bracher R, Liechti-Gallati S, et al. The age at onset of chronic pseudomonas aeruginosa colonization in cystic fibrosis—prognostic significance. Eur J Pediatr 1995;154:S69-S73.	Not evaluating the link between intermediate outcomes and important health outcomes
Amadori A, Antonelli A, Balteri I, et al. Recurrent exacerbations affect FEV(1) decline in adult patients with cystic fibrosis. Respir Med 2009;103:407-413.	Not evaluating the link between intermediate outcomes and important health outcomes
Amelina E, Senkevich N, Cherniak A, et al. Home intravenous therapy in adult cystic fibrosis patients. The impact on lung function and quality of life [abstract]. European Respiratory Journal 2000;16:123s.	Not evaluating the link between intermediate outcomes and important health outcomes
Aris RM, Stephens AR, Ontjes DA, et al. Adverse alterations in bone metabolism are associated with lung infection in adults with cystic fibrosis. Am J Respir Crit Care Med 2000;162:1674-1678.	Not evaluating the link between intermediate outcomes and important health outcomes

Reference	Reason for Exclusion
Arrington-Sanders R, Yi MS, Tsevat J, et al. Gender differences in health-related quality of life of adolescents with cystic fibrosis. Health Qual Life Outcomes 2006;4:5.	Not evaluating the link between intermediate outcomes and important health outcomes
Assael BM, Casazza G, Iansa P, et al. Growth and long-term lung function in cystic fibrosis: A longitudinal study of patients diagnosed by neonatal screening. Pediatr Pulmonol 2009;44:209-215.	Not evaluating the link between intermediate outcomes and important health outcomes
Aurora P, Whitehead B, Wade A, et al. Lung transplantation and life extension in children with cystic fibrosis. Lancet 1999;354:1591-1593.	Evaluating terminal outcomes after an intervention
Berlinski A, Fan LL, Kozinetz CA, et al. Invasive mechanical ventilation for acute respiratory failure in children with cystic fibrosis: Outcome analysis and case-control study. Pediatr Pulmonol 2002;34:297-303.	Not evaluating the link between intermediate outcomes and important health outcomes
Bismuth E, Laborde K, Taupin P, et al. Glucose tolerance and insulin secretion, morbidity, and death in patients with cystic fibrosis. J Pediatr 2008 545.e1;152:540; Ar-545.	Not evaluating the link between intermediate outcomes and important health outcomes
Bizzarri C, Lucidi V, Ciampalini P, et al. Clinical effects of early treatment with insulin glargine in patients with cystic fibrosis and impaired glucose tolerance. J Endocrinol Invest 2006;29:R1-R4.	Not evaluating the link between intermediate outcomes and important health outcomes
Bradley J, McAlister O, Elborn S. Pulmonary function, inflammation, exercise capacity and quality of life in cystic fibrosis. Eur Respir J 2001;17:712-715.	Not evaluating the link between intermediate outcomes and important health outcomes
Britto MT, Kotagal UR, Hornung RW, et al. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. Chest 2002;121:64-72.	Not evaluating the link between intermediate outcomes and important health outcomes
Callaghan BD, Hoo AF, Dinwiddie R, et al. Growth and lung function in Asian patients with cystic fibrosis. Arch Dis Child 2005;90:1029-1032.	Not evaluating the link between intermediate outcomes and important health outcomes
Camargos PA, Guimaraes MD, Reis FJ. Prognostic aspects of cystic fibrosis in Brazil. Ann Trop Paediatr 2000;20:287-291.	Not evaluating the link between intermediate outcomes and important health outcomes
Christian B. The impact of chronic illness on quality of life in children with cystic fibrosis [abstract]. Pediatr Pulmonol 2006;41:398.	Not evaluating the link between intermediate outcomes and important health outcomes

Reference	Reason for Exclusion
Christian B. Functional disability and quality of life of school-age children with cystic fibrosis [abstract]. Pediatr Pulmonol 2004;38:356.	Evaluating terminal outcomes after an intervention
Corey M, Gaskin K, Durie P, et al. Improved prognosis in CF patients with normal fat absorption. J Pediatr Gastroenterol Nutr 1984;3:S99-S105.	Not evaluating the link between intermediate outcomes and important health outcomes
Curtis JR, Burke W, Kassner AW, et al. Absence of health insurance is associated with decreased life expectancy in patients with cystic fibrosis. Am J Respir Crit Care Med 1997;155:1921-1924.	Not evaluating the link between intermediate outcomes and important health outcomes
Dalzell AM, Shepherd RW, Dean B, et al. Nutritional rehabilitation in cystic fibrosis: A 5 year follow-up study. J Pediatr Gastroenterol Nutr 1992;15:141-145.	Not evaluating the link between intermediate outcomes and important health outcomes
Dodd ME, Abbott J, Haworth CS, et al. Validity of a visual numerical general quality of life scale and chest scale in adults with cystic fibrosis [abstract]. Thorax 1997;52:A45.	Not evaluating the link between intermediate outcomes and important health outcomes
Dodge JA, Lewis PA, Stanton M, et al. Cystic fibrosis mortality and survival in the UK: 1947-2003. Eur Respir J 2007;29:522-526.	Not evaluating the link between intermediate outcomes and important health outcomes
Dodge JA, Morison S, Lewis PA, et al. Cystic fibrosis in the United Kingdom, 1968-1988: Incidence, population and survival. Paediatr Perinat Epidemiol 1993;7:157-166.	Not evaluating the link between intermediate outcomes and important health outcomes
Doull IJM, Ryley HC, Weller P, et al. Death from cystic fibrosis in the first five years of life and the effect of newborn screening [abstract]. XIIIth International Cystic Fibrosis Congress; 2000 Jun 4-8; Stockholm, Sweden.	Not evaluating the link between intermediate outcomes and important health outcomes
Dunnink MA, Doeleman WR, Trappenburg JC, et al. Respiratory muscle strength in stable adolescent and adult patients with cystic fibrosis. J Cyst Fibros 2009;8:31-36.	Not evaluating the link between intermediate outcomes and important health outcomes
Escobar MA, Grosfeld JL, Burdick JJ, et al. Surgical considerations in cystic fibrosis: A 32-year evaluation of outcomes. Surgery 2005;138:560-571.	Not evaluating the link between intermediate outcomes and important health outcomes
Filliozat AM, Hennequet A. Psychological development and cystic fibrosis. Ann Pediatr (Paris) 1976;23:47-52.	Not in CF patients
Hodson ME, Simmonds NJ, Warwick WJ, et al. An international/multicentre report on patients with cystic fibrosis (CF) over the age of 40 years. J Cyst Fibros 2008;7:537-542.	Not evaluating the link between intermediate outcomes and important health outcomes

Reference	Reason for Exclusion
Hogg M, Braithwaite M, Bailey M, et al. Work disability in adults with cystic fibrosis and its relationship to quality of life. J Cyst Fibros 2007;6:223-227.	Not evaluating the link between intermediate outcomes and important health outcomes
Jarad NA, Giles K. Risk factors for increased need for intravenous antibiotics for pulmonary exacerbations in adult patients with cystic fibrosis. Chron respir dis 2008;5:29-33.	Not evaluating the link between intermediate outcomes and important health outcomes
Kalish LA, Waltz DA, Dovey M, et al. Impact of burkholderia dolosa on lung function and survival in cystic fibrosis. Am J Respir Crit Care Med 2006;173:421-425.	Not evaluating the link between intermediate outcomes and important health outcomes
Kulich M, Rosenfeld M, Goss CH, et al. Improved survival among young patients with cystic fibrosis. J Pediatr 2003;142:631-636.	Not evaluating the link between intermediate outcomes and important health outcomes
Liou TG, Adler FR, Cox DR, et al. Lung transplantation and survival in children with cystic fibrosis. N Engl J Med 2007;357:2143-2152.	Evaluating terminal outcomes after an intervention
Liou TG, Adler FR, Huang D. Use of lung transplantation survival models to refine patient selection in cystic fibrosis. Am J Respir Crit Care Med 2005;171:1053-1059.	Not evaluating the link between intermediate outcomes and important health outcomes
Maisonneuve P, FitzSimmons SC, Neglia JP, et al. Cancer risk in nontransplanted and transplanted cystic fibrosis patients: A 10-year study. J Natl Cancer Inst 2003;95:381-387.	Not evaluating the link between intermediate outcomes and important health outcomes
Milla CE, Billings J, Moran A. Diabetes is associated with dramatically decreased survival in female but not male subjects with cystic fibrosis. Diabetes Care 2005;28:2141-2144.	Not evaluating the link between intermediate outcomes and important health outcomes
Miller RJ, Tildesley HD, Wilcox PG, et al. Sex disparities in effects of cystic fibrosis-related diabetes on clinical outcomes: A matched study. Can Respir J 2008;15:291-294.	Not evaluating the link between intermediate outcomes and important health outcomes
Munzenberger PJ, Van Wagnen CA, Abdulhamid I, et al. Quality of life as a treatment outcome in patients with cystic fibrosis. Pharmacotherapy 1999;19:393-398.	Not evaluating the link between intermediate outcomes and important health outcomes
Neglia JP, FitzSimmons SC, Maisonneuve P, et al. The risk of cancer among patients with cystic fibrosis. cystic fibrosis and cancer study group. N Engl J Med 1995;332:494-499.	Not evaluating the link between intermediate outcomes and important health outcomes

Reference	Reason for Exclusion
Neglia JP, Wielinski CL, Warwick WJ. Cancer risk among patients with cystic fibrosis. J Pediatr 1991;119:764-766.	Not evaluating the link between intermediate outcomes and important health outcomes
Palermo TM, Harrison D, Koh JL. Effect of disease-related pain on the health-related quality of life of children and adolescents with cystic fibrosis. Clin J Pain 2006;22:532-537.	Not evaluating the link between intermediate outcomes and important health outcomes
Quittner AL, Modi AC, Accurso FJ, et al. Treatment satisfaction, health-related quality of life and airway clearance therapies in patients with cystic fibrosis [abstract]. Pediatr Pulmonol 2004;38:314.	Not evaluating the link between intermediate outcomes and important health outcomes
Rosenecker J, Hofler R, Steinkamp G, et al. Diabetes mellitus in patients with cystic fibrosis: The impact of diabetes mellitus on pulmonary function and clinical outcome. Eur J Med Res 200127;6:345-350.	Not evaluating the link between intermediate outcomes and important health outcomes
Rovner AJ, Zemel BS, Leonard MB, et al. Mild to moderate cystic fibrosis is not associated with increased fracture risk in children and adolescents. J Pediatr 2005;147:327-331.	Not evaluating the link between intermediate outcomes and important health outcomes
Saltzman DA, Johnson EM, Feltis BA, et al. Surgical experience in patients with cystic fibrosis: A 25-year perspective. Pediatr Pulmonol 2002;33:106-110.	Not evaluating the link between intermediate outcomes and important health outcomes
Schluchter MD, Konstan MW, Davis PB. Jointly modelling the relationship between survival and pulmonary function in cystic fibrosis patients. Stat Med 2002;21:1271-1287.	Not evaluating the link between intermediate outcomes and important health outcomes
Selvadurai HC, Blimkie CJ, Cooper PJ, et al. Gender differences in habitual activity in children with cystic fibrosis. Arch Dis Child 2004;89:928-933.	Not evaluating the link between intermediate outcomes and important health outcomes
Sheldon CD, Hodson ME, Carpenter LM, et al. A cohort study of cystic fibrosis and malignancy. Br J Cancer 1993;68:1025-1028.	Not evaluating the link between intermediate outcomes and important health outcomes
Slieker MG, van Gestel JP, Heijerman HG, et al. Outcome of assisted ventilation for acute respiratory failure in cystic fibrosis. Intensive Care Med 2006;32:754-758.	Not evaluating the link between intermediate outcomes and important health outcomes
Sood N, Paradowski LJ, Yankaskas JR. Outcomes of intensive care unit care in adults with cystic fibrosis. Am J Respir Crit Care Med 2001;163:335-338.	Not evaluating the link between intermediate outcomes and important health outcomes

Reference	Reason for Exclusion
Stern M, Picard C, Grenet D. Mucoviscidosis in adults. Presse Med 2002;31:263-270.	Not in CF patients
Street ME, Spaggiari C, Volta C, et al. The IGF system and cytokine interactions and relationships with longitudinal growth in prepubertal patients with cystic fibrosis. Clin Endocrinol (Oxf) 2009;70:593-598.	Not evaluating the link between intermediate outcomes and important health outcomes
Suri R, Metcalfe C, Wallis C, et al. Assessing the usefulness of outcomes measured in a cystic fibrosis treatment trial. Respir Med 2007;101:254-260.	Evaluating terminal outcomes after an intervention
Thomas C, Mitchell P, O'Rourke P, et al. Quality-of-life in children and adolescents with cystic fibrosis managed in both regional outreach and cystic fibrosis center settings in Queensland. J Pediatr 2006;148:508-516.	Not evaluating the link between intermediate outcomes and important health outcomes
Venuta F, Rendina EA, Rocca GD, et al. Pulmonary hemodynamics contribute to indicate priority for lung transplantation in patients with cystic fibrosis. J Thorac Cardiovasc Surg 2000;119:682-689.	Not evaluating the link between intermediate outcomes and important health outcomes
Wahl AK, Rustoen T, Hanestad BR, et al. Living with cystic fibrosis: Impact on global quality of life. Heart Lung 2005;34:324-331.	Not evaluating the link between intermediate outcomes and important health outcomes
Waterhouse DF, McLaughlin AM, Gallagher CG. Time course and recovery of arterial blood gases during exacerbations in adults with cystic fibrosis. J Cyst Fibros 2009;8:9-13.	Not evaluating the link between intermediate outcomes and important health outcomes
Watts KD, Seshadri R, Sullivan C, et al. Increased prevalence of risk factors for morbidity and mortality in the US hispanic CF population. Pediatr Pulmonol 2009;44:594-601.	Not evaluating the link between intermediate outcomes and important health outcomes

