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

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm

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Structured Abstract

Objectives: This is an evidence report prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center (EPC) examining the benefits and harms associated with using recombinant human growth hormone (rhGH) in patients with cystic fibrosis (CF).

Data Sources: MEDLINE (starting from 1950), Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews from the earliest possible date through July 2009.

Review Methods: The methods used to answer questions of rhGH usage in CF patients specifically are given. Randomized controlled trials, observational studies, systematic reviews/meta-analyses, or case reports were included if they: administered rhGH therapy to patients with CF and reported data on pre-specified harms, intermediate outcomes or final health outcomes. Using a standardized protocol with predefined criteria, data on study design, interventions, quality criteria, study population, baseline characteristics, and outcomes was extracted. Some of the data allowed for statistical pooling. When pooling continuous endpoints, weighted mean differences (WMD) with 95 percent confidence intervals (CIs) were calculated using a DerSimonian and Laird random effects model. I^2 was used to detect statistical heterogeneity. Visual inspection of funnel plots and Egger's weighted regression statistics were used to assess for publication bias. The overall body of evidence was graded for each outcome as insufficient, low, moderate, or high.

Results: Ten articles based on unique trials, eight articles based on trials reported in previous articles, and eight articles based on observational studies met our inclusion criteria. Upon quantitative synthesis of controlled trials, several markers of pulmonary function [forced vital capacity (FVC) (WMD 0.67 L, 95 percent CI 0.24 to 1.09 L), percent predicted FVC (WMD 9.34 percent, 95 percent CI 3.41 to 15.27 percent), and forced expiratory flow in one second (FEV_1) (WMD 0.23 L, 95 percent CI 0.01 to 0.46 L)], anthrometrics [change in height (WMD 3.13 cm, 95 percent CI 0.88 to 5.38 cm), height velocity (WMD 3.27 cm/year, 95 percent CI 2.33 to 4.21 cm/year), and height Z-score (WMD 0.51, 95 percent CI 0.35 to 0.66), weight (WMD 1.48 kg, 95 percent CI 0.62 to 2.33 kg), weight velocity (WMD 2.15 kg/year, 95 percent CI 1.52 to 2.78 kg/year), body mass index (BMI) (WMD 2.08 kg/m^2, 95 percent CI 1.20 to 2.96 kg/m^2), percent ideal body weight (IBW) (WMD 12.57, 95 percent CI 7.01 to 18.12), lean body mass (LBM) (WMD 1.92 kg, 95 percent CI 1.47 to 2.37 kg)] and bone strength (bone mineral content (WMD 192 g, 95 percent CI 110 to 273 g)] were significantly improved versus control. A moderate to high degree of statistical heterogeneity was seen for many of these intermediate outcomes, but the directions of effect for individual studies were almost always consistent. Single-arm observational studies for the aforementioned outcomes were generally supportive of findings in clinical trials. Patients receiving rhGH therapy in controlled trials had nonsignificant improvements in percent predicted FEV_1 (WMD 2.43 percent , 95 percent CI -3.99 to 8.85 percent), weight Z-score (WMD 0.49, 95 percent CI -0.02 to 1.00), and exercise work rate (WMD 11.80 W, 95 percent CI -0.44 to 24.04 W) but no improvement in FEV_1 Z-score (WMD

-0.005, 95 percent CI -0.22 to 0.21) or BMI Z-score (WMD -0.05, 95 percent CI -0.30 to 0.20) versus control therapy.

Despite promising findings on intermediate outcomes, there is insufficient evidence to determine the effect of rhGH on IV antibiotic use during therapy, pulmonary exacerbations, health-related quality-of-life (HRQoL), bone consequences, or total mortality. There is moderate evidence to suggest that rhGH therapy reduces the rate of hospitalization (WMD -1.62 hospitalizations per year, 95 percent CI -1.98 to -1.26 hospitalizations per year) versus control although one trial not amenable for quantitative synthesis reported that there were no statistically significant differences in hospitalization days between groups. In qualitative assessment, rhGH therapy does not seem to improve sexual maturation in males and the impact in females cannot be determined at this time.

In quantitative synthesis of controlled trials, rhGH therapy significantly increases fasting blood glucose (WMD 5.68 mg/dl, 95 percent CI 0.43 to 10.93 mg/dl) and nonsignificantly increases stimulated glucose concentrations (WMD 4.93 mg/dl (95, percent CI -15.13 to 24.98 mg/dl) but long term glucose control, as assessed by hemoglobin A1c, is not impacted (WMD -0.10 percent, 95 percent CI -0.40 to 0.20 percent) versus control. In qualitative analysis, insulin-like growth factor-I (IGF-I) concentrations in rhGH treated patients are more than 100 ng/mL higher than control. While IGF-I is a marker for malignancy, insufficient evidence exists to determine the impact of rhGH on cancer incidence.

In patients with CF not receiving rhGH, the associations between the aforementioned intermediate outcomes and final health outcomes were generally weak.

Conclusions: rhGH improved almost all intermediate measures of pulmonary function, height, and weight in patients with CF. Improvements in bone mineral content are also promising. However, with the exception of hospitalizations, the benefits on final health outcomes cannot be directly determined at this time. In the relatively low doses used in CF patients for a time period of 6 to 12 months, rhGH therapy may worsen short term markers of glucose control but may not impact long terms glucose control. The increase in IGF-I with rhGH therapy is above a threshold thought to increase the risk of malignancy but the strength of this marker in determining malignancy is not firmly established.

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Executive Summary

Background

Cystic fibrosis (CF) is the second most common life-shortening, childhood-onset genetic disease in the United States, affecting approximately 30,000 people in the U.S. The gene responsible for CF encodes the cystic fibrosis transmembrane regulator (CFTR) protein, which regulates sodium and chloride transport across epithelial membranes. This affects nearly all exocrine glands, with abnormally viscous mucus and excessive secretions. The dominant clinical features are chronic lung disease and pancreatic insufficiency with poor nutrition and growth.

Treatment advances in CF over the past 25 years have improved measures of nutrition, pulmonary function, and mortality. The median age of survival has improved consistently from 1955 to the most recent data in 2006 (37 year survival).

Growth and nutritional indices [weight-for-age, height-for-age, and percent ideal body weight (IBW)] may be predictive of future pulmonary function in children with CF. It has been suggested that improvement of linear growth in children with CF may allow more lung mass and better pulmonary function, independent of improved weight gain. Poor weight and shorter height have also each been shown to be independently associated with increased morbidity and mortality in CF patients in some studies.

Recombinant human growth hormone (rhGH) is an anabolic agent with a wide variety of actions. It is approved by the United States Food and Drug Administration (FDA) for the treatment of growth hormone deficiency, idiopathic short stature, Turner syndrome, Prader-Willi Syndrome, chronic renal insufficiency and for children who are small for gestational age. It has been investigated for the treatment of CF because of the decreased growth measures and increased energy expenditures in CF patients.

Scope and Key Questions

This is an evidence report prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center (EPC) examining the benefits and harms associated with using rhGH in patients with CF.

KQ 1: In patients with CF, does treatment with rhGH as an adjuvant to usual care improve intermediate outcomes, including: pulmonary function [percent predicted forced expiratory volume in one second (FEV_1) and change in FEV_1]; growth [height, weight, lean body mass (LBM), protein turnover]; exercise tolerance; and bone mineralization, compared with usual care alone?

KQ 2: In patients with CF, does treatment with rhGH as an adjuvant to usual care improve health outcomes, including: frequency of required intravenous antibiotic treatments; frequency of hospitalization; quality of life; bone fracture or development of osteoporosis/osteopenia; or mortality, compared with usual care alone?

KQ 3: In patients with CF, what is the strength of evidence that intermediate outcomes of pulmonary function, growth, and bone mineralization are associated with improvements in health outcomes of quality of life, bone fracture or development of osteoporosis/osteopenia, or mortality?

KQ 4: In patients with CF, what is the frequency of nonmalignant serious adverse effects resulting from treatment with rhGH in patients with CF? Adverse effects of interest include, but are not limited to: glucose intolerance, diabetes, and hypoglycemia.

KQ 5: What is the risk of malignancy associated with rhGH use as determined by: (a) markers of cancer risk with rhGH [insulin-like growth factor-I (IGF-I) increases over 100 ng/ml or insulin-like growth factor binding protein-3 (IGFBP-3) decreases over 1000 ng/ml] from studies of rhGH in people with CF and by (b) assessment of evidence on cancer incidence from non-CF patients receiving modest doses of rhGH (0.2mg/kg/week to 0.6mg/kg/week) for disorders such as growth hormone deficiency (CHD) and idiopathic short stature (ISS)?

KQ 6: In patients with CF, how is efficacy, effectiveness, safety or adverse events impacted by rhGH dose, therapy duration, baseline nutritional status, and concurrent medical therapies?

KQ 7: In patients with CF, how do the efficacy, effectiveness, safety or adverse events of treatment with rhGH differ between subgroups of patients? Subgroup characteristics of interest include, but are not limited to: age (pre-pubertal, pubertal, post-pubertal); gender; baseline clinical status (height, weight, LBM, pulmonary function, exercise tolerance, nutritional status); and/or the nature, extent, and effectiveness of prior treatment.

Methods

Literature Search Strategy

Two independent investigators conducted systematic literature searches of MEDLINE (starting from 1950), the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews from the earliest possible date through July 2009. Three separate searches were conducted. The first search was used to identify trials and studies which explicitly evaluated the impact of rhGH on outcomes in patients with CF. The two other searches were used to answer questions regarding the impact of intermediate health outcomes on final health outcomes in patients with CF and evaluated the potential for malignant effects of rhGH as assessed in a CF population and those with idiopathic short stature or growth hormone deficiency. With these two additional searches, we utilized Cochrane's Highly Sensitive Search Strategy (Sensitivity Maximizing Version 2008) to limit to randomized controlled trials and the Scottish Intercollegiate Guidelines Network Observational Study Search Filter to limit to observational studies. No language restrictions were imposed and a manual search of references from reports of clinical trials or review articles was conducted.

Study Selection

Studies were included in the evaluation of key questions 1, 2, 4, 6, and 7 if they were 1) studies of rhGH therapy, 2) conducted in patients with CF, 3) studies that reported data on pre-specified clinical or humanistic outcomes, and 4) reports of new discovery (specifically, randomized controlled trials, observational trials, systematic review/meta-analyses, or case reports). Studies were included in the key question 3 evaluation if they were 1) conducted in patients with CF, 2) either randomized controlled trials or observational studies, and 3) report linkages between intermediate outcomes and health outcomes. Studies which reported on linkages between intermediate and final health outcomes subsequent to a medical or behavioral intervention were excluded from this evaluation. Studies were included in the key question 5 evaluation if they were 1) studies of rhGH therapy, 2) conducted in patients with CF, idiopathic

short stature, or growth hormone deficiency, 3) either randomized controlled trials or observational studies, and 4) studies that reported data on malignant outcomes.