Legend: CF=cystic fibrosis

Excluded Studies from Full-Text Review of Key Question 5 Search

Reference	Reason for Exclusion
Abs R, Bengtsson BA, Hernberg-Stahl E, et al. GH replacement in 1034 growth hormone deficient hypopituitary adults: Demographic and clinical characteristics, dosing and safety. Clin Endocrinol (Oxford) 1999;50:703-713.	Not evaluating malignancy outcomes
Abs R, Mattsson AF, Bengtsson BA, et al. Isolated growth hormone (GH) deficiency in adult patients: Baseline clinical characteristics and responses to GH replacement in comparison with hypopituitary patients. A sub-analysis of the KIMS database. Growth Horm IGF Res 2005;15:349-359.	Not evaluating malignancy outcomes

Reference	Reason for Exclusion
Ahmad AM, Guzder R, Wallace AM, et al. Circadian and ultradian rhythm and leptin pulsatility in adult GH deficiency: Effects of GH replacement. J Clin Endocrinol Metab 2001;86:3499-3506.	Not in CF, ISS, or GHD patients
Ahmad AM, Hopkins MT, Thomas J, et al. Body composition and quality of life in adults with growth hormone deficiency; effects of low-dose growth hormone replacement. Clin Endocrinol (Oxford) 2001;54:709-717.	Not in CF, ISS, or GHD patients
Ahmad AM, Hopkins MT, Weston PJ, et al. Effects of GH replacement on 24-h ambulatory blood pressure and its circadian rhythm in adult GH deficiency. Clin Endocrinol (Oxford) 2002;56:431-437.	Not in CF, ISS, or GHD patients
Andiran N, Yordam N. TNF-alpha levels in children with growth hormone deficiency and the effect of long-term growth hormone replacement therapy. Growth Horm IGF Res 2007;17:149-153.	Not evaluating malignancy outcomes
Bozzola M, De Amici M, Zecca M, et al. Modulating effect of human growth hormone on tumour necrosis factor-alpha and interleukin-1beta. Eur J Endocrinol 1998;138:640-643.	Not evaluating malignancy outcomes
Brandou F, Aloulou I, Razimbaud A, et al. Lower ability to oxidize lipids in adult patients with growth hormone (GH) deficiency: Reversal under GH treatment. Clin Endocrinol (Oxf) 2006;65:423-428.	Not in CF, ISS, or GHD patients
Buchanan CR, Preece MA, Milner RD. Mortality, neoplasia, and creutzfeldt-jakob disease in patients treated with human pituitary growth hormone in the United Kingdom. BMJ 1991;302:824-828.	Not in CF, ISS, or GHD patients
Butenandt O, Jocham A, Schwarz HP, et al. Childhood onset of GH deficiency: Reassessment of GH status and effects of substitution. Growth Horm IGF Res 1998;8:9-13.	Not evaluating malignancy outcomes
Carmona M, Jordan J, Fernandez F, et al. Growth retardation, GH deficiency, hyperprolactinemia and delayed puberty. An Esp Pediatr 1985;22:397-401.	Not evaluating malignancy outcomes
Colao A, Di Somma C, Spiezia S, et al. Effect of growth hormone (GH) and/or testosterone replacement on the prostate in GH-deficient adult patients. J Clin Endocrinol Metab 2003;88:88-94.	Not in CF, ISS, or GHD patients
Feldt-Rasmussen U, Wilton P, Jonsson P, et al. Aspects of growth hormone deficiency and replacement in elderly hypopituitary adults. Growth Horm IGF Res 2004;14:S51-S58.	Not in CF, ISS, or GHD patients
Fernholm R, Bramnert M, Hagg E, et al. Growth hormone replacement therapy improves body composition and increases bone metabolism in elderly patients with pituitary disease. J Clin Endocrinol Metab 2000;85:4104-4112.	Not in CF, ISS, or GHD patients
Finkenstedt G, Hofle G, Pallua A, et al. Changes in the volume of residual pituitary adenomas in patients with adult-onset growth hormone deficiency during replacement therapy with the recombinant human growth hormone. Wien Klin Wochenschr 1999;111:887-890.	Not in CF, ISS, or GHD patients

Reference	Reason for Exclusion
Fradkin JE, Mills JL, Schonberger LB, et al. Risk of leukemia after treatment with pituitary growth hormone. JAMA 1993;270:2829-2832.	Not in CF, ISS, or GHD patients
Hatrick AG, Boghalo P, Bingham JB, et al. Does GH replacement therapy in adult GH-deficient patients result in recurrence or increase in size of pituitary tumours?. Eur J Endocrinol 2002;146:807-811.	Not in CF, ISS, or GHD patients
Hilczer M, Smyczynska J, Stawerska R, et al. Final height and growth hormone secretion after completion of growth hormone therapy in patients with idiopathic growth hormone deficiency and with abnormalities of the hypothalamic-pituitary region. Neuroendocrinol Lett 2005;26:19-24.	Not evaluating malignancy outcomes
Hoybye C, Jonsson P, Monson JP, et al. Impact of the primary aetiology upon the clinical outcome of adults with childhood-onset GH deficiency. Eur J Endocrinol 2007;157:589-596.	Not evaluating malignancy outcomes
Kaplowitz PB, Rundle AC, Blethen SL. Weight relative to height before and during growth hormone therapy in prepubertal children. Horm Metab Res 1998;30:565-569.	Not evaluating malignancy outcomes
Koranyi J, Bosaeus I, Alpsten M, et al. Body composition during GH replacement in adults—methodological variations with respect to gender. Eur J Endocrinol 2006;154:545-553.	Not in CF, ISS, or GHD patients
Lanes R, Paoli M, Carrillo E, et al. Peripheral inflammatory and fibrinolytic markers in adolescents with growth hormone deficiency: Relation to postprandial dyslipidemia. J Pediatr 2004;145:657-661.	Not in CF, ISS, or GHD patients
le Roux CW, Jenkins PJ, Chew SL, et al. Growth hormone replacement does not increase serum prostate-specific antigen in hypopituitary men over 50 years. Eur J Endocrinol 2002;147:59-63.	Not in CF, ISS, or GHD patients
Mills JL, Schonberger LB, Wysowski DK, et al. Long-term mortality in the United States cohort of pituitary-derived growth hormone recipients. J Pediatr 2004;144:430-436.	Not evaluating use of rhGH
Milner RD, Preece MA, Tanner JM. Growth in height compared with advancement in skeletal maturity in patients treated with human growth hormone. Arch Dis Child 1980;55:461-466.	Not evaluating malignancy outcomes
Pagani S, Meazza C, Travaglino P, et al. Serum cytokine levels in GH-deficient children during substitutive GH therapy. Eur J Endocrinol 2005;152:207-210.	Not evaluating malignancy outcomes
Pincelli AI, Brunani A, Scacchi M, et al. The serum concentration of tumor necrosis factor alpha is not an index of growth-hormone- or obesity-induced insulin resistance. Horm Res 2001;55:57-64.	Not in CF, ISS, or GHD patients
Price DA, Ranke MB, Guilbaud O. Growth response in the first year of growth hormone treatment in prepubertal children with organic growth hormone deficiency: A comparison with idiopathic growth hormone deficiency. the executive scientific committee of the kabi international growth study. Acta Paediatr Scand Suppl 1990;370:131-137.	Not evaluating malignancy outcomes

Reference	Reason for Exclusion
Rosenfalck AM, Fisker S, Hilsted J, et al. The effect of the deterioration of insulin sensitivity on -cell function in growth-hormone-deficient adults following 4-month growth hormone replacement therapy. Growth Horm IGF Res 1999;9:96-105.	Not in CF, ISS, or GHD patients
Schneider HJ, Oertel H, Murck H, et al. Night sleep EEG and daytime sleep propensity in adult hypopituitary patients with growth hormone deficiency before and after six months of growth hormone replacement. Psychoneuroendocrinology 2005;30:29-37.	Not in CF, ISS, or GHD patients
Scire G, Del Bianco C, Spadoni GL, et al. Growth hormone therapy does not alter the insulin-like growth factor-I/insulin-like growth factor binding protein-3 molar ratio in growth hormone-deficient children. J Endocrinol Invest 2008;31:153-158.	Not evaluating malignancy outcomes
Serri O, St-Jacques P, Sartippour M, et al. Alterations of monocyte function in patients with growth hormone (GH) deficiency: Effect of substitutive GH therapy. J Clin Endocrinol Metab 1999;84:58-63.	Not in CF, ISS, or GHD patients
Sheppard L, Eiser C, Davies HA, et al. The effects of growth hormone treatment on health-related quality of life in children. Horm Res 2006;65:243-249.	Not in CF, ISS, or GHD patients
Slyper A. The safety and effectiveness of human growth hormone using pharmacological dosing. Med Hypotheses 1995;45:523-528.	Not a report of a new discovery
Sneppen SB, Steensgaard-Hansen F, Feldt-Rasmussen U. Cardiac effects of low-dose growth hormone replacement therapy in growth hormone-deficient adults. an 18-month randomised, placebo-controlled, double-blind study. Horm Res 2002;58:21-29.	Not in CF, ISS, or GHD patients
Sorgo W, Zachmann M, Tassinari D, et al. Longitudinal anthropometric measurements in patients with growth hormone deficiency. effect of human growth hormone treatment. Eur J Pediatr 1982;138:38-45.	Not evaluating malignancy outcomes
Steinhausen HC, Dorr HG, Malin Z. Behavioral evaluation of GH treatment in short statured children and adolescents: Findings from a pilot study. J Endocrinol Invest 2002;25:351-356.	Not evaluating malignancy outcomes
Ten Have SM, van der Lely AJ, Lamberts SW. Increase in haemoglobin concentrations in growth hormone deficient adults during human recombinant growth hormone replacement therapy. Clin Endocrinol (Oxford) 1997;47:565-570.	Not in CF, ISS, or GHD patients
Ueland T, Bollerslev J, Flyvbjerg A, et al. Effects of 12 months of GH treatment on cortical and trabecular bone content of IGFs and OPG in adults with acquired GH deficiency: A double-blind, randomized, placebo-controlled study. J Clin Endocrinol Metab 2002;87:2760-1763.	Not in CF, ISS, or GHD patients
Ueland T, Odgren PR, Yndestad A, et al. Growth hormone substitution increases gene expression of members of the IGF family in cortical bone from women with adult onset growth hormone deficiency--relationship with bone turn-over. Bone 2003;33:638-645.	Not in CF, ISS, or GHD patients

Reference	Reason for Exclusion
Wilhelm B, Kann PH. Long-term effects of 7-year growth hormone substitution on bone metabolism, bone density, and bone quality in growth hormone-deficient adults. Med Klin 2004;99:569-577.	Not evaluating malignancy outcomes
Wyatt D. Lessons from the national cooperative growth study. Eur J Endocrinol 2004;151:S55-9.	Not evaluating malignancy outcomes
Xu W, Janss A, Moshang T. Adult height and adult sitting height in childhood medulloblastoma survivors. J Clin Endocrinol Metab 2003;88:4677-4681.	Not in CF, ISS, or GHD patients
Zvulunov A, Wyatt DT, Laud PW, et al. Lack of effect of growth hormone therapy on the count and density of melanocytic naevi in children. Br J Dermatol 1997;137:545-548.	Not in CF, ISS, or GHD patients

Legend: CF=cystic fibrosis; GHD=growth hormone deficient; IGF=insulin-like growth factor; IGFBP=insulin-like growth factor-binding protein; ISS=idiopathic short stature; rhGH=recombinant human growth hormone

Appendix D. Glossary

Alltagsleben (Every Day Life): General quality of life measure developed in German-speaking populations. Higher scores indicate higher quality of life.

Anti-Human Growth Hormone (Anti-hGH) Antibodies: Proteins made by the host immune system that bind and neutralize human growth hormone.

Bilirubin: A breakdown product from red blood cell catabolism whose levels are increased in liver disease. Presented in units of mg/dl.

Bio-Electrical Impedance Assessment (BIA): Method for estimation of proportion of lean body mass versus fat mass. Lean body mass includes mass from bone, muscle, water, and other body tissues. BIA utilizes electrical current to determine body content from the rate of electrical flow.

Body Mass Index (BMI): Measure of body fat relative to height. Presented as a ratio of weight to square of the height. Presented in units kg/m^2.

Bone Mineral Content (BMC): Measure of the amount of bone in the body. Measurement is usually done with dual energy x-ray absorptiometry (DEXA). Presented in units of weight such as grams.

Burkholderia cepacia: A pathogenic gram negative bacteria which can cause pneumonia in cystic fibrosis patients with underlying lung problems.

Child Health Questionnaire (CHQ): General health measure containing 75 items in 10 health concepts: physical functioning, bodily pain, role/social limitations attributable to physical condiction, general health perceptions, role/social limitations attributable to emotions, role/social limitations attributable to behavior, mental health behavior problems, self-esteem, and limitations in family activities. Higher scores indicate higher quality of life.

Confidence Intervals (CIs): A range that is likely to include the given value. Usually presented as a percent (%). For example, a value with 95% confidence interval implies that when a measurement is made 100 times, it will fall within the given range 95% of the time.

Correlation Coefficient: A value (which usually ranges from zero to one) that indicates the degree of relationship between two variables. For example, a correlation coefficient of one would indicate a strong relationship.

Cystic Fibrosis Quality of Life (CFQoL) Questionnaire: Disease-specific questionnaire consisting of 52 items across nine domains: physical functioning, social functioning, treatment issues, chest symptoms, emotional functioning, concerns for the future, interpersonal relationships, body image, and career issues. Higher scores indicate higher quality of life.

Cystic Fibrosis Questionnaire (CFQ): Disease-specific questionnaire with 44 items across 12 dimensions: physical functioning, role, vitality, emotional functioning, social, body image, eating

disturbances, treatment burden, health perceptions, weight, respiratory symptoms, and digestive symptoms. Higher scores indicate higher quality of life.

Cystic Fibrosis Transmembrane Regulator (CFTR): Protein that is responsible for transport of sodium and chloride across epithelial membranes. Defects in the protein are responsible for the viscous and excessive secretions in cystic fibrosis.

Cystic Fibrosis-Related Diabetes (CFRD): A type of glucose intolerance caused by insulin resistance and decreased insulin production (due to scarring of the pancreas).

DerSimonian and Laird Random-Effects Model: A statistical method based on the assumption that the effects observed in different studies (in a meta-analysis) are truly different.