Data Abstraction

Through the use of a standardized data abstraction tool, two reviewers independently collected data, with disagreement resolved through discussion. The following information was obtained from each trial, where applicable: author identification, year of publication, source of study funding, study design characteristics and methodological quality criteria, study population [including study inclusion and exclusion criteria, run-in period, study withdrawals, dose of rhGH utilized, length of study, duration of patient followup, and disease state (CF, idiopathic short stature, or growth hormone deficiency)], patient baseline characteristics (sex, age, ethnicity, nutritional status), comorbidities, and use of concurrent standard medical therapies (corticosteroids, antibiotics, etc). Endpoints included: pulmonary function, anthropometrics (height, weight, LBM, protein turnover), exercise tolerance, intravenous antibiotic use, hospitalizations, HRQoL, bone mineralization, bone fracture or development of osteoporosis/osteopenia, mortality, glucose measures, and development of diabetes or malignancy.

Literature Synthesis

Regarding the intermediate outcomes within KQ1, there are distinct clusters of outcomes which may be reported in a variety of ways. For pulmonary function, trials and studies report a wide range of outcomes, such as absolute values of FEV1 and FVC along with the percent-predicted FEV1 and FVC. The most commonly reported of these were selected for meta-analysis, while the remaining outcomes were reported qualitatively. Anthropometrics are also reported in many ways, including absolute values of height, height percentile, height Z-scores, height velocity, absolute values of weight, weight percentile, weight Z-scores, weight velocity, and weight for height Z-scores. Those endpoints amenable for meta-analysis were quantitatively synthesized and the rest were qualitatively described.

Important health outcomes in KQ2 and harms in KQ4 associated with rhGH were meta-analyzed where appropriate and the rest were qualitatively described. The remaining KQs (3, 5-7) were not amenable for quantitative synthesis and were answered qualitatively.

Quantitative Analysis

Randomized controlled trials and prospective cohort studies were pooled together when trials evaluated both an rhGH and a control group, henceforth described as controlled trials. Single-arm observational studies were described qualitatively in all cases.

When pooling continuous endpoints, a weighted mean difference (WMD) was calculated using a DerSimonian and Laird random effects model. In cases where mean change scores from baseline for each group were not reported, we calculated the difference between the mean baseline and mean followup scores for each group. Standard deviations (SDs) of the change scores were calculated using the method proposed by Follman and colleagues. In the event where there was more than one treatment group versus control, each treatment group was treated as a separate trial for meta-analysis, by dividing the control group equally between the treatment groups. For dichotomous endpoints, weighted averages were reported as relative risks (RRs) with associated 95 percent confidence intervals (CIs). As heterogeneity between included studies is

expected, a DerSimonian and Laird random-effects model was used when pooling data and calculating RRs and 95 percent CIs.

Statistical heterogeneity was addressed using the I2 statistic which assesses the degree of inconsistency not due to chance across studies and ranges from 0-100 percent with values of 25 percent, 50 percent and 75 percent representing low, medium and high statistical heterogeneity, respectively. Visual inspection of funnel plots and Egger's weighted regression statistics were used to assess for the presence of publication bias.

Statistics were performed using StatsDirect statistical software, version 2.4.6 (StatsDirect Ltd, Cheshire, England). A p-value of <0.05 was considered statistically significant for all analyses.

Subgroup and Sensitivity Analyses

To assess the effect of heterogeneity on our meta-analysis' conclusions, subgroup and sensitivity analyses were conducted. Subgroup analyses were conducted to assess the effect of treatment duration and patient pubertal status on the efficacy of rhGH. Trials with duration of 6 months were meta-analyzed separately from trials with a duration of 1 year. Trials which enrolled prepubertal patients were meta-analyzed and compared to the one trial which enrolled pubertal patients alone. Trials which enrolled patients with a range of pubertal status were excluded in subgroup analysis.

Results

When conducting the literature search to identify articles which evaluated the use of rhGH in CF populations, we retrieved 44 unique citations and another citation was identified from other sources. Eighteen articles were excluded during the title and abstract review and two articles were excluded during the full text review. A total of 26 articles were found to match our inclusion criteria.

From the literature search for studies which evaluated the linkages between intermediate and important health outcomes, we retrieved 1126 unique citations. An additional 16 references were obtained from other sources. After a review of the titles and abstracts, 113 were deemed eligible for further review, and the full articles were retrieved. A total of 53 articles were found to match our inclusion criteria. Three studies reported on the same population as another included publication, and they were included as they provided additional data. Therefore, a total of 50 unique studies were included in our evaluation.

When we conducted the literature search for cancer in non-CF populations, 159 unique citations were retrieved and another two citations were identified through other sources. One hundred-sixteen citations were excluded during the title and abstract review and 44 from the full text review. Three articles were included.

A summary of the results and the strength of evidence for all key questions can be found in Table ES-1.

Key Question 1

Five markers of pulmonary function were evaluated in patients with CF receiving rhGH therapy. In controlled trials, the FVC and percent predicted FVC significantly increased from baseline in trials comparing patients with CF receiving chronic rhGH therapy to control therapy.

Single-arm observational studies support these findings. In controlled trials, the FEV_1 significantly increased from baseline in patients with CF receiving chronic rhGH therapy versus control therapy and the percent predicted FEV_1 showed a nonsignificant improvement versus control. Single-arm observational studies support the FEV_1 findings but the percent predicted FEV_1 findings are mixed. In the one available controlled trial, no change in FEV_1 Z-score occurred in patients receiving rhGH for CF versus placebo therapy and no observational studies evaluated this parameter.

In controlled trials suitable for pooling, significant improvements in height were observed for patients with CF receiving rhGH therapy versus control therapy as measured by the change in height, height velocity, height Z-score, and height percentile. Observational studies or other trials not suitable for pooling support these findings. In controlled trials, significant improvements in weight were observed for patients with CF receiving rhGH therapy versus control therapy as measured by change in weight, weight velocity, body mass index (BMI), percent IBW, LBM, and weight percentile. Patients receiving rhGH therapy had a trend towards a higher weight Z-score but did not have a higher BMI Z-score than those receiving control therapy. Observational studies evaluating change in weight, weight velocity, and weight Z-score were generally supportive of improvements associated with rhGH therapy, although one crossover trial not amenable for pooling did not show any improvement in LBM in patients receiving rhGH compared with those who received glutamine therapy.

Four markers of protein turnover were evaluated in patients with CF receiving rhGH therapy. In controlled trials, rhGH therapy significantly improved two markers of protein turnover (LeuOx and NOLD) and nonsignificantly improved LeuRa concentrations. In one observational trial, nitrogen balance was qualitatively impacted but protein synthesis was unchanged. In controlled trials, rhGH therapy significant improved exercise work rate. Qualitative improvements in several measures of exercise tolerance were seen after rhGH therapy in patients with CF but in most cases do not reach statistical significance. Given the few trials evaluating this type of endpoint and the various markers being evaluated, the impact is difficult to determine at this time.

In controlled trials and single-arm observational studies, treating patients with rhGH therapy does not improve bone age in patients with CF. However, bone mineral content does significantly improve with rhGH therapy in trials, and bone mineral content Z-score was also improved in the one trial in which it was assessed.

rhGH therapy in patients with CF does not seem to improve sexual maturation in males and the impact in females cannot be determined at this time. Controlled trials were not amenable to pooling and no single-arm observational data was available. In five controlled trials, rhGH therapy did not improve sexual maturation regardless of gender. In one controlled trial, mean Tanner stage regardless of gender improved and in an analysis of three controlled trials, rhGH therapy significantly improved sexual maturation in females but not in males.

Key Question 2

There is insufficient evidence to determine the effect of rhGH on important health outcomes. Preliminary data suggests that rhGH may have benefit on IV antibiotic use. However, there is insufficient evidence to determine the effect of rhGH on pulmonary exacerbations, HRQoL, bone consequences or mortality. There is moderate evidence to suggest that rhGH therapy reduces the rate of hospitalization.

Key Question 3

The association between pulmonary function and mortality in patients with CF was evaluated in 28 studies. Only one of three studies that evaluated FVC at baseline and mortality found a univariate association and only two of five that evaluated percent predicted FVC at baseline and mortality found a univariate association. However, only one of the aforementioned studies performed multivariate analysis and found that percent predicted FVC at baseline was a multivariate predictor. Decrease in FVC was a univariate and multivariate predictor of mortality in two trials but not in two other trials. Some studies using univariate analysis found an association between measures of absolute FEV_1 and mortality but other studies did not. In the only two multivariate analyses, an association was found between FEV_1 and mortality in one study but no association was seen between the decline in FEV_1 and mortality. The link between percent predicted FEV_1 and mortality is stronger with a majority of studies finding an association between percent predicted FEV_1 and mortality.

The association between anthropometrics and mortality in patients with CF was evaluated in 26 studies. The link between height and mortality is weak with only a minority of studies reporting an association. The link between different measures of weight and mortality was supported in a majority of studies by univariate analysis. Only one study found a multivariate relationship between weight and mortality but another multivariate analysis did not. The link between BMI and mortality is controversial with some studies showing no association, others showing only a univariate association, and very few showing a multivariate association. The link between IBW and mortality was supported by several univariate associations and in the only multivariate analysis. The only study evaluating the association between percent predicted weight-for-height and mortality found a multivariate association.

No studies evaluated the association between protein turnover and mortality.

The association between exercise tolerance and mortality in patients with CF was evaluated in 10 studies. The link between walk testing and mortality is weak with some studies finding no association, some finding only a univariate association, and very few finding a multivariate association. The link between peak oxygen uptake during exercise testing and mortality was only supported by univariate analyses.

No studies evaluated the association between bone mineralization and mortality.

The association between pulmonary function and HRQoL in patients with CF was evaluated in 14 studies but using 10 different scales. All studies but one, specified that they explored the association between percent predicted FEV_1 and HRQoL. The last study did not specify whether the FEV_1 was the absolute or percent predicted. Only four studies employed multivariate analyses (each using different questionnaires to rate HRQoL). In multivariate analyses, higher percent predicted FEV_1 was associated with improvements in “ways of coping” but not subjective health perception in one study, but whether this is absolute or percent predicted FEV_1 is not specified. Higher percent predicted FEV_1 was associated with improvements in seven of nine health domains (including social and physical functioning and chest symptoms) in another study and general well being in another study, but no association was seen between FEV_1 and general health perception in the final study.

The association between anthropometrics and HRQoL in patients with CF was evaluated in 10 studies but using 9 different scales and different anthropometric parameters. Only five studies employed multivariate analyses (each using different questionnaires to rate HRQoL). In

multivariate analysis, greater percent IBW was not associated with subjective health perception or coping in one study, greater BMI was only associated with improvements in body image but not any other factor including social and physical functioning and chest symptoms in another study, adequate weight gain over 2 years was associated with improvements in physical functioning but not social or emotional functioning, BMI Z-score was not associated with any of the three dimensions in one study, greater BMI was associated with lower general health perception in one study, and BMI was not associated with life satisfaction.

No studies evaluated the association between protein turnover and HRQoL.