Dual Energy X-Ray Absorptiometry (DEXA): A common method of measuring bone mineral content (BMC) using two x-ray beams with different energy levels. Absorption due to soft tissue is taken into account (and subtracted out) when determining BMC.

Egger's Weighted Regression Statistics: A method of identifying and measuring publication bias.

Euro-QOL 5D (EQ-5D): A multidimension descriptive system of health status. Five dimensions are: mobility, self care, usual activity, pain, discomfort, and anxiety-depression. Higher scores indicate higher quality of life.

Forced Expiratory Volume in One Second (FEV1): Volume of air forcefully exhaled in one second. Usually presented in units of liters.

Forced Vital Capacity (FVC): Total volume of air that can be exhaled forcefully after a deep inhalation. Usually presented in units of liters.

Gallstones: Concentrated deposits of bile that can vary in size and usually form in the gallbladder or bile duct.

Glutamate (GLN): A nonessential amino acid whose levels may be depleted in cystic fibrosis patients due to malnutrition and acute stress from infections.

Glutamate-Oxaloacetate Transaminase: Liver enzyme whose levels are increased during liver damage.

Glutamate-Pyruvate Transaminase: Liver enzyme whose levels are increased during liver damage.

Glycosylated Hemoglobin A1c (A1c): Measure of the amount of sugar-bound hemoglobin. Marker of plasma sugar concentrations over the past three months. Presented in units of percent (%) of total hemoglobin.

Health Related Quality of Life (HRQoL): Assessment of the overall well-being of a patient. Usually in the form of questionnaires that can be tailored to specific disease states such as cystic fibrosis.

Human Growth Hormone (hGH): Also known as somatotropin. A naturally occurring peptide that is responsible for growth of cells in several areas of the body including muscle and bone.

Hypoalbuminemia: A condition where levels of albumin, which is produced by the liver, are low in the blood. Usually indicative of liver damage.

$\mathbf{I^2}$: Measure of degree of variation due to statistical heterogeneity. Usually reported as a percent ranging from 0 to 100.

Idiopathic Short Stature (ISS): An unexplained condition where the patient has a significantly lower-than-expected height.

Insulin-Like Growth Factor 1 (IGF-1): Protein hormone responsible for growth and development. Levels increase and decrease with growth hormone levels and malnutrition respectively. Also, a potent inhibitor of cell apoptosis; therefore, it is used as a lab marker to evaluate cancer risk in patients receiving recombinant human growth hormone therapy. Presented in units ng/ml.

Insulin-Like Growth Factor-Binding Protein 3 (IGFBP-3): Protein that binds and regulates insulin-like growth factors including insulin-like growth factor 1 (IGF-1). Used as a lab marker to evaluated cancer risk in patients receiving recombinant human growth hormone therapy. Presented in units ng/ml.

Interquartile Range (IQR): Collection of values that fall between the 25th percentile and 75th percentile.

Lean Body Mass (LBM): Total weight of all components of the body (muscle, bone, and other tissues) excluding the weight from fat. Used as an efficacy endpoint in recombinant growth hormone therapy. Usually presented in kilograms.

Lean Tissue Mass (LTM): See lean body mass.

Leucine (Leu): An amino acid whose isotope is used to determine protein turnover.

Leucine Oxidation (LeuOX): Measurement made with leucine isotope that represents protein oxidation, which represents elimination of amino acids from the body. Presented in units µmol/kg*h.

Liver Cirrhosis: A condition resulting from chronic disease of the liver where normal tissue has been replaced by fibrous scar tissue.

Medical Outcomes Short Form 36 (SF-36): General quality of life scale. Contains eight domains: physical functioning, role limiations due to physical problems, social functioning, bodily pain, mental health, role limitations due to emotional problems, vitality, and general health perceptions. Higher scores indicate higher quality of life.

Meta-Analysis: The process of extracting and pooling data from several studies investigating a similar topic to synthesize a final outcome.

Nonoxidative Leucine Disappearance (NOLD): Measurement made with leucine isotope that represents overall body protein synthesis. Presented in units μmol/kg*h.

Nottingham Health Profile (NHP): General quality of life questionnaire designed to measure perceived health problems and their impact on activities of daily living. Higher scores indicate poorer health.

Oxidation/[Nonoxidative Leucine Disappearance (NOLD)]: Ratio of leucine oxidation to NOLD provides an estimate of whole body protein catabolism. Presented in units μmol/kg*h.
Oxygen Pulse$_{peak}$: Amount of oxygen consumed per heart beat during exercise. Presented in units ml/beat.

Oxygen Uptake (Vo_2): Volume of oxygen used per unit of time. Presented in units mL/min.
Peak Oxygen Uptake (Vo_2-Peak): Volume of oxygen used during the last 30 seconds of exercise. Presented in units mL.

Prader-Willi Syndrome: A genetic disorder characterized by short stature, low muscle tone, cognitive disabilities, incomplete sexual development, behavioral problems, and constant feeling of hunger.

Publication Bias: The possibility that published studies may not represent all the studies that have been conducted, and therefore, create bias by being left out of a meta-analysis.

Q Statistic: A test to assess the presence of statistical heterogeneity among several studies.

Quality of Well-Being Scale (QWB): General health status measurement system, which assigns scores to levels of well-being based on social preferences and physical function. Three dimensions measure are mobility, physical activity, and social activity. Higher scores indicate higher quality of life.

Questions on Life Satisfaction: General health status measure on eight dimensions (friends/acquaintances, leisure time/hobbies, general health, income/financial security, occupation/work, housing/living condition, family life/children, and partner relationship/sexuality) and eight health-related dimensions (physical condition/fitness, ability to relax, energy/zest for life, mobility, vision and hearing, freedom from anxiety, freedom from aches and pain, and independence from help/care). Higher score indicates higher quality of life.

Rate of Appearance of Leucine (LeuRa): Measurement made with leucine isotope that represents the rate of protein breakdown. Presented in units μmol/kg*h.

Recombinant Human Growth Hormone (rhGH): Also known as somatropin. A synthetic form of the naturally occurring human growth hormone that is used for a variety of disorders including growth hormone deficiency, weight management, and possibly cystic fibrosis.

Relative Risks (RRs): The ratio of an event occurring in an exposed group to an event occurring in a non-exposed group in a given population.

Sensitivity Analyses: A 'what if' analysis that helps determine the robustness of a study. Helps determine the degree of importance of each variable for a given outcome.

Sickness Impact Profile (SIP): Quality of life assessment tool which contains 136 items grouped into 12 categories of activity, evaluating behavioral dysfunction, physical dysfunction which summarizes three categories (ambulation, mobility, body care and movement), and psychosocial dysfunction which summarizes four categories (social interaction, communication, alertness, and emotional behavior). Higher scores indicate poorer health.

Skinfold Thickness: Measure of the amount of fat under the skin, determined by caliper. Measurements at several sites are required because the proportion of fat at each site varies with age, gender, and race. Skinfold measurements typically taken at triceps, subscapular, and supra-ileac sites.

Standard Deviations (SDs): A measure of the variability of a data set. For a simple data set with numbers, can be calculated using the following formula:

$$\sigma = ((\sum(x-x_m))^2/N)^{0.5}$$

σ is standard deviation
x_m is the average
$\sum(x-x_m)$ is the sum of x_m subtracted from each individual number x
N is the total number of values
Note: Other formulas also exist.

Standard Deviation Scores (SDS): See Z-Scores.

Statistical Heterogeneity: Variability in the observed effects among studies in a meta-analysis. Steatorrhea: The presence of excessive amounts of fat in stools. Usually occurs secondary to pancreatic disease.

Sweat Test: A standard diagnostic test for cystic fibrosis that measures the concentration of chloride in a patient's sweat after induction of sweat glands via iontophoresis. A chloride concentration of 60 mmol/L or greater is consistent with the diagnosis of cystic fibrosis, while a concentration of 40 to 60 mmol/L is borderline.

Tanner Staging: A scale based of the physical development of primary and secondary sexual characteristics including presence and quality of pubic hair (males and females), breast size (females), and testicular volume (males). Stages range from 1 to 5 in increasing development.

Thyroxin: Hormone produced by the thyroid gland that regulates the metabolic rate of the body.

Trim-and-Fill Method: In cases where publication bias is detected, theoretical studies are statistically either imputed or removed to yield a theoretical result.

Turner Syndrome: A genetic disorder of the sex chromosomes resulting in a variety of physical abnormalities including short stature.

$\text{Ventilation}_{\text{peak}}$: Volume of air obtained during the last 30 seconds of exercise. Presented in units L/min.

Watt: Unit of power that helps measure rate of energy expenditure.

Weighted Mean Difference (WMD): Composite endpoint determined by the pooling of continuous data from all studies in the meta-analysis. Each study's mean, standard deviation, and sample size is taken into account to determine its level of contribution to the composite endpoint. For example, a study with a large sample size will have a greater impact on the composite endpoint than a similar study with a small sample size.

Weight-for-Height: The expected weight for a given height on a reference population growth chart.

Z-Scores: Difference between the value for an individual and the median value of the reference population, divided by the standard deviation of the reference population.

$$\text{Z-Score (or SD Score or SDS)} = \frac{\text{(observed value)} - \text{(median reference value)}}{\text{Standard deviation of reference population}}$$

Appendix E. Abbreviations

Acronym/Abbreviation	Definition
A1c	Glycosylated hemoglobin A1c
AHRQ	Agency for Healthcare Research and Quality
BG	Blood glucose
BIA	Bio-electrical impedance assessment
BMC	Bone mineral content
BMI	Body mass index
cc	Cubic centimeters, also milliters
CDC	Centers for Disease Control and Prevention
CER	Comparative effectiveness review
CF	Cystic fibrosis
CFRD	Cystic fibrosis-related diabetes
CFTR	Cystic fibrosis transmembrane regulator
CI	Confidence interval
DEXA	Dual energy x-ray absorptiometry
EPC	Evidence-based Practice Center
^{f}	Value for females
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GHD	Growth hormone deficiency
GLN	Glutamate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
hGH	Human growth hormone
HRQoL	Health-related quality-of-life
IGF-I	Insulin-like growth factor-1
IGFBP-3	Insulin-like growth factor binding protein-3
IQR	Interquartile range
ISS	Idiopathic short stature
LBM	Lean body mass
Leu	Leucine
LeuRa	Rate of appearance of leucine
LeuOx	Rate of oxidation of leucine
^{m}	Value for males
NOLD	Rate of nonoxidative leucine disappearance
NR	Not reported
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trials
rhGH	Recombinant human growth hormone
RR	Relative risk, also risk ratio
SD	Standard deviation
SDS	Standard deviation score
SMD	Standardized mean difference

TEP	Technical Expert Panel
ULN	Upper limit of normal
Vo_2	Oxygen uptake
Vo_2-max	Maximum oxygen uptake
Vo_2-peak	Peak oxygen uptake
W	Watt
WHO	World Health Organization
WMD	Weighted mean difference

Appendix F. Additional Evidence Tables

Appendix Table F1. Trials reporting the relationship between pulmonary function and mortality

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Predictor	Univariate Relationship	Multivariate Relationship	Comments
Huang, 1987[1] N=142	Patients with CF seen at the clinic who had attained age 18 by the end of 1984.	Until death or Dec 1984	Student's t test or Chi-square test and Cox proportional hazards model	%FVC at baseline	ES NR NS	NR	
				FEV_1/FVC at baseline	ES NR NS	NR	
Corey, 1988[2] N=1033	All patients with CF seen in established clinics for CF in Boston or Toronto in 1982.	1 year	Student's t test	$\%FEV_1$ at baseline in Boston	MD -40% p<0.05	NR	
				$\%FEV_1$ at baseline in Toronto	MD -40% p<0.001	NR	
Kerem, 1992[3] N=673	Patients with CF followed between 1977 and 1989, whose pulmonary function was evaluated at least once before the end of 1987.	2 years	Cox proportional hazards model	%FVC (10% decrease)	RR 1.9 (95%CI 1.8, 2.1)	RR 2.0 (95%CI 1.8, 2.2)	Univariate and Multivariate results reported as relative risk, likely reflect hazard ratio
				$\%FEV_1$ (10% decrease)	RR 1.8 (95%CI 1.7, 2.0)	RR 2.0 (95%CI 1.9, 2.2)	Univariate and Multivariate results reported as relative risk, likely reflect hazard ratio
Nixon, 1992[4] N=109	Patients with CF aged 7 to 35, who underwent pulmonary function and exercise testing in the late 1970s.	8 years	Cox proportional hazards model	$\%FEV_1 \leq 50$ versus ≥65%	RR 3.7 (95%CI 1.8, 7.9)	RR 1.1 (95%CI 0.4, 2.7)	Univariate and Multivariate results reported as relative risk, likely reflect hazard ratio

Appendix Table F1. Trials reporting the relationship between pulmonary function and mortality

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Predictor	Univariate Relationship	Multivariate Relationship	Comments
Sharples, 1993[5] N=67	Adult patients with CF accepted for heart-lung transplantation between Jan 1, 1985 and Dec 31, 1990.	Until death or transplant by Dec 31, 1990	Cox proportional hazards model	FEV_1 at baseline	RR 0.28 (95%CI 0.08, 0.97)	NR	Univariate results reported as relative risk, likely reflects hazard ratio
				$\%FEV_1$ at baseline	RR 0.96 (95%CI 0.92, 1.00)	NR	Univariate results reported as relative risk, likely reflects hazard ratio
				FEV_1/FVC at baseline	RR 1.00 (95%CI 0.98, 1.03)	NR	Univariate results reported as relative risk, likely reflects hazard ratio
Ciriaco, 1995[6] N=67	All patients with CF listed for lung transplantation between Jan 1990 and July 1993.	Until death or transplant by July 1993	Student's t test	FVC at baseline	MD 0 L (95%CI -0.48,0.48)	NR	
				%FVC at baseline	MD -2% (95%CI -5.35,9.35)	NR	
				FEV_1 at baseline	MD -0.149 L (95%CI -0.08,0.38)	NR	
				$\%FEV_1$ at baseline	MD -5 % p<0.02	NR	
Corey, 1996[7] N=3,795	Patients from the Canadian Patient Data Registry, operated from the Canadian Cystic Fibrosis Foundation, between 1970 and 1989.	Until death or 1989	Cox proportional hazards model	$\%FEV_1$	HR 0.93 (95%CI 0.92, 0.94)	HR 0.93 (95%CI 0.92, 0.94)	
Corey, 1997[8] N=366	All patients with CF born between 1960 and 1974 who had at least two recorded pulmonary function tests, and whose first test was performed before age 10.	25 years	Mixed-model regression analysis	$\%FEV_1$ decline	NR	SS	
				%FVC decline	NR	SS	

Appendix Table F1. Trials reporting the relationship between pulmonary function and mortality

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Predictor	Univariate Relationship	Multivariate Relationship	Comments
Hayllar, 1997[9] N=403	Patients with CF seen between 1969 and 1987, followed until death or 1989.	Until death or 1989	Cox proportional hazards model	%FVC at baseline	ES NR p<0.001	RR 0.963 p<0.0001	Multivariate results reported as relative risk, likely reflects hazard ratio
				$\%FEV_1$ at baseline	ES NR p<0.001	RR 0.943 p<0.0001	Multivariate results reported as relative risk, likely reflects hazard ratio
Moorcroft, 1997[10] N=92	Patients with CF who underwent exercise testing between 1986 and 1989.	5 years	Student's t test	$\%FEV_1$ at baseline	MD -29.2% p<0.001	ES NR SS	
Rosenfeld, 1997[11] N=21,047	All patients with CF seen at a Cystic Fibrosis Foundation-accredited clinic between Jan 1988 and Dec 1992.	2 years	Cox proportional hazards model	$\%FEV_1$ 60-80 versus >80	HR 2.7 (95%CI 1.4, 5.5)	HR 1.8 (95%CI 0.7, 4.3)	
				$\%FEV_1$ 40-59 versus >80	HR 14.0 (95%CI 7.8, 25.1)	HR 11.3 (95%CI 4.9, 26.3)	
				$\%FEV_1$ <40 versus >80	HR 56.7 (95%CI 32.6, 98.5)	HR 27.5 (95%CI 11.2, 67.8)	
Bell, 1998[12] N=84	All patients with CF seen for routine clinic appointment within 3 months of Feb 1994.	4 years	Kaplan-Meier survival analysis and Cox proportional hazards model	$\%FEV_1$ at baseline	ES NR p<0.00001	ES NR SS	
Milla, 1998[13] N=61	All patients with CF followed up since 1975 in whom at least 3 years of follow-up data were available and who had FEV_1 <30% predicted in more than three measurements within a single year and who did not have a subsequent value >30% predicted on more than one occasion.	Until death or time of analysis NR	Cox proportional hazards model	%FVC decline	MD 0.39% per year p=0.1	ES NR NS	
				$\%FEV_1$ decline	MD 1.07% per year p=0.0001	HR 1.3 p=0.0001	

Appendix Table F1. Trials reporting the relationship between pulmonary function and mortality

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Predictor	Univariate Relationship	Multivariate Relationship	Comments
Venuta, 1998[14] N=22	Patients with CF evaluated for lung transplantation.	NR	Student's t test	FVC at baseline	MD 0 L (95%CI -0.58,0.58)	NR	
				%FVC at baseline	MD -2% (95%CI -6.89,10.89)	NR	
				FEV_1 at baseline	MD -0.09 L (95%CI -0.17,0.36)	NR	
				$\%FEV_1$ at baseline	MD 3.4% (95%CI -1.53,8.33)	NR	
Robinson, 2000[15] N=56	Patients with CF between 7-18 years of age, followed at the Children's Hospital in Boston, Massachusetts between 1980 and 1997.	4 years	Fisher's exact test	$\%FEV_1$ decline in 4 years preceding death	MD 6.1%/year p<0.01	NR	
				$\%FEV_1$ decline in 2 years preceding death	MD 9.7%/year p<0.01	NR	
				$\%FEV_1$ decline in 2 to 4 years preceding death	MD 4.25%/year p=0.22	NR	
Vizza, 2000[16] N=146	Patients with CF listed for lung transplantation at Barnes-Jewish Hospital between Jan 1, 1989 and May 12, 1998.	Until death or Feb 1999	Student's t test	FVC at baseline	MD -0.27 L p=0.006	NR	
				%FVC at baseline	MD -4% p=0.031	NR	
				FEV_1 at baseline	MD -0.04 L p=0.251	NR	
				$\%FEV_1$ at baseline	MD 0% p=0.823	NR	
				FEV_1/FVC at baseline	MD 0.04 p=0.011	NR	

Appendix Table F1. Trials reporting the relationship between pulmonary function and mortality

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Predictor	Univariate Relationship	Multivariate Relationship	Comments
Liou, 2001[17] N=5820	Patients in the Cystic Fibrosis Foundation Patient Registry who were alive in Jan 1993, and for whom follow-up data were available through Dec 1997.	5 years	Cox proportional hazards model	$\%FEV_1$	ES NR SS	OR 0.96 NR	Multivariate results reported as odds ratio, likely reflects hazard ratio
Sharma, 2001[18] N=584	Patients with CF attending to Royal Brompton Hospital between 1985 and 1996.	Until death or 1996	Cox proportional hazards model	FEV_1 at baseline	HR 0.999 (95%CI 0.998, 0.999)	NR	
				$\%FEV_1$ at baseline	HR 0.945 (95%CI 0.934, 0.956)	HR 0.953 (95%CI 0.931, 0.975)	
				$\%FEV_1 \leq 30$	HR 4.83 (95%CI 3.44, 6.78)	NR	
Mayer-Hamblett, 2002[19] N=14,572	All patients in the Cystic Fibrosis Foundation National Patient Registry who were age 6 years or older on Dec 31, 1996, who had not previously undergone lung transplantation, and were seen at a CFF-accredited care center in 1996.	2 years	Logistic regression	Mean FEV_1 in 1996	ES NR SS	OR 0.09 (95%CI 0.07, 0.11)	Multivariate results reported as odds ratio, likely reflects hazard ratio
Schaedel, 2002[20] N=377	Patients with CF attending one of four CF centers in Sweden, born before Jan 1,1993 and having undergone at least two lung function tests	Median 8.5 years	Mixed-model regression analysis	FEV_1 decline	NR	SS	
Stanchina, 2002[21] N=44	Patients with CF who underwent evaluation for lung transplantation between Nov 1990 and Jan 1999 at Massachusetts General Hospital.	Until death or Jan 1999	Student's t test and Cox proportional hazards model	FEV_1 at baseline	MD -0.142 L (95%CI -0.05,0.33)	NR	
				$\%FEV_1$ at baseline	MD 4.8% (95%CI -0.78,10.38)	NR	
Vedam, 2004[22] N=20	All adult patients with CF admitted to the ICU at Royal Prince Alfred Hospital between 1988 and Apr 13, 2003.	Until death or 1 year following ICU discharge	Relative risk calculation	$\%FEV_1 < 24$ upon admission	RR 3.68 (95%CI 1.11, 16.33)	NR	Univariate results reported as relative risk, likely reflects hazard ratio

Appendix Table F1. Trials reporting the relationship between pulmonary function and mortality

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Predictor	Univariate Relationship	Multivariate Relationship	Comments
Ellaffi, 2005[23] N=69	Adult patients with CF followed at the CF center at Cochin Hospital, that were admitted to the Pulmonary Department or ICU of the hospital for severe pulmonary exacerbations between Jan 1, 1997 and Jun 30, 2001.	1 year	Cox proportional hazards model	$\%FEV_1$ in stable state prior to admission	HR 1.00 (95%CI 0.91,1.02)	NS	
				FEV_1 decline	HR 0.70 (95%CI 0.49, 1.00)	NS	
Pianosi, 2005[24] N=28	Children with CF seen at the CF clinic of the Winnipeg Health Sciences Center, old enough (≥7 years) to perform a progressive exercise test, at a scheduled clinic appointment when the patient was clinically stable, between 1991 and 1996.	Until death or Jan 2004	Cox proportional hazards model	FEV_1 decline	HR 0.959 (95%CI 0.928, 0.0991)	NR	
				FEV_1 at last visit	HR 0.928 (95%CI 0.894, 0.968)	NR	
Belkin, 2006[25] N=346	Adult and pediatric patients with CF listed for lung, heart-lung, or heart-lung-liver transplantation at the University of Pennsylvania, Stanford University Medical Center, Children's Hospital of Philadelphia, Toronto General Hospital and the Hospital for Sick Children in Toronto between Jan 1990 and Dec 31, 2002.	Until death or Dec 31, 2002	Cox proportional hazards model	$\%FEV_1$ (10% decrease)	HR 2.1 (95%CI 1.5, 3.0)	NS	
				%FVC (10% decrease)	HR 1.3 (95%CI 1.1, 1.6)	NS	
				$FEV_1 \leq 30\%$ at baseline	HR 3.8 (95%CI 2.0, 7.5)	HR 6.8 (95% CI 2.4, 19.3)	
Texereau, 2006[26] N=42	Adult CF patients admitted to the ICU, who had never received a solid-organ transplant, between Jan 2000 and Jun 2003.	1 year	Cox proportional hazards model	$\%FEV_1$, best value within six months preceding ICU admission	HR 0.97 (95%CI 0.93, 1.02)	NR	
				$\%FEV_1$ decline per year	HR 1.25 (95%CI 1.04, 1.52)	HR 1.47 (95%CI 1.18, 1.85)	
Courtney, 2007[27] N=183	Adult patients (age≥17 in 2000) from Belfast and Cork, between 1995 and 2005.	10 years	Cox proportional hazards model	$\%FEV_1$ at baseline	MD -28.3% p<0.001	ES NR p<0.0001	

Appendix Table F1. Trials reporting the relationship between pulmonary function and mortality

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Predictor	Univariate Relationship	Multivariate Relationship	Comments
Rosenthal, 2008[28] N=298	Patients with CF born before 1993 with at least 4 annual lung function measurements in the patient database at the Royal Brompton Hospital in London,UK.	Until death or transplant by Jan 4, 2007	Positive predictive value and sensitivity for mortality and Mann Whitney U test	FEV_1 Z-score threshold -2 at age 8	PPV 47 Sens 70	NR	
				FEV_1 Z-score threshold -2 at age 9	PPV 13 Sens 33	NR	
				FEV_1 Z-score threshold -2 at age 10	PPV 25 Sens 68	NR	
				FEV_1 Z-score threshold -2 at age 11	PPV 25 Sens 76	NR	
				FEV_1 Z-score threshold -2 at age 12	PPV 10 Sens 64	NR	
				FEV_1 Z-score decline in 2 year prior to age 10	MD 0.04 (95%CI -1.52,1.60)	NR	
				FEV_1 Z-score decline in 2 year prior to age 11	MD 0.21 (95%CI -0.35,0.77)	NR	
				FEV_1 Z-score decline in 2 year prior to age 12	MD 0.35 (95%CI -0.31,1.01)	NR	

*Mean differences presented as values in patients who died versus those who survived ($mean_{died} - mean_{survived}$)

Legend: CF=cystic fibrosis; CI=confidence interval; ES=effect size; FEV_1=forced expiratory volume in 1 second; $\%FEV_1$=percent predicted forced expiratory volume in 1 second; FVC=forced vital capacity; %FVC=percent predicted forced vital capacity; HR=hazard ratio; MD=mean difference; NR=not reported; NS=not significant; OR=odds ratio; PPV=positive predictive value; RR=relative risk; Sens=sensitivity; SS=statistically significant

Appendix Table F2. Trials reporting the relationship between anthropometrics and mortality

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Predictor	Univariate Relationship	Multivariate Relationship	Comments
Kraemer, 1978[29] N=117	Children with CF seen between Jan 1956 and Jun 1976, divided into three groups based on symptoms at diagnosis.	Until death or age 10	Chi-square test	Relative underweight	ES NR p<0.05	NR	
Huang, 1987[1] N=142	Patients with CF seen at the clinic who had attained age 18 by the end of 1984.	Until death or Dec 1984	Student's t test or Chi-square test and Cox proportional hazards model	Weight percentile	MD -10.8% p=0.0001	NR	
				Weight percentile <5 at age 18	MD -39% p=0.0004	ES NR p<0.0001	
Corey, 1988[2] N=1033	All patients with CF seen in established clinics for CF in Boston or Toronto in 1982.	1 year	Student's t test	Height percentile at baseline in Boston	MD -1% (95%CI -12.29,10.29)	NR	
				Height percentile at baseline in Toronto	MD -10% P<0.05	NR	
				Weight percentile at baseline in Boston	MD -25% P<0.001	NR	
				Weight percentile at baseline in Toronto	MD -25% P<0.001	NR	
Kerem, 1992[3] N=673	Patients with CF followed between 1977 and 1989, whose pulmonary function was evaluated at least once before the end of 1987.	2 years	Cox proportional hazards model	%Weight-for-height	RR 1.4 (95%CI 1.3, 1.5)	RR 1.4 (1.3, 1.5)	
Nixon, 1992[4] N=109	Patients with CF aged 7 to 35, who underwent pulmonary function and exercise testing in the late 1970s.	8 years	Cox proportional hazards model	BMI ≤16 versus ≥18.6	RR 1.6 (95%CI 0.8, 3.1)	NR	Univariate results reported as relative risk, likely reflects relative risk
Sharples, 1993[5] N=67	Adult patients with CF accepted for heart-lung transplantation, between Jan 1, 1985 and Dec 31, 1990.	Until death or transplant by Dec 31, 1990	Cox proportional hazards model	Weight-for-height	RR 0.96 (95%CI 0.92, 0.99)	NR	Univariate results reported as relative risk, likely reflects relative risk

Appendix Table F2. Trials reporting the relationship between anthropometrics and mortality (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Predictor	Univariate Relationship	Multivariate Relationship	Comments
Corey, 1996[7] N=3795	Patients from the Canadian Patient Data Registry, operated from the Canadian Cystic Fibrosis Foundation, between 1970 and 1989.	Until death or 1989	Cox proportional hazards model	%Weight	HR 0.95 (95%CI 0.93, 0.96)	HR 0.99 (95%CI 0.98, 1.00)	
Hayllar, 1997[9] N=403	Patients with CF seen between 1969 and 1987, followed until death or 1989.	Until death or 1989	Cox proportional hazards model	Height	ES NR p<0.001	RR 0.033 p<0.0001	
				% Weight	ES NR p<0.001	NR	
Moorcroft, 1997[10] N=92	Patients with CF who underwent exercise testing between 1986 and 1989.	5 years	Student's t test	BMI at baseline	MD -1.9 kg/m^2 p=0.001	ES NR NS	