Two studies evaluated the impact between exercise tolerance and HRQoL using two different questionnaires. Greater exercise capacity (determined by VO_{2peak} or maximal workload) is associated with better measures of HRQoL scores in univariate analyses.

No studies evaluated the association between bone mineralization and HRQoL.

Only one study evaluated the association between pulmonary function or anthropometrics and bone consequences. In univariate analyses, there was no relationship between FEV_1, FVC, or BMI and bone fracture.

No studies evaluated the association between protein turnover, exercise tolerance, or bone mineralization and bone consequences.

Key Question 4

Therapy with rhGH causes a small but nonsignificant decrease in A1c in CF patients. In CF patients, rhGH therapy significantly increases fasting blood glucose concentrations but does not significantly alter random, postprandial and stimulated blood glucose concentrations. Most CF patients receiving rhGH do not develop glucose intolerance or diabetes. In CF patients receiving rhGH, injection site reactions are a rare and insignificant adverse effect. CF patients on rhGH may rarely experience a transient increase in liver transaminases. Study withdrawals were rare in trials evaluating rhGH in CF patients.

Key Question 5

In patients with CF, there appears to be an increase in IGF-I levels in patients treated with rhGH compared to control. There is insufficient evidence to determine the impact of rhGH treatment on IGFBP-3 levels. In patients with GHD or ISS, there is little evidence to evaluate the effects of rhGH treatment on cancer risk.

Key Question 6

Only one trial provided insight into the dose response nature of rhGH in patients with CF. In this trial, no significant differences were seen between the higher and the lower dose groups for any evaluated parameter. We cannot be sure that any qualitative differences are not due to chance. Pulmonary function, as measured by percent predicted FVC and percent predicted FEV_1, tended towards greater improvement in the higher dose group than the lower dose group but no difference was seen with FEV_1 Z-score. Slightly greater increases in height velocity and height velocity Z-score was seen in the higher dose group but similar increases in weight were seen. Higher dose rhGH therapy trends toward causing higher IGF-I Z-scores, which is a potential surrogate outcome for cancer but does not impact IGFBP-3 Z-scores.

Several trials allow the evaluation of the duration of rhGH therapy and outcomes, suggesting that greater benefits are derived from longer-term therapy but that hyperglycemia is also more common. These are qualitative differences however, and we cannot be sure that they are not due to chance. Trials with 1 year of rhGH therapy tend towards greater improvements in percent predicted FVC, absolute FEV_1, height, height velocity, weight, and exercise work rate than trials of 6 months duration. Trials with 1 year of rhGH therapy show slight improvements in LBM than trials of 6-months duration and no impact on percent predicted FEV_1 was seen. Trials with 1 year of rhGH therapy tend towards greater increases in fasting glucose concentrations than trials of 6-months duration.

rhGH has not been studied in patients with CF who have nutritional deficiencies that are not being addressed with enteral nutrition. We cannot determine the benefits of rhGH therapy in patients with unaddressed nutritional deficiencies.

The usage of concurrent medical therapies in patients enrolled in trials evaluating rhGH therapy was sparingly reported, so the differential effect on rhGH efficacy could not be assessed.

Key Question 7

A patient's age may impact rhGH efficacy, as seen in an individual patient data merged-analysis and subgroup analysis. In an individual patient data merged analysis of trials, both prepubertal and adolescent patients had significant improvements in height, weight, LBM, and hospitalizations as compared to their respective control populations. Prepubertal patients receiving rhGH did not have significant increases in FEV_1 and the percent predicted FEV_1 was significantly lower than prepubertal control patients. In contrast, adolescent patients receiving rhGH had significant improvements in FEV_1 and percent predicted FEV_1 as compared to adolescent control patients. In a pooled analysis that should only be viewed qualitatively, prepubertal patients receiving rhGH seem to derive greater benefits on height than pubertal patients receiving rhGH but lesser benefits on weight, BMI, and percent IBW. Pubertal patients receiving rhGH also seem to derive greater increases in absolute FVC, FEV_1, and bone mineral content but experience fewer hospitalizations and smaller increases in percent predicted FVC than prepubertal patients.

While most trials were conducted predominantly in males, the impact of gender on outcomes of rhGH therapy could be qualitatively assessed in one pooled analysis. The authors of the analysis did not report p-values or whether the comparisons were statistically significant and did not provide patient numbers precluding our ability to calculate these p-values. In prepubertal patients not receiving rhGH therapy, no difference in height velocity occurred between the genders in the year before treatment allocation but females had greater weight velocity. In pubertal patients not receiving rhGH therapy, females had greater height and weight velocity than males in the year before treatment allocation. In prepubertal patients, the first 6 months of rhGH therapy provided similar increases in height and weight velocity between genders but in months 6 to 12, females had greater height velocity while males had greater weight velocity. In pubertal patients, the first 6 months of rhGH therapy provided similar increases in height velocity between genders but females had greater increases in weight velocity. In months 6 to 12, females had greater height and weight velocities than males. The occurrence of adverse effects associated with rhGH therapy in males and females was not individually determined.

The impact of baseline clinical status on rhGHs clinical outcomes was assessed in two trials. In the first trial, those with a baseline height Z-score below -2.2 had a similar increase in height

Z-score on rhGH therapy. In the second trial, a higher baseline percent predicted FEV_1 was positively correlated with the change of weight associated with rhGH therapy. The occurrence of adverse events associated with rhGH therapy in patients with different baseline clinical status could not be determined.

Conclusions

rhGH improved almost all intermediate measures of pulmonary function, height, and weight in patients with CF. Improvements in bone mineral content are also promising. However, with the exception of hospitalizations, the benefits on final health outcomes cannot be directly determined at this time. In the relatively low doses used in CF patients for a time period of 6 to 12 months, rhGH therapy may worsen short term markers of glucose control but not long term glucose control. The increase in IGF-I with rhGH therapy is above a threshold thought to increase the risk of malignancy but the strength of this marker in determining malignancy is not firmly established.

Future Research

Individual Patient Data Meta-Analysis

- We believe that an individual patient data meta-analysis of completed trials evaluating rhGH therapy in patients with CF would yield important information if original trial investigators were willing to report on hospitalizations, deaths, or bone fractures. We attempted to contact all of the authors and explicitly ask for any information they had on these final health outcomes but were unsuccessful.
- An individual patient data meta-analysis could allow the determination of the benefits of rhGH therapy in patients with varying levels of nutritional status, pubertal status, age, and concurrent medical therapy; all important unanswered questions.

Clinical Trials

- We believe that a large, multicenter, randomized, placebo-controlled trial should be conducted to determine the impact of rhGH therapy on hospitalizations, mortality, bone fractures, and HRQoL.
    - Such a trial should be powered and conducted to analyze data in pubertal and prepubertal patients separately.
    - It may be worthwhile for the Cystic Fibrosis Foundation and key trialists to appoint a working group and establish a network of sites interested in prospectively evaluating the impact of rhGH in patients with CF so that such as trial could be conducted. The working group could also specify the HRQoL scale to be used in the trial.
- Even if a large multicenter trial is not feasible, we suggest that smaller future trials evaluating the impact of rhGH in patients with CF should be placebo controlled and prospectively collect data on hospitalizations, mortality, bone fractures, and HRQoL and report on their results even if they are not powered to be quantitatively analyzed.
    - There is value in conducting smaller scale trials with primary objectives to discern the impact of rhGH on pulmonary parameters, exercise tolerance, and HRQoL. While there was no significant improvement in percent predicted FEV_1 or

exercise tolerance in our CER, there were qualitative improvements, and future studies would allow us to determine if these were real but underpowered effects.
  - For exercise tolerance and HRQoL, the Cystic Fibrosis Foundation and trialists should specify which exercise tolerance tests and HRQoL questionnaires should be used across future studies to facilitate pooling.
  - Like with the evaluation of benefits, future trials should prespecify the harms they will assess and report on their results even if they are underpowered to perform quantitative synthesis.
  - Trials with treatment durations of 6 or 12 months or longer would be helpful in subsequently determining the adequate duration of therapy.

Observational Studies

- Future observational trials should evaluate the relationship between:
  - The absolute change in FEV_1 and final health outcomes in patients with CF.
  - Bone mineralization and final health outcomes in patients with CF.
  - IGF-I concentrations on the occurrence of cancer in patients with CF.

Table 1. Summary of results

Outcome	Type of Study	Number of Studies	Pooled	Conclusion	Strength of Evidence
KQ1. In patients with CF, does treatment with rhGH as an adjuvant to usual care improve intermediate outcomes, including: pulmonary function (percent predicted FEV_1 and change in FEV_1); growth (height, weight, LBM, protein turnover); exercise tolerance; and bone mineralization, compared with usual care alone?					
Pulmonary Function					
Absolute FVC	Controlled	3	Yes	rhGH better than control	Moderate
	Single-arm	1	No	Nonsignificant increase from baseline	Very Low
Percent predicted FVC	Controlled	5	Yes	rhGH better than control	Low
	Single-arm	2	No	Mixed results from baseline	Very Low
Absolute FEV_1	Controlled	4	Yes	rhGH better than control	Moderate
	Single-arm	1	No	Nonsignificant increase from baseline	Very Low
Percent predicted FEV_1	Controlled	4	Yes	No effect	Moderate
	Single-arm	2	No	No effect	Very Low
FEV_1 Z-score	Controlled	1	Yes	No effect	Very Low
	Single-arm	No data are available			Insufficient
Anthropometrics					
Height	Controlled	3	Yes	rhGH better than control	Low
	Single-arm	1	No	Improvement from baseline	Very Low
Height velocity	Controlled	3	Yes	rhGH better than control	Moderate
	Single-arm	4	No	Improvement from baseline	Very Low
Height Z-score	Controlled	3	Yes	rhGH better than control	Moderate
	Single-arm	3	No	Improvement from baseline	Low
Height percentile	Controlled	1	No	rhGH better than control	Very Low
	Single-arm	No data are available			NA
Weight	Controlled	5	Yes	rhGH better than control	Moderate
	Single-arm	1	No	Improvement from baseline	Very Low
Weight velocity	Controlled	2	Yes	rhGH better than control	Moderate
	Single-arm	3	No	Nonsignificant increase from baseline	Low
Weight Z-score	Controlled	4	Yes	No effect	Low
	Single-arm	1	No	Improvement from baseline	Very Low
Weight percentile	Controlled	1	No	rhGH better than control	Very Low
	Single-arm	No data are available			Insufficient
Body mass index	Controlled	2	Yes	rhGH better than control	Moderate
	Single-arm	1	No	No effect	Very Low
BMI Z-score	Controlled	1	Yes	No effect	Very Low
	Single-arm	No data are available			Insufficient
Percent IBW	Controlled	2	Yes	rhGH better than control	Low
	Single-arm	No data are available			Insufficient
Lean body mass	Controlled	8	Yes	rhGH better than control	Moderate
	Single-arm	No data are available			Insufficient