Appendix Table F2. Trials reporting the relationship between anthropometrics and mortality (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Predictor	Univariate Relationship	Multivariate Relationship	Comments
Rosenfeld, 1997[11] N=21,047	All patients with CF seen at a Cystic Fibrosis Foundation-accredited clinic between Jan 1988 and Dec 1992.	2 years	Cox proportional hazards model	Height z-score -0.46 to -1.32 versus >-0.46	HR 1.4 (95%CI 0.9, 2.1)	HR 1.1 (95%CI 0.6, 1.9)	
				Height z-score -1.33 to -2.21 versus >-0.46	HR 1.6 (95%CI 1.1, 2.5)	HR 1.0 (95%CI 0.5, 1.9)	
				Height z-score -2.22 to -3.25 versus >-0.46	HR 4.6 (95%CI 3.1, 6.7)	HR 1.9 (95%CI 0.9, 4.1)	
				Height Z-score ≤-3.26 versus >-0.46	HR 8.8 (95%CI 5.9, 13.1)	HR 2.9 (95%CI 1.2, 7.0)	
				Weight Z-score -0.49 to -1.25 versus >-0.49	HR 1.2 (95%CI 0.7, 2.1)	NR	
				Weight Z-score -1.26 to -1.98 versus >-0.49	HR 2.8 (95%CI 1.7, 4.4)	NR	
				Weight Z-score -1.98 to -2.74 versus >-0.49	HR 7.8 (95%CI 5.0, 12.2)	NR	
				Weight Z-score ≤-2.75 versus >-0.49	HR 16.4 (95%CI 10.5, 25.6)	NR	
				%IBW 98 to 104.9 versus ≥105	HR 0.9 (95%CI 0.6, 1.5)	NR	
				%IBW 90 to 97.9 versus ≥105	HR 1.6 (95%CI 1.1, 2.3)	NR	
				%IBW 84 to 89.9 versus ≥105	HR 3.2 (95%CI 2.2, 4.7)	NR	
				%IBW <84 versus ≥105	HR 7.1 (95%CI 5.0, 10.2)	NR	
Bell, 1998 N=81	All patients with CF seen for routine clinic appointment within 3 months of Feb 1994.	4 years	Kaplan-Meier survival analysis and Cox proportional hazards model	BMI at baseline	ES NR p=0.05	ES NR SS	

Appendix Table F2. Trials reporting the relationship between anthropometrics and mortality (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Predictor	Univariate Relationship	Multivariate Relationship	Comments
Venuta, 1998[14] N=22	Patients with CF evaluated for lung transplantation.	NR	Student's t test	%Weight	MD -3.3% (95%CI -6.25,12.85)	NR	
Vizza, 2000[16] N=146	Patients with CF listed for lung transplantation at Barnes-Jewish Hospital between Jan 1, 1989 and May 12, 1998.	Until death or Feb 1999	Student's t test	Height	MD -3 cm p=0.073	NR	
				Weight	MD -2.4 kg p=0.200	NR	
				%IBW	MD 1% p=0.685	NR	
Beker, 2001[30] N=2273	Patients from the Cystic Fibrosis Foundation registry born between 1980 and 1989, who had a minimum of four records, were alive at age 7, and contained a recorded height measurement at age 7 to 8.	Until death or 1993	Cox proportional hazards model	Height-for-age below 5th percentile, males at age 5	HR 2.9 (95%CI 1.23, 6.91)	NR	
				Height-for-age below 5th percentile, males at age 7	HR 6.3 (95%CI 2.10, 18.87)	NR	
				Height-for-age below 5th percentile, females at age 5	HR 4.3 (95%CI 2.54, 7.31)	NR	
				Height-for-age below 5th percentile, females at age 7	HR 5.8 (95%CI 2.53, 13.11)	NR	
Liou, 2001[17] N=5820	Patients in the Cystic Fibrosis Foundation Patient Registry who were alive in Jan 1993, and for whom follow-up data were available through Dec 1997.	5 years	Cox proportional hazards model	Weight-for-age Z-score	ES NR SS	OR 0.75 NR	Univariate results reported as odds ratio, likely reflects hazard ratio
Sharma, 2001[18] N=584	Patients with CF attending to Royal Brompton Hospital between 1985 and 1996.	Until death or 1996	Cox proportional hazards model	%IBW at baseline	HR 0.955 (95%CI 0.944, 0.967)	HR 0.968 (95%CI 0.947, 0.99)	
				%IBW ≤85	HR 2.64 (95%CI 1.85, 3.75)	NR	

Appendix Table F2. Trials reporting the relationship between anthropometrics and mortality (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Predictor	Univariate Relationship	Multivariate Relationship	Comments
Emerson, 2002[31] N=3213	Patients with CF who were age 1 to 5 years as of Dec 31, 1990, with a date of CF diagnosis before or during 1990, and seen at a CF clinic during 1990 and alive at the end of 1990 that were registered with the US Cystic Fibrosis Foundation National Patient Registry	8 years	Kaplan-Meier estimate of survival and Cox regression model	Weight percentile ≤5 versus percentile >50	NR	HR 3.9 (95%CI 2.1, 7.3)	
				Weight percentile 5-15 versus percentile >50	NR	HR 2.4 (95%CI 1.2, 4.8)	
				Weight percentile 15-50 versus percentile >50	NR	HR 1.5 (95%CI 0.8, 2.9)	
Mayer-Hamblett, 2002[19] N=14,572	All patients in the Cystic Fibrosis Foundation National Patient Registry who were age 6 years or older on Dec 31, 1996, who had not previously undergone lung transplantation and were seen at a CFF-accredited care center in 1996.	2 years	Logistic regression	Mean height in 1996	ES NR SS	OR 1.04 (95%CI 1.03, 1.05)	
				Mean weight in 1996	ES NR SS	ES NR NS	
Oliveira, 2002[31] N=127	Patients with CF followed at the Hospital das Clinicas in Brazil between March 1977 and December 1997.	12 years	Cox proportional hazards model	Height Z-score threshold at -1.29	RR 4.06 p=0.06	NR	Univariate and multivariate results reported as relative risk, likely reflects hazard ratio
				Birth weight (kg)	RR 3.81 p=0.01	RR 7 p<0.001	
Stanchina, 2002[21] N=44	Patients with CF who underwent evaluation for lung transplantation between Nov 1990 and Jan 1999 at Massachusetts General Hospital.	Until death or Jan 1999	Student's t test Cox proportional hazards model	Height at baseline	MD 0.6 in (95% CI -3.44,2.24)	NR	
				Weight	MD 6.5 lbs (95 CI -26.61,13.61)	NR	
				BMI	MD 1.26 kg/m^2 (95%CI -3.91,1.39)	NR	
Banjar, 2003[32] N=190	All CF patients referred to the CF clinic at the King Faisal Specialist Hospital and Research Center in	9 years	Student's t test	Weight-for-height at baseline	MD -13 p=0.01	NR	

Appendix Table F2. Trials reporting the relationship between anthropometrics and mortality (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Predictor	Univariate Relationship	Multivariate Relationship	Comments
	Riyadh, Kingdom of Saudi Arabia during a 9 year period between Nov 1993 and Nov 2002.			Height-for-age at baseline	MD -1 p=0.8	NR	
Vedam, 2004[22] N=20	All adult patients with CF admitted to the ICU at Royal Prince Alfred Hospital between 1988 and Apr 13 2003.	Until death or 1 year following ICU discharge	Relative risk calculation	BMI <18 upon admission	RR 3.25 (95%CI 1.27, 3.25)	NR	Univariate results reported as relative risk, likely reflects hazard ratio
Ellaffi, 2005[23] N=69	Adult patients with CF followed at the CF center at Cochin Hospital, that were admitted to the Pulmonary Department or ICU of the hospital for severe pulmonary exacerbations between Jan 1, 1997 and Jun 30, 2001.	1 year	Cox proportional hazards model	BMI on admission	HR 0.87 (95% CI 0.69, 1.11)	NR	
Belkin, 2006[25] N=346	Adult and pediatric patients with CF listed for lung, heart-lung, or heart-lung-liver transplantation at the University of Pennsylvania, Stanford University Medical Center, Children's Hospital of Philadelphia, Toronto General Hospital and the Hospital for Sick Children in Toronto between Jan 1990 and Dec 2002.	Until death or Dec 31, 2002	Cox proportional hazards model, Student t test	Shortest height quartile	HR 1.4 (95% CI 0.9, 2.4)	NS	
				BMI	HR 1.0 (95% CI 0.9, 1.1)	NS	
				Height	MD -1 cm p=0.30	NR	
Texereau, 2006[26] N=42	Adult CF patients admitted to the ICU, who had never received a solid-organ transplant, between Jan 2000 and Jun 2003.	1 year	Cox proportional hazards model	BMI	HR 0.95 (95%CI 0.80, 1.13)	NR	
Courtney, 2007[27] N=183	Adult patients (age≥17 in 2000) from Belfast and Cork, between 1995 and 2005.	10 years	Cox proportional hazards model	BMI at baseline	MD -1.5 kg/m^2 P=0.008	ES NR P=0.31	

Appendix Table F2. Trials reporting the relationship between anthropometrics and mortality (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Predictor	Univariate Relationship	Multivariate Relationship	Comments
Rosenthal, 2008[28] N=298	Patients with CF born before 1993 with at least four annual lung function measurements in the patient database at Royal Brompton Hospital in London,UK.	Until death or transplant by Jan 4, 2007	Positive predictive value and sensitivity for mortality and Mann Whitney U test	BMI Z-score threshold -2 at age 8	PPV 33 Sens 9	NR	
				BMI Z-score threshold -2 at age 9	PPV 0 Sens 0	NR	
				BMI Z-score threshold -2 at age 10	PPV 0 Sens 0	NR	
				BMI Z-score threshold -2 at age 11	PPV 7 Sens 6	NR	
				BMI Z-score threshold -2 at age 12	PPV 20 Sens 20	NR	
				BMI Z-score decline in 2 year prior to age 10	MD -0.05 (95%CI (-0.17,0.07)	NR	
				BMI Z-score decline in 2 year prior to age 11	MD 0.53 (95%CI -0.25,1.31)	NR	
				BMI Z-score decline in 2 year prior to age 12	MD 0.32 (95%CI -1.14, 0.50)	NR	

*Mean differences presented as values in patients who died versus those who survived ($mean_{died} - mean_{survived}$)

Legend: BMI=body mass index; CF=cystic fibrosis; CI=confidence interval; ES=effect size; HR=hazard ratio; IBW=ideal body weight; MD=mean difference; NR=not reported; NS=not significant; OR=odds ratio; PPV=positive predictive value; RR=relative risk; Sens=sensitivity; SS=statistically significant

Appendix Table F3. Trials reporting the relationship between exercise tolerance and mortality

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Predictor	Univariate Relationship	Multivariate Relationship	Comments
Nixon, 1992[4] N=109	Patients with CF aged 7 to 35, who underwent pulmonary function and exercise testing in the late 1970s.	8 years	Cox proportional hazards model	$Vo_{2\text{-peak}}$ ≤58 versus ≥82%	RR 6.4 (95%CI 2.6, 15.7)	RR 3.2 (95%CI 1.2, 8.6)	Univariate and Multivariate results reported as relative risk, likely reflects hazard ratio
Sharples, 1993[5] N=67	Adult patients with CF accepted for heart-lung transplantation, between Jan 1, 1985 and Dec 31, 1990.	Until death or transplant by Dec 31, 1990	Cox proportional hazards model	12 minute walk test (>540 meters)	RR 0.89 (95%CI 0.41,1.95)	NR	Univariate results reported as relative risk, likely reflects hazard ratio
Ciriaco, 1995[6] N=67	All patients with CF listed for lung transplantation.	Until death or transplant by July 1993	Student's t test	6 minute walk test	MD -101.7 m NS	NR	
Kadikar, 1997[33] N=41	Patients assessed for lung transplant at the Toronto Lung Transplant Program and either were accepted to the program or died during assessment were retrospectively reviewed between Jan 1991 and Jun 1995.	Until death or transplant by Jun 1995	Student's t test	6 minute walk test	MD -137.4 m p=0.016	NR	
Moorcroft, 1997[10] N=92	Patients with CF who underwent exercise testing between 1986 and 1989.	5 years	Student's t test	$Vo_{2\text{-peak}}$ % predicted	MD -12.9% p=0.022	ES NR NS	
				W_{peak} % predicted	MD -18.1% p=0.015	ES NR NS	
				VE/Vo_2	MD 6.3 p=0.002	ES NR NS	
				VE_{peak}	MD -8.1 L/min p=0.04	ES NR NS	
Venuta, 1998[14] N=22	Patients with CF evaluated for lung transplantation.	NR	Student's t test	6 minute walk test	MD -43 m (95%CI -53.23, 139.23)	NR	

Appendix Table F3. Trials reporting the relationship between exercise tolerance and mortality (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Predictor	Univariate Relationship	Multivariate Relationship	Comments
Vizza, 2000[16] N=146	Patients with CF listed for lung transplantation at Barnes-Jewish Hospital between Jan 1, 1989 and May 12, 1998.	Until death or Feb 1999	Cox proportional hazards model	6 minute walk test, 50 m increment	RR 0.73 (95%CI 0.62, 0.87)	RR 0.69 (95%CI 0.57, 0.84)	Univariate and Multivariate results reported as relative risk, likely reflects hazard ratio
				6 minute walk test, 5% increment	RR 0.82 (95%CI 0.72, 0.94)	NR	Univariate results reported as relative risk, likely reflects hazard ratio
Stanchina, 2002[21] N=44	Patients with CF who underwent evaluation for lung transplantation between Nov 1990 and Jan 1999 at Massachusetts General Hospital.	Until death or Jan 1999	Student's t test and Cox proportional hazards model	$Vo_{2\text{-max}}$ initial	MD -0.171 L/min (95%CI -1.85,2.19)	NR	
Pianosi, 2005[24] N=28	Children with CF seen at the CF clinic of the Winnipeg Health Sciences Center, old enough (≥7 years) to perform a progressive exercise test, at a scheduled clinic appointment when the patient was clinically stable, between 1991 and 1996.	Until death or Jan 2004	Cox proportional hazards model	$Vo_{2\text{-peak}}$ final	HR 0.953 (95%CI 0.865, 1.051)	NR	
				$Vo_{2\text{-peak}}$ at last visit	HR 0.845 (95%CI 0.757, 0.944)	NR	
Belkin, 2006[25] N=346	Adult and pediatric patients with CF listed for lung, heart-lung, or heart-lung-liver transplantation at the University of Pennsylvania, Stanford University Medical Center, Children's Hospital of Philadelphia, Toronto General Hospital and the Hospital for Sick Children in Toronto between Jan 1990 and Dec 31, 2002.	Until death or Dec 31, 2002	Cox proportional hazards model	6 minute walk distance, ft	HR 1.0 (95%CI 0.99, 1.0)	NR	