Table 1. Summary of results

Outcome	Type of Study	Number of Studies	Pooled	Conclusion	Strength of Evidence
Protein Markers					
Various	Controlled	2	No	Mixed results	Very Low
	Single-arm	1	No	Nonsignificant improvements from baseline	Very Low
Exercise Tolerance					
Various	Controlled	3	No	No effect	Very Low
	Single-arm	1	No	No effect	Very Low
Bone Mineralization					
Bone age	Controlled	2	No	No effect	Very Low
	Single-arm	3	No	No effect	Low
BMC	Controlled	4	Yes	rhGH better than control	Low
	Single-arm	No data are available			Insufficient
BMC Z-score	Controlled	1	No	rhGH better than control	Very Low
	Single-arm	No data are available			Insufficient
Sexual Maturation					
	Controlled	7	No	rhGH better than control	Low
	Single-arm	No data are available			Insufficient
KQ2. In patients with CF, does treatment with rhGH as an adjuvant to usual care improve health outcomes, including: frequency of required intravenous antibiotic treatments; frequency of hospitalization; quality of life; bone fracture or development of osteoporosis/osteopenia; or mortality, compared with usual care alone?					
Antibiotic Usage	Controlled	3	No	rhGH better than control	Very Low
	Single-arm	No data are available			Insufficient
Pulmonary Exacerbations	Controlled	1	No	No effect	Very Low
	Single-arm	No data are available			Insufficient
Hospitalization Rate	Controlled	4	Yes	rhGH better than control	Moderate
	Single-arm	No data are available			Insufficient
HRQoL	Controlled	2	No	rhGH better than control	Very Low
	Single-arm	No data are available			Insufficient
Bone Consequences	No data are available.				Insufficient
Mortality	No data are available.				Insufficient
KQ3. In patients with CF, what is the strength of evidence that intermediate outcomes of pulmonary function, growth, and bone mineralization are associated with improvements in health outcomes of quality of life, bone fracture or development of osteoporosis/osteopenia, or mortality?					
Mortality					
Pulmonary function	Observational	28	No	Mixed results	NA
Anthropometrics	Observational	26	No	Mixed results	NA
Protein turnover	Observational	No data are available			NA
Exercise tolerance	Observational	10	No	Mixed results	NA
Bone mineralization	Observational	No data are available			NA
HRQoL					
Pulmonary function	Observational	14	No	Improved pulmonary function relates to improved HRQoL	NA
Anthropometrics	Observational	10	No	Mixed results	NA
Protein turnover	Observational	No data are available			NA

Table 1. Summary of results

Outcome	Type of Study	Number of Studies	Pooled	Conclusion	Strength of Evidence
Exercise tolerance	Observational	2	No	Improved exercise tolerance relates to improved HRQoL	NA
Bone mineralization	Observational	No data are available			NA
Bone Consequences					
Pulmonary function	Observational	1	No	No association found	NA
Anthropometrics	Observational	1	No	No association found	NA
Protein turnover	Observational	No data are available			NA
Exercise tolerance	Observational	No data are available			NA
Bone mineralization	Observational	No data are available			NA
KQ4. In patients with CF, what is the frequency of nonmalignant serious adverse effects resulting from treatment with rhGH in patients with CF? Adverse effects of interest include, but are not limited to: glucose intolerance, diabetes, and hypoglycemia.					
Glucose Parameters					
A1c	Controlled	2	Yes	No effect	Low
	Single-arm	2	No	Nonsignificant increases from baseline	Low
Random BG	Controlled	3	Yes	Glucose levels remained stable	Very Low
	Single-arm	No data are available			Insufficient
Fasting BG	Controlled	2	Yes	Increased with rhGH compared to control	Moderate
	Single-arm	1	No	Nonsignificant increases from baseline	Very Low
Stimulated BG	Controlled	1	Yes	No effect	Very Low
	Single-arm	No data are available			Insufficient
Postprandial BG	Controlled	1	Yes	No effect	Very Low
	Single-arm	No data are available			Insufficient
Glucose Intolerance					
	Controlled	7	No	No patients developed	Low
	Single-arm	3	No	Few patients developed	Very Low
Diabetes					
	Controlled	7	No	No patients developed	Low
	Single-arm	1	No	One case report of diabetes	Very Low
Injection Site Reactions					
	Controlled	No data are available			NA
	Single-arm	2	No	Minor discomfort and bruising reported	NA
Liver Transaminases					
	Controlled	No data are available			NA
	Single-arm	2	No	Limited report of liver transaminase elevations	NA
Study Withdrawals					
	Controlled	10	No	Majority of trials reported no withdrawals	NA
	Single-arm	No data are available			NA

Table 1. Summary of results

Outcome	Type of Study	Number of Studies	Pooled	Conclusion	Strength of Evidence
KQ5. What is the risk of malignancy associated with rhGH use as determined by: (a) markers of cancer risk with rhGH (IGF-I increases over 100 ng/ml or IGFBP-3 decreases over 1000 ng/ml) from studies of rhGH in people with CF and by (b) assessment of evidence on cancer incidence from non-CF patients receiving modest doses of rhGH (0.2mg/kg/week to 0.6mg/kg/week) for disorders such as growth hormone deficiency and idiopathic short stature?					
Biomarkers					
IGF-I	Controlled	4	No	rhGH increases more than control	Very Low
	Single-arm	2	No	Increased from baseline	Very Low
IGFBP-3	Controlled	1	No	RhGH increases more than control	Very Low
	Single-arm	1	No	Increased from baseline	Very Low
Cancer Incidence in CF Patients					
	Controlled	No data are available			Insufficient
	Single-arm	1	No	Case report shows probable relationship between rhGH and cancer	Very Low
Cancer in non-CF Patients					
	Controlled	No data are available			Insufficient
	Single-arm	3	No	Insufficient data to conclude on rhGH effect on cancer	Low
KQ6. In patients with CF, how is efficacy, effectiveness, safety or adverse events impacted by rhGH dose, therapy duration, baseline nutritional status, and concurrent medical therapies?					
Dose	Controlled	1	No	No significant differences between dose groups in endpoints	NA
Duration	Controlled	9	Yes	One year therapy trends towards improved efficacy versus 6 months therapy. One year therapy trends towards increased glucose parameters versus 6 months therapy.	NA
Baseline nutritional status	Controlled	1	No	There is limited evidence in patients with variable nutritional status. Efficacy exists in patients receiving enteral nutrition.	NA
Concurrent medical therapies	Controlled	No data are available			NA

Table 1. Summary of results

Outcome	Type of Study	Number of Studies	Pooled	Conclusion	Strength of Evidence
KQ7. In patients with CF, how do the efficacy, effectiveness, safety or adverse events of treatment with rhGH differ between subgroups of patients? Subgroup characteristics of interest include, but are not limited to: age (pre-pubertal, pubertal, post-pubertal); gender; baseline clinical status (height, weight, LBM, pulmonary function, exercise tolerance, nutritional status); and/or the nature, extent, and effectiveness of prior treatment.					
Age	Controlled	6	Yes	Pubertal patients may derive greater benefit in pulmonary function, weight, and bone mineral content than prepubertal patients. Prepubertal patients may derive greater benefit in height than pubertal patients.	NA
Gender	Controlled	3	Yes[a]	Females (both prepubertal and pubertal) may experience greater benefit in height and weight than males.	NA
Baseline clinical status	Controlled	2	No	Patients with lower baseline height Z-score experienced greater height improvement than those with higher height Z-score. Higher baseline weight was correlated with greater improvement in pulmonary function.	NA
Prior treatment	No data are available				NA

Legend: A1c=glycosylated hemoglobin; BG=blood glucose; BMC=bone mineral content; BMI=body mass index; CF=cystic fibrosis; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; HRQoL=health-related quality-of-life; %IBW=percent ideal body weight; IGF-I=insulin-like growth factor-1; IGFBP-3=insulin-like growth factor binding protein-3; NA=not assessed

[a]Data pooled from three trials by Vanderwel and Hardin.

Evidence Report

Chapter 1. Introduction

Definition and Prevalence of Cystic Fibrosis

Cystic fibrosis (CF) is the second most common life-shortening, childhood-onset genetic disease in the United States, affecting approximately 30,000 people in the U.S.[1, 2] It is most common among Caucasians, occurring in approximately 1 per 2,500 Caucasian births, compared with 1 per 15,100 African-American births and between 1 per 31,000 to 1 per more than 100,000 Asian-American births.[3] CF is carried as an autosomal recessive trait in approximately 10 million Americans, and in approximately 3 percent of the Caucasian population. The gene responsible for CF encodes the cystic fibrosis transmembrane regulator (CFTR) protein, which regulates sodium and chloride transport across epithelial membranes. Defects in the CFTR protein result in a multisystem disorder affecting nearly all exocrine glands, with abnormally viscous mucus and excessive secretions. The dominant clinical features are chronic lung disease and pancreatic insufficiency with poor nutrition and poor growth.[4, 5]

Treatment has improved considerably over the past 25 years, resulting in improvements in measures of nutrition, pulmonary function, and mortality among children and adolescents with CF. The median age of survival has improved consistently from 1955 (5 year survival) to 1969 (14 year survival), 1985 (25 year survival), and to the most recent data in 2006 (37 year survival).[2] The estimated annual direct medical costs per CF patient are more than $40,000, with an estimated $9,000 in secondary costs per year per patient.[6]

Complications Associated with Cystic Fibrosis

Although the morbidity and mortality associated with CF is most directly due to progressive lung disease, growth and nutritional indices (weight-for-age, height-for-age, and percent ideal body weight) have been shown to be predictive of future pulmonary function in children with CF.[7] It has been suggested that improvement of linear growth in children with CF may allow more lung mass and better pulmonary function, independent of improved weight gain.[8, 9] Poor weight and shorter height have also been shown to be independently associated with increased morbidity and mortality in CF patients.[7-10]

Pulmonary function is most commonly assessed by forced expiratory volume in one minute (FEV_1), which is the volume of air forcefully exhaled in one minute, and forced vital capacity (FVC), which is the total volume of air that can be exhaled forcefully after a deep inhalation.[11] Both of these values can be reported as absolute values or as the percent of the predicted value based upon a patient's height.[11] Absolute changes in FEV_1 or FVC can be sensitive to changes in pulmonary function, but they do not account for changes in pulmonary function with regard to changes in height. Percent predicted values are useful in comparisons between patients of different height or age because it normalizes these variables. However, issues arise in its clinical interpretation because of its basis on height; a CF patient with poor pulmonary function combined with short stature may exhibit a normal percent predicted FEV_1.[5] While both have some limitations, both are useful to assess in CF patients.

Patients with CF also exhibit poor measures of growth compared to normal healthy children and these measures can be reported in a variety of ways.[12] Anthropometrics such as height and weight are reported as either absolute values or as comparisons to healthy children. Growth charts summarize the height and weight of a large number of healthy children by plotting either

height or weight on the y-axis compared to age on the x-axis.[12] Assuming normal distribution, 95 percent of children will fall within two standard deviations of the mean height and weight for the age. Height and weight Z-scores (also called standard deviation scores or SDS) provide a relationship with the mean based on age and gender. The median Z-score for height and weight in patients with CF is –0.81 and –0.74, respectively, for both males and females,[13] representing height and weight lower than the population norms. Percentile height or weight is another method to describe how a child compares to the norm.[12] Approximately one-third of children with CF in the US are below the 10th percentile for height and for weight.[13] Percentage weight-for-height may also be used to assess improvements in weight, while normalizing the patient's height.[12] All of these measures show that patients with CF are at a disadvantage in terms of height and weight, and treatments are aimed at getting these measures closer to that of healthy children.