*Mean differences presented as values in patients who died versus those who survived ($mean_{died} - mean_{survived}$)

Legend: CF=cystic fibrosis; CI=confidence interval; ES=effect size; HR=hazard ratio; MD=mean difference; NR=not reported; NS=not significant; RR=relative risk; SS=statistically significant; VE_{peak}=peak ventilation in one minute; $Vo_{2\text{-peak}}$=peak oxygen uptake; W_{peak}=peak work rate

Appendix Table F4. Trials reporting the relationship between pulmonary function and health-related quality of life

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Outcome	Predictor	Univariate Relationship	Multivariate Relationship
Orenstein, 1989[34] N=44	Patients with CF, aged 7 to 36 years, seen at the Pittsburgh Cystic Fibrosis Center	Cross-sectional	Pearson product moment correlation analysis	QWB	FEV_1	r=0.5518 p<0.0001	NR
Czyzewski, 1994[35] N=54	Patients with CF from two metropolitan CF centers, younger than age 18 years that read and spoke English.	Cross-sectional	Pearson product moment correlation analysis	QWB	$\%FEV_1$	r=-0.07 NS	NR
					%FVC	r=0.00 NS	NR
Congleton, 1996[36] N=240	Patients with CF aged at least 16 years that attended the CF clinic at the National Heart and Lung Institute in Sydney, Australia for at least two years.	Cross-sectional	Spearman's rank correlation coefficient	NHP Energy Subscore	$\%FEV_1$	r=-0.43 p<0.0001	NR
				NHP Pain Subscore	$\%FEV_1$	r=-0.43 p<0.0001	NR
				NHP Emotion Subscore	$\%FEV_1$	r=-0.15 p<0.05	NR
				NHP Sleep Subscore	$\%FEV_1$	r=-0.3 p<0.0001	NR
				NHP Social isolation Subscore	$\%FEV_1$	r=-0.17 p<0.01	NR
				NHP Physical mobility Subscore	$\%FEV_1$	r=-0.51 p<0.0001	NR
de Jong, 1997[37] N=15	Clinically stable patients with CF, aged 16 to 40 years.	Cross-sectional	Spearman's rank correlation coefficient	SIP Overall Score	$\%FEV_1$	r=-0.33 NS	NR
				SIP Physical Subscore	$\%FEV_1$	r=-0.40 NS	NR
				SIP Psychosocial Subscore	$\%FEV_1$	r=0.05 NS	NR
Staab, 1998[38] N=89	Adolescent and adult patients (n=89) attending four outpatient clinics in Germany.	Cross-Sectional	Multiple regression analyses	Alltagsleben (Every Day Life)	FEV_1	Model 1 (n=83) r=0.31 p<0.01 Model 2 (n=84) r=0.36 p<0.001	Model 1 (n=83) β=0.12 NS Model 2 (n=84) β=0.24 p<0.05

Appendix Table F4. Trials reporting the relationship between pulmonary function and health-related quality of life (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Outcome	Predictor	Univariate Relationship	Multivariate Relationship
Johnson, 2000[39] N=39 at initial survey N=32 at 1 year	All patients with CF over age 18 years at the University of Alberta Hospital CF clinic.	Cross-sectional, with one 1 follow-up survey	Spearman correlations and multivariate regression models	SF-36 PCS	$\%FEV_1$	Spearman's p=0.396 p=0.025	NR
				SF-36 MCS	$\%FEV_1$	ES NR NS	NR
				EQ-5D VAS	$\%FEV_1$	Spearman's p=0.427 p=0.017	NR
				EQ-5D VAS after one year	$\%FEV_1$	NR	β=+0.00 p=0.005
Abbott, 2001[40] N=84	English patients (n=58) with CF attending two outpatient clinics who were aged between 14 and 18 years. German patients (n=26) with CF attending outpatient clinics aged between 13 and 17 years.	Cross-sectional	Pearson's correlation coefficient	SF-36 Physical functioning subscore	$\%FEV_1$	English Patients r=0.39 p<0.003 German Patients r=0.43 p<0.03	NR
				SF-36 Physical role limitation subscore	$\%FEV_1$	ES NR NS	NR
				SF-36 Social functioning subscore	$\%FEV_1$	ES NR NS	NR
				SF-36 Mental health subscore	$\%FEV_1$	ES NR NS	NR
				SF-36 Mental role limitation subscore	$\%FEV_1$	ES NR NS	NR
				SF-36 Energy and vitality subscore	$\%FEV_1$	ES NR NS	NR
				SF-36 General health perceptions subscore	$\%FEV_1$	ES NR NR	NR
				SF-36 Changes in health subscore	$\%FEV_1$	ES NR NS	NR

Appendix Table F4. Trials reporting the relationship between pulmonary function and health-related quality of life (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Outcome	Predictor	Univariate Relationship	Multivariate Relationship
Powers, 2001[41] N=24	Adolescents with CF aged 11 to 18 years at two CF clinics in Massachusetts, USA, who spoke English.	Cross-sectional	Pearson's correlation coefficient	CHQ Physical function subscore	$\%FEV_1$	r=0.37 NS	NR
				CHQ Role/social limitations – physical subscore	$\%FEV_1$	r=0.47 p≤0.05	NR
				CHQ General health perceptions subscore	$\%FEV_1$	r=0.73 p≤0.001	NR
				CHQ Bodily pain/discomfort subscore	$\%FEV_1$	r=0.42 p≤0.05	NR
				CHQ Role/social limitations – emotional subscore	$\%FEV_1$	r=0.39 NS	NR
				CHQ Role/social limitations – behavioral subscore	$\%FEV_1$	r=-0.21 NS	NR
				CHQ Self-esteem subscore	$\%FEV_1$	r=0.24 NS	NR
				CHQ Mental health subscore	$\%FEV_1$	r=0.27 NS	NR
				CHQ General behavior subscore	$\%FEV_1$	r=-0.04 NS	NR
				CHQ Family activities subscore	$\%FEV_1$	r=0.34 NS	NR

Appendix Table F4. Trials reporting the relationship between pulmonary function and health-related quality of life (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Outcome	Predictor	Univariate Relationship	Multivariate Relationship
Gee, 2003 and 2005[42,43] N=223	Patients with CF attending regional adult CF centers.	Cross-sectional	Pearson's correlation coefficient Multiple regression analysis	CFQoL Physical functioning subscore	FEV_1	Males r=0.50 p=0.001 Females r=0.25 p=0.005	β=0.20 (95%CI 0.11, 0.29)
				CFQoL Social functioning subscore	FEV_1	Males r=0.26 p=0.007 Females r=NS p=NS	β=0.12 (95%CI 0.004, 0.25)
				CFQoL Treatment issues subscore	$\%FEV_1$	Males r=0.27 p=0.005 Females r=0.17 p=0.05	β=0.17 (95%CI 0.03, 0.32)
				CFQoL Chest symptoms subscore	$\%FEV_1$	Males r=0.38 p=0.001 Females r=0.21 p=0.02	β=0.29 (95%CI 0.14, 0.43)
				CFQoL Emotional functioning subscore	$\%FEV_1$	Males r=0.27 p=0.005 Females r=0.60 p=0.001	β=0.14 (95%CI 0.02, 0.24)
				CFQoL Concerns for the future subscore	$\%FEV_1$	Males r=0.22 p=0.02 Females r=NS p=NS	β=0.15 (95%CI 0.01, 0.28)

Appendix Table F4. Trials reporting the relationship between pulmonary function and health-related quality of life (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Outcome	Predictor	Univariate Relationship	Multivariate Relationship
				CFQoL Interpersonal relationships subscore	$\%FEV_1$	Males r=NS p=NS Females r=0.28 p=0.002	β=0.18 (95%CI 0.06, 0.30)
				CFQoL Body image subscore	$\%FEV_1$	Males r=0.41 p=0.001 Females r=0.25 p=0.005	β=0.10 (95%CI -0.05, 0.23)
				CFQoL Career concerns subscore	$\%FEV_1$	Males r=0.22 p=0.02 Females r=0.18 p=0.03	β=0.11 (95%CI -0.05, 0.30)

Appendix Table F4. Trials reporting the relationship between pulmonary function and health-related quality of life (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Outcome	Predictor	Univariate Relationship	Multivariate Relationship
Koscik, 2005[44] N=36	Patients with CF from the Wisconsin Newborn Screening (NBS) Project, at least age 6.5 years.	Cross-sectional	Spearman's rank correlation coefficient	CHQ Physical function subscore	FEV_1	ES NR NS	NR
				CHQ Role/social limitations – physical subscore	FEV_1	ES NR NS	NR
				CHQ General health perceptions subscore	FEV_1	ES NR NS	NR
				CHQ Bodily pain/discomfort subscore	FEV_1	ES NR NS	NR
				CHQ Role/social limitations – emotional subscore	FEV_1	ES NR NS	NR
				CHQ Role/social limitations – behavioral subscore	FEV_1	ES NR NS	NR
				CHQ Self-esteem subscore	FEV_1	ES NR NS	NR
				CHQ Mental health subscore	FEV_1	ES NR NS	NR
				CHQ General behavior subscore	FEV_1	ES NR NS	NR
				CHQ Family activities subscore	FEV_1	ES NR NS	NR
				CHQ Family cohesion subscore	FEV_1	r=0.37 p=0.05	NR
				CHQ Change in health subscore	FEV_1	ES NR NS	NR

Appendix Table F4. Trials reporting the relationship between pulmonary function and health-related quality of life (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Outcome	Predictor	Univariate Relationship	Multivariate Relationship
Quittner, 2005[45] N=212	Adolescents and adults with CF at 18 centers across the United States.	Cross-sectional	NR	CFQ Physical domain	$\%FEV_1$	r=0.42 p<0.01	NR
				CFQ Role domain	$\%FEV_1$	r=0.28 p<0.01	NR
				CFQ Vitality domain	$\%FEV_1$	r=0.26 p<0.01	NR
				CFQ Emotion domain	$\%FEV_1$	r=0.28 p<0.01	NR
				CFQ Social domain	$\%FEV_1$	r=0.33 p<0.01	NR
				CFQ Body image domain	$\%FEV_1$	r=0.38 p<0.01	NR
				CFQ Eating domain	$\%FEV_1$	r=0.23 p<0.01	NR
				CFQ Treatment burden domain	$\%FEV_1$	r=0.11 NS	NR
				CFQ Health perceptions domain	$\%FEV_1$	r=0.45 p<0.01	NR
				CFQ Respiratory domain	$\%FEV_1$	r=0.39 p<0.01	NR
				CFQ Digestive domain	$\%FEV_1$	r=0.03 NS	NR
				CFQ Weight domain	$\%FEV_1$	r=0.35 p<0.01	NR
Goldbeck, 2007[46] N=108	Adolescent and adult patients with CF, at least age 15 years.	18 months	Multiple regression analysis	Questions on Life Satisfaction	$\%FEV_1$ at second visit	NR	ES NR NS
					Change in $\%FEV_1$ between two visits	NR	ES NR NS

Appendix Table F4. Trials reporting the relationship between pulmonary function and health-related quality of life (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Outcome	Predictor	Univariate Relationship	Multivariate Relationship
Riekert, 2007[47] N=76	Adults with CF seen at clinic between April 2002 and Nov 2003.	Cross-sectional	Spearman correlation coefficient	CFQ Physical domain	$\%FEV_1$	r=0.57 p<0.001	NR
				CFQ Respiratory domain	$\%FEV_1$	r=0.39 p<0.001	NR
				CFQ Vitality domain	$\%FEV_1$	r=0.33 p<0.01	NR
				CFQ Social domain	$\%FEV_1$	r=0.38 p<0.001	NR
				CFQ Health perceptions domain	$\%FEV_1$	r=0.51 p<0.001	NR
				CFQ Treatment domain	$\%FEV_1$	r=0.32 p<0.01	NR
				CFQ Role domain	$\%FEV_1$	r=0.35 p<0.01	NR
				CFQ Emotion domain	$\%FEV_1$	r=0.20 NS	NR
				CFQ Body image domain	$\%FEV_1$	r=0.38 p<0.001	NR
				CFQ Eating domain	$\%FEV_1$	r=0.33 p<0.01	NR
				CFQ Digestion domain	$\%FEV_1$	r=0.01 NS	NR
				CFQ Weight domain	$\%FEV_1$	r=0.41 p<0.001	NR

Appendix Table F4. Trials reporting the relationship between pulmonary function and health-related quality of life (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Outcome	Predictor	Univariate Relationship	Multivariate Relationship
Havermans, 2008 and 2009[48,49] N=57	Adults with CF consecutively attending the Adult CF Center at the University Hospital in Leuven, Belgium clinic between Sept 2006 and Sept 2007.	Cross-sectional	Pearson correlation	CFQ Physical domain	$\%FEV_1$	r=0.27 p<0.05	NR
				CFQ Respiratory domain	$\%FEV_1$	NR	NR
				CFQ Vitality domain	$\%FEV_1$	NR	NR
				CFQ Social domain	$\%FEV_1$	NR	NR
				CFQ Health perceptions domain	$\%FEV_1$	r=0.38 p<0.05	NR
				CFQ Treatment domain	$\%FEV_1$	NR	NR
				CFQ Role domain	$\%FEV_1$	NR	NR
				CFQ Emotion domain	$\%FEV_1$	NR	NR
				CFQ Body image domain	$\%FEV_1$	NR	NR
				CFQ Eating domain	$\%FEV_1$	NR	NR
				CFQ Digestion domain	$\%FEV_1$	NR	NR
				CFQ Weight domain	$\%FEV_1$	NR	NR