Recombinant Human Growth Hormone

Recombinant human growth hormone (rhGH) is an anabolic agent with a wide variety of actions. It is approved by the United States Food and Drug Administration (FDA) for the treatment of growth hormone deficiency, idiopathic short stature, Turner syndrome, Prader-Willi Syndrome, chronic renal insufficiency and for children who are small for gestational age.[14] It has been investigated for the treatment of CF because of the decreased growth measures and increased energy expenditures in CF patients.[9] In CF, there are multiple targets at which rhGH may provide benefit. First, it may improve linear growth, as seen in children with growth failure, including those with CF.[5] rhGH may also decrease protein turnover, improve protein synthesis, and enhance bone mineralization.[9, 15] Because of the complications that may result from poor growth in patients with CF, rhGH is a worthwhile therapy to evaluate. The 2008 average wholesale price per milligram of rhGH (somatropin, various manufacturers) ranged from $36 to $65, so it would cost $16,848 to $30,420 annually to treat a 30 kg adolescent receiving a dose of 0.3mg/kg/week.[15, 16]

Scope and Key Questions

This is an evidence report prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center (UCONN/HH EPC) examining the benefits and harms associated with using rhGH in patients with CF.

KQ 1: In patients with CF, does treatment with rhGH as an adjuvant to usual care improve intermediate outcomes, including: pulmonary function (percent predicted FEV1 and change in FEV1); growth (height, weight, lean body mass, protein turnover); exercise tolerance; and bone mineralization, compared with usual care alone?

KQ 2: In patients with CF, does treatment with rhGH as an adjuvant to usual care improve health outcomes, including: frequency of required intravenous antibiotic treatments; frequency of hospitalization; quality of life; bone fracture or development of osteoporosis/osteopenia; or mortality, compared with usual care alone?

KQ 3: In patients with CF, what is the strength of evidence that intermediate outcomes of pulmonary function, growth, and bone mineralization are associated with improvements in health outcomes of quality of life, bone fracture or development of osteoporosis/osteopenia, or mortality?

KQ 4: In patients with CF, what is the frequency of nonmalignant serious adverse effects resulting from treatment with rhGH in patients with CF? Adverse effects of interest include, but are not limited to: glucose intolerance, diabetes, and hypoglycemia.

KQ 5: What is the risk of malignancy associated with rhGH use as determined by: (a) markers of cancer risk with rhGH (IGF-I increases over 100 ng/ml or IGFBP-3 decreases over 1000 ng/ml) from studies of rhGH in people with CF and by (b) assessment of evidence on cancer incidence from non-CF patients receiving modest doses of rhGH (0.2mg/kg/week to 0.6mg/kg/week) for disorders such as growth hormone deficiency (GHD) and idiopathic short stature (ISS)?

KQ 6: In patients with CF, how is efficacy, effectiveness, safety or adverse events impacted by rhGH dose, therapy duration, baseline nutritional status, and concurrent medical therapies?

KQ 7: In patients with CF, how do the efficacy, effectiveness, safety or adverse events of treatment with rhGH differ between subgroups of patients? Subgroup characteristics of interest include, but are not limited to: age (pre-pubertal, pubertal, post-pubertal); gender; baseline clinical status (height, weight, lean body mass, pulmonary function, exercise tolerance, nutritional status); and/or the nature, extent, and effectiveness of prior treatment.

Chapter 2. Methods

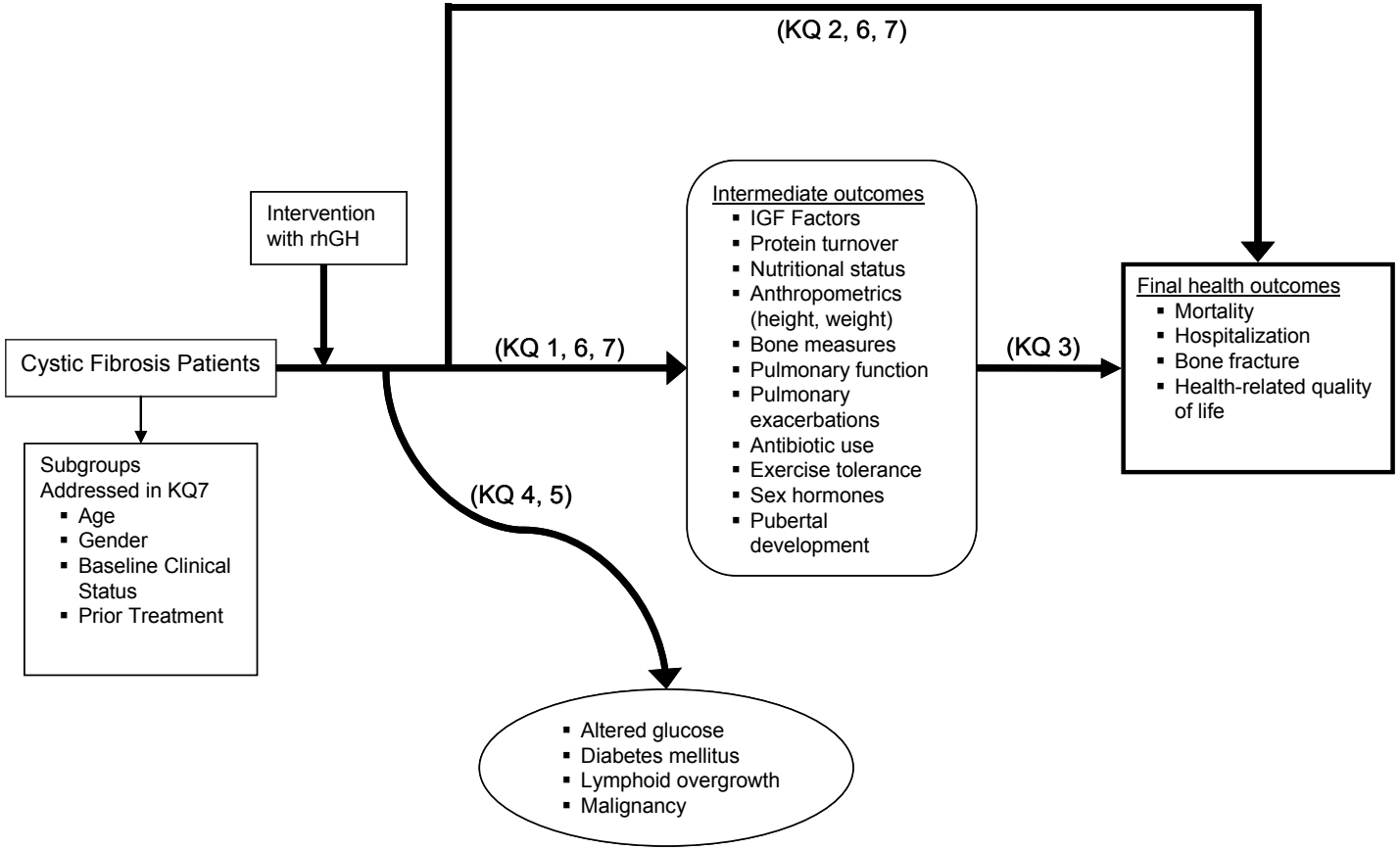
Topic Development

The topic for this report was nominated in a public process. With input from technical experts, the Scientific Resource Center (SRC) for the AHRQ Effective Health Care Program drafted the initial key questions and, after approval from AHRQ, posted them to a public Web site. The UCONN/HH EPC drafted a topic refinement document with proposed key questions after consult with key experts in the field. The public was invited to comment on the topic refinement document and key questions. After reviewing the public commentary, the final key questions were approved by AHRQ.

Analytic Framework

To guide our assessment of studies examining the association rhGH on benefits and harms in our target population, we developed an analytic framework mapping specific linkages from comparisons to subpopulations of interest, mechanisms of benefit, and outcomes of interest (Figure 1). It is a logic chain that supports the link from the intervention to the outcomes of interest.

Figure 1. Analytic Framework



Legend: KQ=key question; rhGH=recombinant human growth hormone

Narrative: Figure 1 shows the analytic framework of this report. In patients with cystic fibrosis and relevant subgroups based upon gender, age, baseline clinical status, and prior therapy, we seek to answer the effect that intervention with rhGH may have. The first step in the analytic framework deals with intermediate outcomes from rhGH treatment, which includes IGF factors, protein turnover markers, nutritional status, anthropometrics, bone measures, pulmonary function, pulmonary exacerbations, exercise tolerance, antibiotic use, sex hormones and pubertal development. Final health outcomes can either be answered from the direct evidence that exists in cystic fibrosis patients treated with rhGH or by assessing the link between intermediate and final health outcomes (which include health-related quality-of-life, hospitalization, bone fracture, or mortality). Adverse events associated with rhGH use are also evaluated, including altered glucose metabolism, development of diabetes mellitus, lymphoid overgrowth, or malignancy.

Literature Search Strategy

Two independent investigators conducted systematic literature searches of MEDLINE (starting from 1950), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews from the earliest possible date through July 2009. Three separate searches were conducted. The first search was used to identify trials and studies which explicitly evaluated the impact of rhGH on outcomes in patients with CF. The two other searches were used to answer key questions 3 (where the impact of surrogate markers on terminal endpoints in patients with CF are evaluated) and 5 (where the malignant effects of rhGH are assessed in a CF population and those with idiopathic short stature or growth hormone deficiency). With the searches for key questions 3 and 5, we utilized Cochrane's Highly Sensitive Search Strategy (Sensitivity Maximizing Version 2008)[17] to limit to randomized controlled trials and the Scottish Intercollegiate Guidelines Network Observational Study Search Filter to limit to observational studies. No language restrictions were imposed. In addition, a manual search of references from reports of clinical trials or review articles was conducted. The complete search strategy is included in Appendix A.

Study Selection

Studies were included in the evaluation of key questions 1, 2, 4, 6, and 7 if they were 1) studies of rhGH therapy, 2) conducted in patients with CF, 3) studies that reported data on pre-specified clinical or humanistic outcomes (Figure 1), and 4) reports of new discovery (specifically, randomized controlled trials, observational trials, systematic review/meta-analyses, or case reports). Studies were included in the key question 3 evaluation if they were 1) conducted in patients with CF, 2) either randomized controlled trials or observational studies, and 3) report linkages between intermediate outcomes and health outcomes. Studies which reported on linkages between intermediate outcomes and health outcomes subsequent to a medical or behavioral intervention were excluded from this evaluation. Studies were included in the key question 5 evaluation if they were 1) studies of rhGH therapy, 2) conducted in patients with CF, idiopathic short stature, or growth hormone deficiency, 3) either randomized controlled trials or observational studies, and 4) studies that reported data on malignant outcomes.