Legend: CF=cystic fibrosis; CFQ=Cystic Fibrosis Questionnaire; CFQoL=Cystic Fibrosis Quality of Life questionnaire; CHQ=Child Health Questionnaire; CI=confidence interval; ES=effect size; EQ-5D=EuroQol 5D; FEV_1=forced expiratory volume in 1 second; $\%FEV_1$=percent predicted forced expiratory volume in 1 second; FVC=forced vital capacity; %FVC=percent predicted forced vital capacity; MCS=mental composite score; NHP=Nottingham Health Profile; NR=not reported; NS=not significant; PCS=physical composite score; QWB=Quality of Well-Being Scale; SF-36=Medical Outcomes Short-Form 36; SIP=Sickness Impact Profile; SS=statistically significant; VAS=visual analog scale

Appendix Table F5. Trials reporting the relationship between anthropometrics and health-related quality of life

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Outcome	Predictor	Univariate Relationship	Multivariate Relationship
Congleton, 1996[36] N=240	Patients with CF aged at least 16 years that attended the CF clinic at the National Heart and Lung Institute in Sydney, Australia for at least 2 years.	Cross-sectional	Spearman's rank correlation coefficient	NHP Energy Subscore	BMI	r=-0.20 p<0.001	NR
				NHP Pain Subscore	BMI	r=-0.02 NS	NR
				NHP Emotion Subscore	BMI	r=-0.07 NS	NR
				NHP Sleep Subscore	BMI	r=-0.15 p<0.05	NR
				NHP Social isolation Subscore	BMI	r=-0.04 NS	NR
				NHP Physical mobility Subscore	BMI	r=-0.30 p<0.0001	NR
Staab, 1998[38] N=89	Adolescent and adult patients (n=89) attending four outpatient clinics in Germany.	Cross-Sectional	Multiple regression analyses	Alltagsleben (Every Day Life)	%IBW	Model 1 (n=83) r=0.11 NS Model 2 (n=84) r=0.10 NS	Model 1 (n=83) β=0.05 NS Model 2 (n=84) β=-0.11 NS
Johnson, 2000[39] N=39 at initial survey N=32 at 1 year	All patients with CF over age 18 years at the University of Alberta Hospital CF clinic.	Cross-sectional, with one 1 follow-up survey	Spearman correlations and multivariate regression models	SF-36 PCS	BMI	ES NR NS	NR
				SF-36 MCS	BMI	ES NR NS	NR
				EQ-5D VAS	BMI	ES NR NS	NR
				EQ-5D VAS after one year	BMI	ES NR NR	β=-0.002 p=0.005

Appendix Table F5. Trials reporting the relationship between anthropometrics and health-related quality of life (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Outcome	Predictor	Univariate Relationship	Multivariate Relationship
Abbott, 2001[40] N=84	English patients (n=58) with CF attending two outpatient clinics who were aged between 14 and 18 years. German patients (n=26) with CF attending outpatient clinics aged between 13 and 17 years.	Cross-sectional	Pearson's correlation coefficient	SF-36 Physical functioning subscore	BMI	ES NR NS	NR
				SF-36 Physical role limitation subscore	BMI	ES NR NS	NR
				SF-36 Social functioning subscore	BMI	ES NR NS	NR
				SF-36 Mental health subscore	BMI	ES NR NS	NR
				SF-36 Mental role limitation subscore	BMI	ES NR NS	NR
				SF-36 Energy and vitality subscore	BMI	ES NR NR	NR
				SF-36 General health perceptions subscore	BMI	ES NR NS	NR
				SF-36 Changes in health subscore	BMI	ES NR NS	NR

Appendix Table F5. Trials reporting the relationship between anthropometrics and health-related quality of life (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Outcome	Predictor	Univariate Relationship	Multivariate Relationship
Gee, 2003 and 2005[42,43] N=223	Patients with CF attending regional adult CF centers.	Cross-sectional	Pearson's correlation coefficient Multiple regression analysis	CFQoL Physical functioning subscore	BMI	Males ES NR NS Females ES NR NS	ES NR NS
				CFQoL Social functioning subscore	BMI	Males ES NR NS Females ES NR NS	ES NR NS
				CFQoL Treatment issues subscore	BMI	Males ES NR NS Females ES NR NS	ES NR NS
				CFQoL Chest symptoms subscore	BMI	Males r=0.21 p=0.02 Females ES NR NS	ES NR NS
				CFQoL Emotional functioning subscore	BMI	Males ES NR NS Females ES NR NS	ES NR NS
				CFQoL Concerns for the future subscore	BMI	Males ES NR NS Females r=0.20 p=0.02	ES NR NS

Appendix Table F5. Trials reporting the relationship between anthropometrics and health-related quality of life (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Outcome	Predictor	Univariate Relationship	Multivariate Relationship
				CFQoL Interpersonal relationships subscore	BMI	Males ES NR NS Females ES NR NS	ES NR NS
				CFQoL Body image subscore	BMI	Males r=0.34 p=0.001 Females r=0.55 p=0.001	β=3.4 (95%CI 2.1, 4.6)
				CFQoL Career concerns subscore	BMI	Males ES NR NS Females ES NR NS	ES NR NS

Appendix Table F5. Trials reporting the relationship between anthropometrics and health-related quality of life (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Outcome	Predictor	Univariate Relationship	Multivariate Relationship
Koscik, 2005[44] N=36	Patients with CF from the Wisconsin Newborn Screening (NBS) Project, at least age 6.5 years.	Cross-sectional	Spearman's rank correlation coefficient	CHQ Physical function subscore	Height-for age	ES NR NS	NR
					Weight-for-age	ES NR NS	NR
				CHQ Role/social limitations – physical subscore	Height-for age	ES NR NS	NR
					Weight-for-age	ES NR NS	NR
				CHQ General health perceptions subscore	Height-for age	ES NR NS	NR
					Weight-for-age	ES NR NS	NR
				CHQ Bodily pain/discomfort subscore	Height-for age	ES NR NS	NR
					Weight-for-age	ES NR NS	NR
				CHQ Role/social limitations – emotional subscore	Height-for age	ES NR NS	NR
					Weight-for-age	ES NR NS	NR
				CHQ Role/social limitations – behavioral subscore	Height-for age	ES NR NS	NR
					Weight-for-age	ES NR NS	NR
				CHQ Self-esteem subscore	Height-for age	ES NR NS	NR
					Weight-for-age	ES NR NS	NR
				CHQ Mental health subscore	Height-for age	ES NR NS	NR
					Weight-for-age	ES NR NS	NR
				CHQ General behavior subscore	Height-for age	ES NR NS	NR
					Weight-for-age	ES NR NS	NR

Appendix Table F5. Trials reporting the relationship between anthropometrics and health-related quality of life (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Outcome	Predictor	Univariate Relationship	Multivariate Relationship
				CHQ Family activities subscore	Height-for age	ES NR NS	NR
					Weight-for-age	ES NR NS	NR
				CHQ Family cohesion subscore	Height-for age	ES NR NS	NR
					Weight-for-age	ES NR NS	NR
				CHQ Change in health subscore	Height-for age	ES NR NS	NR
					Weight-for-age	ES NR NS	NR
Quittner, 2005[45] N=212	Adolescents and adults with CF at 18 centers across the United States.	Cross-sectional	NR	CFQ Physical domain	BMI	r=0.11 NS	NR
				CFQ Role domain	BMI	r=0.1 NS	NR
				CFQ Vitality domain	BMI	r=0.07 NS	NR
				CFQ Emotion domain	BMI	r=0.09 NS	NR
				CFQ Social domain	BMI	r=0.02 NS	NR
				CFQ Body image domain	BMI	r=0.38 p<0.01	NR
				CFQ Eating domain	BMI	r=0.16 p<0.05	NR
				CFQ Treatment burden domain	BMI	r=0.16 p<0.05	NR
				CFQ Health perceptions domain	BMI	r=-0.02 NS	NR
				CFQ Respiratory domain	BMI	r=0.11 NS	NR
				CFQ Digestive domain	BMI	r=-0.00 NS	NR
				CFQ Weight domain	BMI	r=0.47 p<0.01	NR

Appendix Table F5. Trials reporting the relationship between anthropometrics and health-related quality of life (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Outcome	Predictor	Univariate Relationship	Multivariate Relationship
Koscik, 2006[50] N=45	Patients with CF from the Wisconsin Newborn Screening (NBS) Project between the age of 8 and 18.	Cross-sectional	Generalized linear model	CFQ Physical dimension	Adequate weight gain within 2 years of diagnosis	Model p=0.04	NR
					BMI Z-score >-1	Model p=0.52	NR
				CFQ Emotional dimension	Adequate weight gain within 2 years of diagnosis	ES NR NS	NR
					BMI Z-score >-1	ES NR NS	NR
				CFQ Social dimension	Adequate weight gain within 2 years of diagnosis	ES NR NS	NR
					BMI Z-score >-1	ES NR NS	NR
Goldbeck, 2007[46] N=108	Adolescent and adult patients with CF, at least age 15 years.	18 months	Multiple regression analysis	Questions on Life Satisfaction	BMI	NR	ES NR NS

Appendix Table F5. Trials reporting the relationship between anthropometrics and health-related quality of life (continued)

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Outcome	Predictor	Univariate Relationship	Multivariate Relationship
Havermans, 2008 and 2009[48,49] N=57	Adults with CF consecutively attending the Adult CF Center at the University Hospital in Leuven, Belgium clinic between Sept 2006 and Sept 2007.	Cross-sectional	Pearson correlation	CFQ Physical domain	BMI	NR	NR
				CFQ Respiratory domain	BMI	NR	NR
				CFQ Vitality domain	BMI	NR	NR
				CFQ Social domain	BMI	NR	NR
				CFQ Health perceptions domain	BMI	NR	NR
				CFQ Treatment domain	BMI	NR	NR
				CFQ Role domain	BMI	NR	NR
				CFQ Emotion domain	BMI	NR	NR
				CFQ Body image domain	BMI	r=0.28 p<0.05	NR
				CFQ Eating domain	BMI	r=0.44 p<0.01	NR
				CFQ Digestion domain	BMI	NR	NR
				CFQ Weight domain	BMI	r=0.43 p<0.01	NR

Legend: BMI=body mass index; CF=cystic fibrosis; CFQ=Cystic Fibrosis Questionnaire; CFQoL=Cystic Fibrosis Quality of Life questionnaire; CHQ=Child Health Questionnaire; CI=confidence interval; ES=effect size; EQ-5D=EuroQol 5D; IBW=ideal body weight; MCS=mental composite score; NHP=Nottingham Health Profile; NR=not reported; NS=not significant; PCS=physical composite score; QWB=Quality of Well-Being Scale; SF-36=Medical Outcomes Short-Form 36; SIP=Sickness Impact Profile; SS=statistically significant; VAS=visual analog scale

Appendix Table F6. Trials reporting the relationship between exercise tolerance and health-related quality of life

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Outcome	Predictor	Univariate Relationship	Multivariate Relationship
Orenstein, 1989[34] N=44	Patients with CF, aged 7 to 36 years, seen at the Pittsburgh Cystic Fibrosis Center	Cross-sectional	Pearson product moment correlation analysis	QWB	$Vo_{2\text{-peak}}$	r=0.5778 p<0.01	NR
de Jong, 1997[37] N=15	Clinically stable patients with CF, aged 16 to 40 years.	Cross-sectional	Spearman's rank correlation coefficient	SIP Overall Score	W_{peak}	r=-0.57 p<0.05	NR
				SIP Physical Subscore	W_{peak}	r=-0.65 p<0.01	NR
				SIP Psychosocial Subscore	W_{peak}	r=-0.09 NS	NR

Legend: CF=cystic fibrosis; NR=not reported; NS=not significant; QWB=Quality of Well-Being Scale; SIP=Sickness Impact Profile; $Vo_{2\text{-peak}}$=peak oxygen uptake; W_{peak}=peak work rate

Appendix Table F7. Trials reporting the relationship between pulmonary function and bone fracture

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Predictor	Univariate Relationship	Multivariate Relationship
Aris, 1998[51] N=70	Adults (age >18 years) with advanced CF referred for lung transplantation at the University of North Carolina between Jan 1994 and Dec 1996 that were assessed retrospectively for bone fracture.	NR	Student's t test	FEV_1	ES NR NS	NR
				FVC	ES NR NS	NR

Legend: ES=effect size; BMI=forced expiratory volume in 1 second; FVC=forced vital capacity; FEV_1=forced expiratory volume in 1 second; NR=not reported; NS=not significant

Table F8. Trials reporting the relationship between anthropometrics and bone fracture

Study, Year	Population/Setting	Duration of Follow-up	Type of Analysis	Predictor	Univariate Relationship	Multivariate Relationship
Aris, 1998[51] N=70	Adults (age >18 years) with advanced CF referred for lung transplantation at the University of North Carolina between Jan 1994 and Dec 1996 that were assessed retrospectively for bone fracture.	NR	Student's t test	BMI	ES NR NS	NR

Legend: BMI=body mass index; ES=effect size; NR=not reported; NS=not significant

Appendix Table F9. Strength of evidence for outcomes evaluated in Key Question 1

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	rhGH	Control	Relative (95% CI)	Absolute		
Pulmonary Function—Change from Baseline in Absolute FVC (L)												
3	Controlled trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	52	48	-	MD 0.67 higher (0.24 to 1.09 higher)	MODERATE	IMPORTANT
1	Single-group observational studies	No serious limitations	Serious[2]	No serious indirectness	Serious[4]	None	9	0	-	Not pooled	INSUFFICIENT	IMPORTANT
Pulmonary Function—Change from Baseline in Percent Predicted FVC												
5	Controlled trials	Serious[1]	Serious[3]	No serious indirectness	No serious imprecision	None	84	60	-	MD 9.34 higher (3.41 to 15.27 higher)	LOW	IMPORTANT
2	Single-group observational studies	No serious limitations	Serious[5]	No serious indirectness	Serious[4]	None	18	0	-	Not pooled	INSUFFICIENT	IMPORTANT
Pulmonary Function—Change from Baseline in Absolute FEV_1 (L)												
4	Controlled trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	58	52	-	MD 0.23 higher (0.01 to 0.46 higher)	MODERATE	IMPORTANT
1	Single-group observational studies	No serious limitations	Serious[2]	No serious indirectness	Serious[4]	None	9	0	-	Not pooled	INSUFFICIENT	IMPORTANT