Validity Assessment

Validity assessment was performed using the recommendations in the EPC Methods Guide. Each study was assessed for the following individual criteria: comparable study groups at baseline, detailed description of study outcomes, blinding of subjects, blinding of outcome assessors, intent-to-treat analysis, description of participant withdrawals, and potential conflict of interest. Additionally, randomized controlled trials were assessed for randomization technique and allocation concealment. Observational studies were assessed for sample size, participant selection method, exposure measurement method, potential design biases, and appropriate analyses to control for confounding. Studies were then given an overall score of good, fair, or poor. (Table 2) This rating system does not attempt to assess the comparative validity across different types of study design. For example, a "fair" controlled trial is not judged to have the same methodologic criteria as a "fair" single-arm observational study. Both study design and quality rating should be considered when interpreting the methodological quality of a study.

Table 2. Summary ratings of quality of individual studies

Quality Rating	Definition
Good (low risk of bias)	These studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality include the following: a formal randomized, controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20 percent dropout; and clear reporting of dropouts.
Fair	These studies are susceptible to some bias, but it is not sufficient to invalidate results. They do not meet all the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
Poor (high risk of bias)	These studies have significant flaws that imply biases of various types that may invalidate the results. They have serious errors in design, analysis, or reporting; large amounts of missing information, or discrepancies in reporting.

Data Abstraction

Through the use of a standardized data abstraction tool (Appendix B), two reviewers independently collected data, with disagreement resolved through discussion. The following information was obtained from each trial, where applicable: author identification, year of publication, source of study funding, study design characteristics and methodological quality criteria, study population [including study inclusion and exclusion criteria, run-in period, study withdrawals, dose of rhGH utilized, length of study, duration of patient followup, and disease state (CF, idiopathic short stature, or growth hormone deficiency)], patient baseline characteristics (sex, age, ethnicity, nutritional status), comorbidities, and use of concurrent standard medical therapies (corticosteroids, antibiotics, etc). Endpoints included: pulmonary function, anthropometrics (height, weight, lean body mass, protein turnover), exercise tolerance, intravenous antibiotic use, hospitalizations, HRQoL, bone mineralization, bone fracture or development of osteoporosis/osteopenia, mortality, glucose measures, and development of diabetes or malignancy.

All authors were contacted for unpublished data. A standardized letter was sent to explain the purpose of our project and include a template with all available outcomes of interest. The template was provided to the author with their published trial or study-specific data filled in and the author was invited to provide any additional data.

Literature Synthesis

The key questions follow the analytic framework along the continuum of intermediate to important health outcomes. Our review continues with this organizational scheme and answers each key question independently.

Regarding the intermediate outcomes within KQ1, there are distinct clusters of outcomes which may be reported in a variety of ways. For pulmonary function, trials and studies report a wide range of outcomes, such as absolute values of FEV_1 and FVC along with the percent-predicted FEV_1 and FVC. The most commonly reported of these were selected for meta-analysis, while the remaining outcomes were reported qualitatively.

Anthropometrics are also reported in many ways, including absolute values of height, height percentile, height Z-scores, height velocity, absolute values of weight, weight percentile, weight Z-scores, weight velocity, and weight for height Z-scores. Because of the variation in reporting, not all of these outcomes were meta-analyzed. While each has merit in clinical interpretation, data handling is difficult. When given multiple height and weight outcomes, the most commonly reported outcomes were selected for meta-analysis and the rest were qualitatively described. Absolute changes in height and weight over a broad age range may be difficult to interpret, as younger children may exhibit more rapid growth than adolescents. Therefore, to place clinical perspective on data that is reported as absolute change in height and weight, we modeled conversions of this data to Z-score data using the WHO AnthroPlus software[18] and growth charts published by the CDC.[19]

Important health outcomes in KQ2 and adverse events in KQ4 associated with rhGH were meta-analyzed when data was adequate. The remaining KQs (3, 5-7) were answered qualitatively.

Quantitative Analysis

Randomized controlled trials and prospective cohort studies were pooled together when trials evaluated both an rhGH and a control group, henceforth described as controlled trials. Single-arm observational studies were described qualitatively in all cases.

In this systematic review, some of the data allowed for meta-analyses to pool the data. When pooling continuous endpoints, weighted mean differences (WMD) along with 95 percent confidence intervals were calculated using a DerSimonian and Laird random effects model.[20] In cases where mean change scores from baseline for each group were not reported, we calculated the difference between the mean baseline and mean followup scores for each group. Standard deviations (SDs) of the change scores were calculated from the SD of the baseline values and of the followup values, using the formula: $SD_{baseline\text{-}followup}=sqrt(SD^2_{baseline} + SD^2_{followup} - 2*(correlation\ coefficient)SD_{baseline}*SD_{followup})$. A correlation coefficient of 0.5 proposed by Follman and colleagues was used.[21] In the event where there was more than one treatment group versus control, each treatment group was treated as a separate trial for meta-analysis, dividing the control group equally among treatment arms.[17] For dichotomous endpoints, weighted averages were reported as relative risks (RRs) with associated 95 percent confidence intervals (CIs). As heterogeneity between included studies was expected, a DerSimonian and Laird random-effects model was used when pooling data and calculating RRs and 95 percent CIs.

Statistical heterogeneity was addressed using the I^2 statistic (which assesses the degree of inconsistency not due to chance across studies and ranges from 0-100 percent with the higher percentage representing a higher likelihood of the existence of heterogeneity) evaluations. While categorization of values for I^2 may not be appropriate in all situations, I^2 values of 25 percent, 50 percent and 75 percent have been regarded as representative of low, medium and high statistical heterogeneity, respectively. Visual inspection of funnel plots and Egger's weighted regression statistics were used to assess for the presence of publication bias.

Statistics were performed using StatsDirect statistical software, version 2.4.6 (StatsDirect Ltd, Cheshire, England).A p-value of <0.05 was considered statistically significant for all analyses.

Subgroup and Sensitivity Analyses

To assess the effect of heterogeneity on our meta-analysis' conclusions, subgroup and sensitivity analyses were conducted. Subgroup analyses were conducted to assess the effect of treatment duration and patient pubertal status on the efficacy of rhGH. Trials with duration of 6 months were meta-analyzed separately from trials with duration of one year. Trials which enrolled prepubertal patients were meta-analyzed and compared to the one trial which enrolled pubertal patients alone. Trials which enrolled patients with a range of pubertal status were excluded in subgroup analysis.

Grading the Strength of Evidence

We used the EPC methodology for grading, which is based on the criteria and methods of GRADE (Grading of Recommendations Assessment, DEvelopment) to assess the strength of evidence. This system uses four required domains – risk of bias, consistency, directness, and precision.[22] Additional domains were not utilized because they were deemed not relevant to this review. All assessments were made by two investigators (with disagreements resolved through discussion). The evidence pertaining to each key question was classified into four broad categories: (1) "high", (2) "moderate", (3) "low", or (4) very low grade (Table 3). Below we describe in more detail the features that determined the strength of evidence for the different outcomes evaluated in this report.

Table 3. Definitions for grading the strength of evidence

Grade	Definition
High	There is high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Very Low	Very low confidence that the evidence reflects the true effect. Any estimate of effect is very uncertain.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect

Risk of bias

Risk of bias is the degree to which the included studies for any given outcome or comparison have a high likelihood of adequate protection against bias. This can be assessed through the evaluation of both design and study limitations. For study design, whether the study was a randomized controlled trial or an observational study was recorded. Studies were also ranked as no limitations, serious limitations, or very serious limitations. Because all of the included studies were randomized controlled trials with few limitations, they were considered to have a low risk of bias.

Consistency

Consistency refers to the degree of similarity in the direction of the effect sizes from included studies within an evidence base. This was assessed in two main ways: 1) the effect sizes had the same sign, in that they were on the same side of unity; 2) the range of effect sizes was narrow. We ranked this domain as no inconsistency, serious inconsistency, and very serious inconsistency. For outcomes whereby only a single study was included, consistency would not

be judged. We also considered measures of heterogeneity from our meta-analyses in evaluating consistency.

Directness

Directness refers to whether the evidence links the compared interventions directly with health outcomes, and compares two or more interventions in head-to-head trials. Indirectness implies that more than one body of evidence is required to link interventions to the most important health outcomes. We ranked this domain as no indirectness, serious indirectness, and very serious indirectness.

Precision

Precision refers to the degree of certainty surrounding an effect estimate with respect to a given outcome. For example, when a meta-analysis was performed, we evaluated the confidence interval around the summary effect size. A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions (e.g. both clinically important superiority and inferiority), a circumstance that will preclude a conclusion.

Peer Review and Public Commentary

Chapter 3. Results

Results of Literature Search

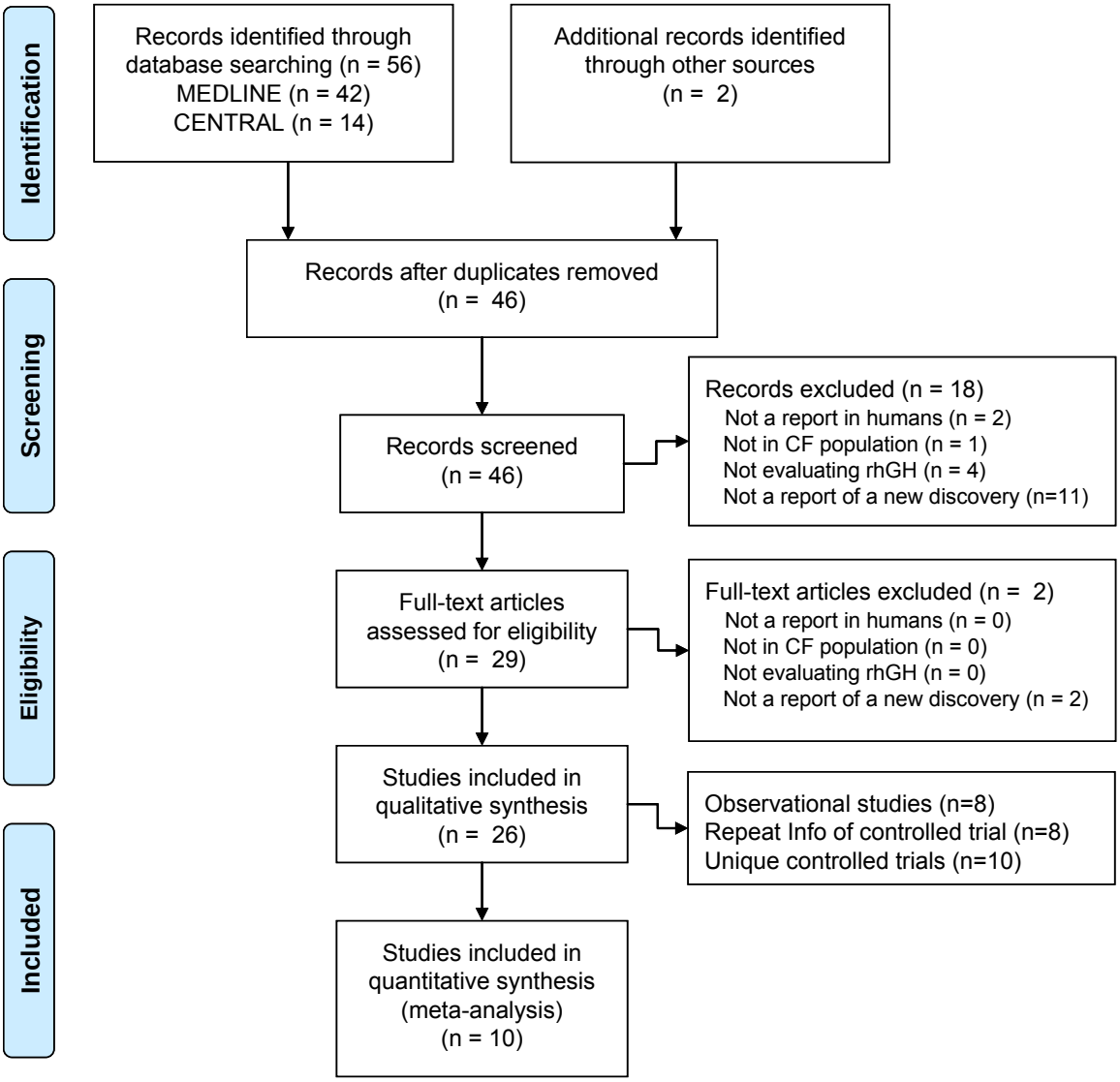
A summary of search results is presented in Figure 2-Figure 4.

Upon conducting the literature search to identify articles that evaluated the use of rhGH in CF populations, we retrieved 44 unique citations and another citation was indentified from other sources. Eighteen articles were excluded during the title and abstract review and two articles were excluded during the full text review. A total of 26 articles were found to match our inclusion criteria.[4, 15, 23-46]

From the literature search for studies which evaluated the linkages between intermediate and important health outcomes, we retrieved 1126 unique citations. An additional 16 references were obtained from other sources. After a review of the titles and abstracts, 113 were deemed eligible for further review, and the full articles were retrieved. A total of 53 articles were found to match our inclusion criteria.[8, 47-98] Three studies[80, 90, 97] reported on the same population as another included publication, and they were included as they provided additional data. Therefore, a total of 50 unique studies were included in our evaluation.

When we conducted the literature search for cancer with rhGH therapy, expanded to include GHD and ISS, 159 unique citations were retrieved and another two citations were identified through other sources. (Figure 4) One hundred-sixteen citations were excluded during the title and abstract review and 44 from the full text review. Three articles were included.[99-101]

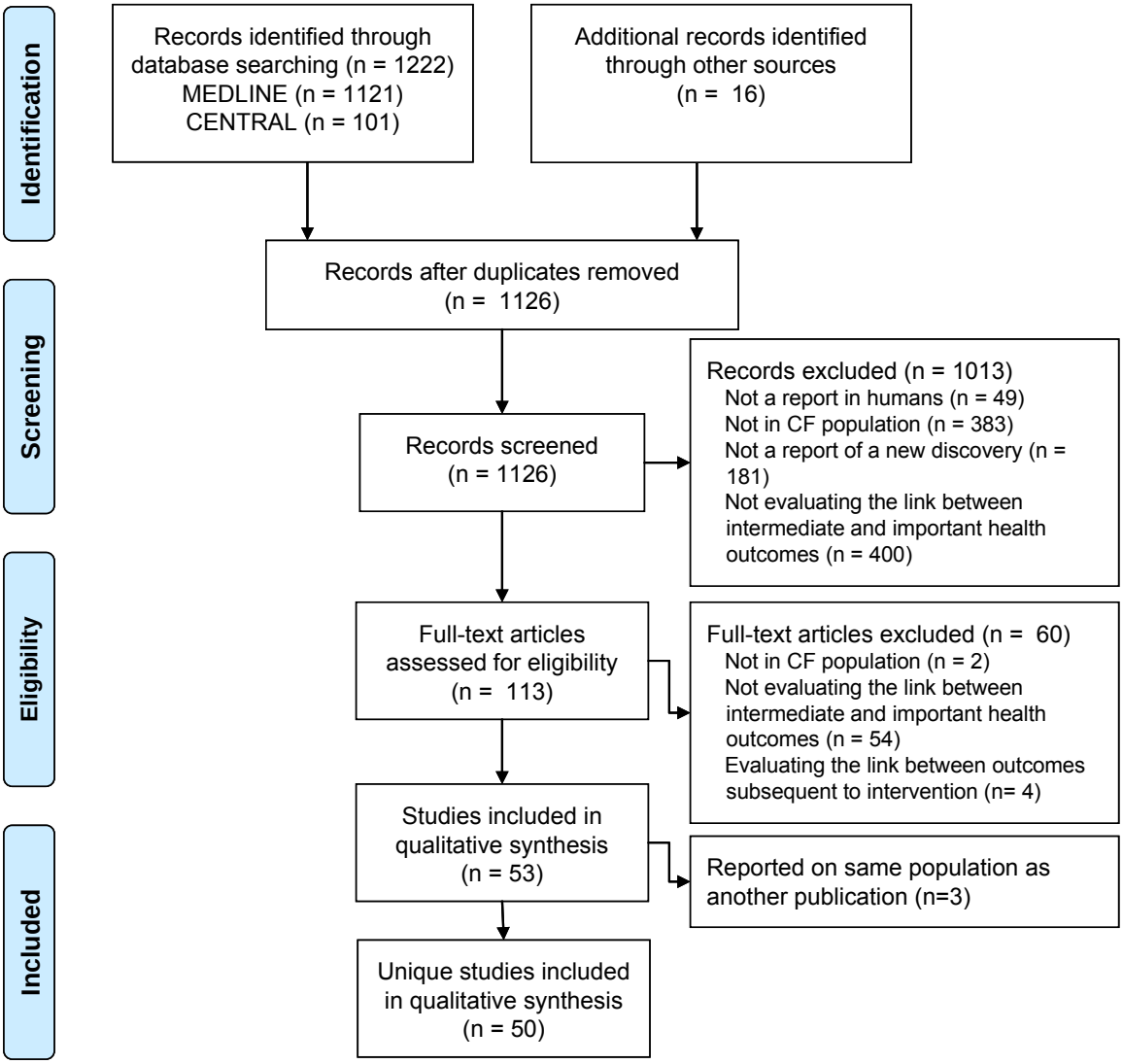
Figure 2. PRISMA flow diagram of search for KQs 1,2,4,6,7



Legend: CF=cystic fibrosis; KQ=key question; PRISMA=preferred reporting items for systematic reviews and meta-analyses; rhGH=recombinant human growth hormone

Narrative: Figure 2 shows the flow of study identification and selection. The initial database search resulted in 42 records from MEDLINE and 14 records from CENTRAL. An additional two records were identified from other sources. After duplicates were removed, there were 46 unique citations eligible for title and abstract screening. The first phase of screening excluded 18 records for the following reasons: 2 records were not reports in humans, 1 record was not in a CF population, 4 records did not evaluate rhGH therapy, and 11 records were not reports of new discovery. This process left 29 records to assess for eligibility by screening the full-text articles. The second phase of screening excluded 2 articles because they were not reports of new discovery. Twenty-six articles were included in qualitative synthesis. Of these, 8 were observational, 8 were repeat information from another trial, and 10 were randomized trials, eligible for quantitative synthesis.

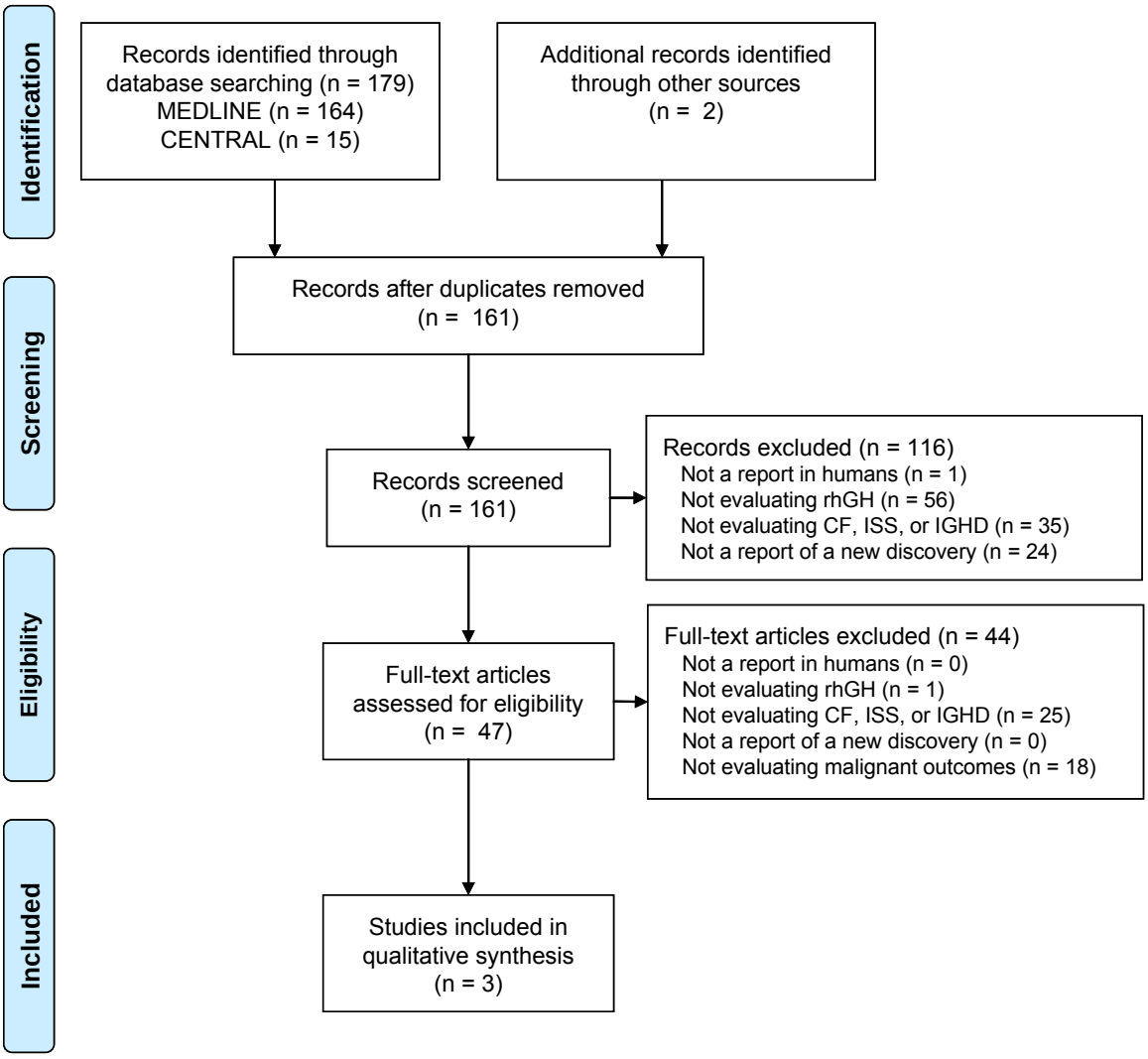
Figure 3. PRISMA flow diagram of search for KQ 3



Legend: CF=cystic fibrosis; KQ=key question; PRISMA=preferred reporting items for systematic reviews and meta-analyses

Narrative: Figure 3 shows the flow of study identification and selection. The original database search resulted in 1121 records from MEDLINE and 101 records from CENTRAL. An additional 16 records were identified from other sources. After duplicates were removed, there were 1126 unique citations eligible for title and abstract screening. The first phase of screening excluded 1013 records for the following reasons: 49 were not reports in humans, 383 were not reports in CF patients, 181 were not reports of new discovery, and 400 did not evaluate the link between intermediate and important health outcomes. This process left 113 records to assess for eligibility by screening the full-text articles. The second phase of screening excluded 60 articles for the following reasons: 2 were not in a CF population, 54 did not evaluate the link between intermediate and important health outcomes, and 4 evaluated this linkage subsequent to an intervention. Fifty-three articles were included in qualitative synthesis. Of these, 3 reported on the same population as another publication, leaving 50 unique articles included in qualitative synthesis.