Appendix Table F9. Strength of evidence for outcomes evaluated in Key Question 1 (continued)

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	rhGH	Control	Relative (95% CI)	Absolute	Quality	Importance
Pulmonary Function—Change from Baseline in Percent Predicted FEV_1												
4	Controlled trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	71	48	-	MD 2.43 higher (3.99 lower to 8.85 higher)	MODERATE	IMPORTANT
2	Single-group observational studies	No serious limitations	Serious[5]	No serious indirectness	Serious[4]	None	14	0	-	Not pooled	INSUFFICIENT	IMPORTANT
Pulmonary Function—Change from Baseline in FEV_1 Z-score												
1	Controlled trials	Serious[1]	Serious[2]	No serious indirectness	Serious[4]	None	42	21	-	MD 0.005 lower (0.22 lower to 0.21 higher)	INSUFFICIENT	IMPORTANT
Anthropometrics—Change from Baseline in Height (cm)												
3	Controlled trials	Serious[1]	Serious[3]	No serious indirectness	No serious imprecision	None	29	25	-	MD 3.13 higher (0.88 to 5.38 higher)	LOW	IMPORTANT
1	Single-group observational studies	No serious limitations	Serious[2]	No serious indirectness	Serious[4]	None	24	0	-	Not pooled	INSUFFICIENT	IMPORTANT
Anthropometrics—Change from Baseline in Height Velocity (cm/year)												
3	Controlled trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	82	57	-	MD 3.27 higher (2.33 to 4.21 higher)	MODERATE	IMPORTANT

Appendix Table F9. Strength of evidence for outcomes evaluated in Key Question 1 (continued)

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	rhGH	Control	Relative (95% CI)	Absolute	Quality	
4	Single-group observational studies	No serious limitations	Serious[5]	No serious indirectness	Serious[4]	None	43	0	-	Not pooled	INSUFFICIENT	IMPORTANT
Anthropometrics—Change from Baseline in Height Z-Score												
3	Controlled trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	48	45	-	MD 0.51 higher (0.35 to 0.66 higher)	MODERATE	IMPORTANT
3	Single-group observational studies	No serious limitations	No serious inconsistency	No serious indirectness	Serious[4]	None	23	0	-	Not pooled	LOW	IMPORTANT
Anthropometrics—Change from Baseline in Height Percentile												
1	Controlled trials	Serious[1]	Serious[2]	No serious indirectness	Serious[4]	None	10	9	-	Not pooled	INSUFFICIENT	IMPORTANT
Anthropometrics—Change from Baseline in Weight (kg)												
5	Controlled trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	100	73	-	MD 1.48 higher (0.62 to 2.33 higher)	MODERATE	IMPORTANT
1	Single-group observational studies	No serious limitations	Serious[2]	No serious indirectness	Serious[4]	None	9	0	-	Not pooled	INSUFFICIENT	IMPORTANT
Anthropometrics—Change from Baseline in Weight Velocity (kg/year)												
2	Controlled trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	40	36	-	MD 2.15 higher (1.52 to 2.78 higher)	MODERATE	IMPORTANT
3	Single-group observational studies	No serious limitations	No serious inconsistency	No serious indirectness	Serious[4]	None	25	0	-	Not pooled	LOW	IMPORTANT

Appendix Table F9. Strength of evidence for outcomes evaluated in Key Question 1 (continued)

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	rhGH	Control	Relative (95% CI)	Absolute	Quality	
Anthropometrics—Change from Baseline in Weight Z-score												
4	Controlled trials	Serious[1]	Serious[3]	No serious indirectness	No serious imprecision	None	45	43	-	MD 0.49 higher (0.02 lower to 1 higher)	LOW	IMPORTANT
1	Single-group observational studies	No serious limitations	Serious[2]	No serious indirectness	Serious[4]	None	5	0	-	Not pooled	INSUFFICIENT	IMPORTANT
Anthropometrics—Change from Baseline in Weight Percentile												
1	Controlled trials	Serious[1]	Serious[2]	No serious indirectness	Serious[4]	None	10	9	-	Not pooled	INSUFFICIENT	IMPORTANT
Anthropometrics—Change from Baseline in Body Mass Index (kg/m^2)												
2	Controlled trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	22	21	-	MD 2.08 higher (1.2 to 2.96 higher)	MODERATE	IMPORTANT
1	Single-group observational studies	No serious limitations	Serious[2]	No serious indirectness	Serious[4]	None	5	0	-	Not pooled	INSUFFICIENT	IMPORTANT
Anthropometrics—Change from Baseline in BMI Z-score												
1	Controlled trials	Serious[1]	Serious[2]	No serious indirectness	Serious[4]	None	42	21	-	MD 0.05 lower (0.3 lower to 0.2 higher)	INSUFFICIENT	IMPORTANT
Anthropometrics—Change from Baseline in Percent Ideal Body Weight												
2	Controlled trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[4]	None	23	21	-	MD 12.57 higher (7.01 to 18.12 higher)	LOW	IMPORTANT
Anthropometrics—Change from Baseline in Lean Body Mass (kg)												
8	Controlled trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	149	121	-	MD 1.92 higher (1.47 to 2.37 higher)	MODERATE	IMPORTANT

Appendix Table F9. Strength of evidence for outcomes evaluated in Key Question 1 (continued)

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	rhGH	Control	Relative (95% CI)	Absolute	Quality	
Protein Turnover												
2	Controlled trials	Serious[1]	Serious[5]	No serious indirectness	Serious[4]	None	28	18	-	Not pooled	INSUFFICIENT	IMPORTANT
1	Single-group observational studies	No serious limitations	Serious[2]	No serious indirectness	Serious[4]	None	9	0	-	Not pooled	INSUFFICIENT	IMPORTANT
Exercise Tolerance												
3	Controlled trials	Serious[1]	Serious[5]	No serious indirectness	Serious[4]	None	58	34	-	Not pooled	INSUFFICIENT	IMPORTANT
1	Single-group observational studies	No serious limitations	Serious[2]	No serious indirectness	Serious[4]	None	5	0	-	Not pooled	INSUFFICIENT	IMPORTANT
Bone Mineralization—Bone Age (years)												
2	Controlled trials	Serious[1]	Serious[5]	No serious indirectness	Serious[4]	None	23	21	-	Not pooled	INSUFFICIENT	IMPORTANT
3	Single-group observational studies	No serious limitations	No serious inconsistency	No serious indirectness	Serious[4]	None	21	0	-	Not pooled	LOW	IMPORTANT
Bone Mineralization—Change from Baseline in Bone Mineral Content (g)												
4	Controlled trials	Serious[1]	Serious[3]	No serious indirectness	No serious imprecision	None	68	64	-	MD 192 higher (110 to 273 higher)	LOW	IMPORTANT
Bone Mineralization—Bone Mineral Content Z-score												
1	Controlled trials	Serious[1]	Serious[2,5]	No serious indirectness	Serious[4]	None	32	29	-	Not pooled	INSUFFICIENT	IMPORTANT
Sexual Maturation												
7	Controlled trials	Serious[1]	Serious[5]	No serious indirectness	No serious imprecision	None	104	88	Not pooled	Not pooled	LOW	IMPORTANT

Legend: BMI=body mass index; CI=confidence interval; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; MD=mean difference; rhGH=recombinant human growth hormone

[1] Lack of or inadequate information about blinding
[2] Single study
[3] Statistical heterogeneity detected
[4] Inadequately powered
[5] Inconsistent study designs or outcomes reporting

Appendix Table F10. Strength of evidence for outcomes evaluated in Key Question 2

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	rhGH	Control	Relative (95% CI)	Absolute		
Antibiotic Usage												
3	Controlled trials	Serious[1]	Serious[2]	No serious indirectness	Serious[3]	None	51	47	-	Not pooled	INSUFFICIENT	IMPORTANT
Pulmonary Exacerbations												
1	Controlled trials	Serious[1]	Serious[4]	No serious indirectness	Serious[3]	None	13/42 (31%)	4/21 (19%)	RR 1.63 (0.60 to 4.38)	12% Risk Increase	INSUFFICIENT	IMPORTANT
Change from Baseline in Rate of Hospitalizations (events per year)												
4	Controlled trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	62	57	-	MD 1.62 lower (1.98 to 1.26 lower)	MODERATE	IMPORTANT
Health-Related Quality of Life												
2	Controlled trials	Serious[1]	Serious[2]	No serious indirectness	Serious[3]	None	74	50	-	Not pooled	INSUFFICIENT	IMPORTANT

Legend: CI=confidence interval; MD=mean difference; rhGH=recombinant human growth hormone
[1] Lack of or inadequate information about blinding
[2] Inconsistent study designs or outcomes reporting
[3] Inadequately powered
[4] Single study

Appendix Table F11. Strength of evidence for outcomes evaluated in Key Question 4

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	rhGH	Control	Relative (95% CI)	Absolute		
Change from Baseline in A1c (%)												
2	Controlled trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	23	21	-	MD 0.10 lower (0.4 lower to 0.2 higher)	LOW	IMPORTANT
2	Single-group observational studies	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	18	0	-	Not pooled	LOW	IMPORTANT
Change from Baseline in Random BG (mg/dl)												
3	Controlled trials	Serious[1]	Serious[3]	No serious indirectness	Serious[2]	None	54	50	-	Not pooled	INSUFFICIENT	IMPORTANT
Change from Baseline in FBG (mg/dl)												
2	Controlled trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	52	30	-	MD 5.68 higher (0.43 to 10.93 higher)	MODERATE	IMPORTANT
1	Single-group observational studies	No serious limitations	Serious[4]	No serious indirectness	Serious[2]	None	9	0	-	Not pooled	INSUFFICIENT	IMPORTANT
Change from Baseline in Stimulated BG (mg/dl)												
1	Controlled trials	Serious[1]	Serious[4]	No serious indirectness	Serious[2]	None	42	21	-	MD 4.93 higher (15.13 lower to 24.98 higher)	INSUFFICIENT	IMPORTANT

Appendix Table F11. Strength of evidence for outcomes evaluated in Key Question 4

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	rhGH	Control	Relative (95% CI)	Absolute		
Change from Baseline in Postprandial BG (mg/dl)												
1	Controlled trials	Serious[1]	Serious[4]	No serious indirectness	Serious[2]	None	10	9	-	MD 10 higher (17.91 lower to 37.91 higher)	INSUFFICIENT	IMPORTANT
Change from Baseline in Other BG Parameters Not Specified (mg/dl)												
1	Controlled trials	Serious[1]	Serious[4]	No serious indirectness	Serious[2]	None	18	9	-	Not pooled	INSUFFICIENT	IMPORTANT
1	Single-group observational studies	Serious[1]	Serious[4]	No serious indirectness	Serious[2]	None	5	0	-	Not pooled	INSUFFICIENT	IMPORTANT
Development of Glucose Intolerance												
7	Controlled trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	0/61 (0%)	0/54 (0%)	Not pooled	Not pooled	LOW	IMPORTANT
3	Observational trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	2/42 (4.8%)	0/0	Not pooled	Not pooled	INSUFFICIENT	IMPORTANT
Development of Diabetes												
7	Controlled trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	0/61 (0%)	0/54 (0%)	Not pooled	Not pooled	LOW	IMPORTANT
1	Single-group observational studies	Serious[1]	Serious[4]	No serious indirectness	Serious[2]	None	1/1 (100%)	0/0	Not pooled	Not pooled	INSUFFICIENT	IMPORTANT

Legend: A1c=glycosylated hemoglobin; BG=blood glucose; CI=confidence interval; MD=mean difference; rhGH=recombinant human growth hormone

[1] Lack of or inadequate information about blinding

[2] Inadequately powered

[3] Inconsistent study designs or outcomes reporting

[4] Single study

Appendix Table F12. Strength of evidence for outcomes evaluated in Key Question 5

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	rhGH	Control	Relative (95% CI)	Absolute	Quality	
Biomarkers – IGF- I (ng/ml)												
4	Controlled trials	Serious[1]	Serious[2]	No serious indirectness	Serious[3]	None	66	55	-	Not pooled	INSUFFICIENT	IMPORTANT
2	Single-group observational studies	No serious limitations	No serious inconsistency	No serious indirectness	Serious[3]	None	14	0	-	Not pooled	INSUFFICIENT	IMPORTANT
Biomarkers – IGFBP-3 (ng/ml)												
1	Controlled trials	Serious[1]	Serious[4]	No serious indirectness	Serious[3]	None	18	9	-	Not pooled	INSUFFICIENT	IMPORTANT
1	Single-group observational studies	No serious limitations	Serious[4]	No serious indirectness	Serious[3]	None	5	0	-	Not pooled	INSUFFICIENT	IMPORTANT
Development of Cancer in CF Populations												
1	Single-group observational studies	Serious[1]	Serious[4]	No serious indirectness	Serious[3]	None	1	0	Not pooled	Not pooled	INSUFFICIENT	IMPORTANT
Development of Cancer in Non-CF Populations												
3	Single-group observational studies	No serious limitations	No serious inconsistency	Serious[5]	No serious imprecision	None	33,172	0	Not pooled	Not pooled	LOW	IMPORTANT

Legend: CF=cystic fibrosis; CI=confidence interval; IGF-I=insulin-like growth factor-1; IGFBP-3=insulin-like growth factor binding protein-3; MD=mean difference; rhGH=recombinant human growth hormone

[1] Lack of or inadequate information about blinding

[2] Inconsistent study designs or outcomes reporting

[3] Inadequately powered

[4] Single study

[5] Studies not in patients with CF

References for Appendix F

Please note that these references are independent of the main report and may have different reference numbers.

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