Figure 4. PRISMA flow diagram of search for KQ 5



Legend: CF=cystic fibrosis; GHD=growth hormone deficiency; ISS=idiopathic short stature; KQ=key question; PRISMA=preferred reporting items for systematic reviews and meta-analyses; rhGH=recombinant human growth hormone

Narrative: Figure 4 shows the flow of study identification and selection. The initial database search resulted in 164 records from MEDLINE and 15 records from CENTRAL. An additional two records were identified from other sources. After duplicates were removed, there were 161 unique citations eligible for title and abstract screening. The first phase of screening excluded 116 records for the following reasons: 1 was not a report in humans, 56 did not evaluate the use of rhGH, 35 were not in patients with CF, GHD, or ISS, and 24 were not reports of new discovery. This process left 47 records to assess for eligibility by screening the full-text articles. The second phase of screening excluded 44 articles for the following reasons: 1 was not in a CF population, 25 were not in patients with CF, GHD, or ISS, and 18 did not report on malignant outcomes. Three studies were included in qualitative synthesis.

Key Question 1

In patients with CF, does treatment with rhGH as an adjuvant to usual care improve intermediate outcomes, including: pulmonary function (percent predicted FEV_1 and change in FEV_1); growth (height, weight, lean body mass, protein turnover); exercise tolerance; and bone mineralization, compared with usual care alone?

Key Points

- Ten controlled trials and eight single-arm observational studies were included.
- Five markers of pulmonary function were evaluated in patients with CF receiving rhGH therapy.
    - In controlled trials, the FVC and percent predicted FVC significantly increased from baseline in trials comparing patients with CF receiving chronic rhGH therapy to control therapy. Single-arm observational studies support these findings.
    - In controlled trials, the FEV_1 significantly increased from baseline in patients with CF receiving chronic rhGH therapy versus control therapy and the percent predicted FEV_1 showed a nonsignificant improvement versus control. Single-arm observational studies support the FEV_1 findings but the percent predicted FEV_1 findings are mixed.
    - In the one available controlled trial, no change in FEV1 Z-score occurred in patients receiving rhGH for CF versus placebo therapy and no observational studies evaluated this parameter.
- In controlled trials suitable for pooling, significant improvements in height were observed for patients with CF receiving rhGH therapy versus control therapy as measured by the change in height, height velocity, height Z-score, and height percentile. Observational studies or other trials not suitable for pooling support these findings.
- In controlled trials, significant improvements in weight were observed for patients with CF receiving rhGH therapy versus control therapy as measured by change in weight, weight velocity, BMI, percent IBW, LBM, and weight percentile. Patients receiving rhGH therapy had a trend towards a higher weight Z-score but did not have a higher BMI Z-score than those receiving control therapy. Observational studies evaluating change in weight, weight velocity, and weight Z-score were generally supportive of improvements associated with rhGH therapy, although one crossover trial not amenable for pooling did not show any improvement in LBM in patients receiving rhGH and who received glutamine therapy.
- Four markers of protein turnover were evaluated in patients with CF receiving rhGH therapy. In controlled trials, rhGH therapy significantly improved two markers of protein turnover (LeuOx and NOLD) and nonsignificantly improved LeuRa concentrations. In one observational trial, nitrogen balance was qualitatively impacted but protein synthesis was unchanged.
- In controlled trials, rhGH therapy significant improved exercise work rate. Qualitative improvements in several measures of exercise tolerance were seen after rhGH therapy in

patients with CF but in most cases do not reach statistical significance. Given the few trials evaluating this type of endpoint and the various markers being evaluated, the impact is difficult to determine at this time.

- In controlled trials and observational studies, treating patients with rhGH therapy does not improve bone age in patients with CF. However, bone mineral content does significantly improve with rhGH therapy in trials, and bone mineral content Z-score was also improved in the one trial in which it was assessed.
- rhGH therapy in patients with CF does not seem to improve sexual maturation in males and the impact in females cannot be determined at this time. Controlled trials were not amenable to pooling and no observational trial data was available. In five controlled trials, rhGH therapy did not improve sexual maturation regardless of gender. In one controlled trial, mean Tanner stage regardless of gender improved and in an analysis of three controlled trials, rhGH therapy significantly improved sexual maturation in females but not in males.

Detailed Analysis

Study Design and Population Characteristics

Controlled Trials

Eighteen publications of controlled trials, which represent ten unique trials (n=312), met inclusion criteria (Table 4-Table 6) [4, 15, 23-46] Three of the identified publications were abstracts,[28, 36, 38] two of which were trials published as full articles (also identified in the search),[28, 36] and one which has not yet been published as a full article.[38]

Four publications reported results on the same patients as another published trial.[27, 30, 35, 37] One publication[30] was an interim analysis, so only results from the latter publication[29] are used in our CER. Another publication was a substudy looking at a single site[35] within a multi-center trial.[4] Another publication[37] reports new data on sexual maturation by pubertal status and gender on patients who were enrolled in three aforementioned prospective trials.[23, 24, 33, 102]

Of the 10 trials, 8 trials compared rhGH to no treatment,[15, 23-26, 32-34] 1 trial used a placebo control,[4] and 1 trial compared rhGH alone to either glutamine or the combination of glutamine and rhGH.[29] Two trials used a crossover design,[25, 29] while the others used a parallel study design.[4, 15, 23, 24, 26, 32-34] Only one trial was double-blinded.[4] Four trials received funding from foundations or government,[15, 23-25] eight trials received funding from industry,[4, 15, 23, 24, 26, 29, 32, 34] and two trials did not report a funding source.[33, 38] Four of the aforementioned trials received both industry and foundation funding to conduct their studies.[23-25, 29, 32]

One of the ten trials treated patients with rhGH for 4 weeks,[29] while the other trials treated patients for 6 months to 1 year.[4, 15, 23-26, 32-34] Chronological age of patients was up to 23 years, but six trials specifically evaluated prepubertal children[15, 23-25, 29, 32-34] and one study evaluated only pubertal adolescents.[33] Doses of rhGH ranged from 0.23 to 0.49 mg/kg/week, with the typical dose being 0.3 mg/kg/week.[15, 23, 24, 32-34] One trial evaluated two doses of rhGH compared to placebo.[4] Males constituted at least half of the patients in trials, ranging from 50 to 83 percent of the total number of subjects.

Single-Arm Observational Studies

Eight observational reports (n=58), not constituted by patients in clinical trials, evaluated the use of rhGH in patients with CF (Table 7-Table 8). Three were case reports,[39, 45, 46] of which, one was in a patient with growth hormone deficiency and short stature,[39] one was in a patient who had previously undergone lung transplantation,[45] and another was in two patients with CF-related liver dysfunction.[46] None of the studies included a comparator group. One study was funded by a foundation grant,[39] four studies were funded by industry,[40-42, 44] and three did not report sources of funding.[43, 45, 46]

The duration of treatment with rhGH ranged from 6 months to 3 years. Ages of patients in the studies ranged from 6 months to 13 years,[39-44, 46] with the exception of one case report in a patient aged 18 years.[45] Doses of rhGH in the studies ranged from 0.16-0.35 mg/kg/wk,[40, 41, 43, 44, 46] with the exception of one case report where the dose was 2.2 mg/day.[45] Two studies did not report the dose of rhGH.[39, 42] Baseline measures of height and weight were inconsistently reported among observational studies, but all patients had deficient height and weight for age.[39-46]

Outcome Evaluations

Pulmonary Function

Seven trials, summarized in Table 9, reported information on various pulmonary measures in CF patients treated with rhGH, including absolute FVC, percent predicted FVC, absolute FEV_1, percent predicted FEV_1, and FEV_1 Z-score.[4, 15, 23, 25, 26, 33, 34] Three observational studies also provided insight on the effect of rhGH on pulmonary function.[40, 41, 44]

Three trials reported the change from baseline in absolute FVC, which was amenable to quantitative synthesis.[15, 33, 34] Upon statistical pooling, patients treated with rhGH had significantly greater improvements in absolute FVC than those without treatment (WMD 0.67 L, 95 percent CI 0.24 to 1.09 L). (Figure 5) A moderate degree of statistical heterogeneity was detected (I^2=55 percent), though all three studies exhibited the same direction of effect. The individual point estimates for two trials[33, 34] were similar and greater in magnitude than the last trial.[15] Since the primary investigator was the same for all three trials and the populations, doses, and durations of therapy were similar, there is not a ready explanation for this heterogeneity. However, the 95 percent CIs for the three trials overlapped and the trial with the greatest weight in the meta-analysis had the smallest magnitude of FVC improvement. Publication bias could not be evaluated due to an insufficient number of studies. In a single-arm, observational study (n=9), there was a nonsignificant increase in absolute FVC over 12 months of rhGH therapy (baseline 1.33±0.32 L; 12 months 1.46±0.49 L, p-value not reported).[41]

Five trials, including a trial with two active rhGH treatment arms, reported percent predicted FVC consistently, allowing for quantitative synthesis.[4, 23, 26, 33, 34] Upon statistical pooling, patients treated with rhGH experienced greater improvements from baseline in percent predicted FVC than patients in the control group (WMD 9.34 percent, 95 percent CI 3.41 to 15.27 percent). (Figure 6) A moderate degree of statistical heterogeneity was detected (I^2=69.2 percent) but all studies exhibited the same direction of effect. The individual point estimates for two trials[23, 33] were greater in magnitude than the other, with one trial's[23] point estimate falling outside the confidence interval for the pooled effect size. However, the doses used and the duration of followup for these two trials were similar to the others, so an explanation for the

heterogeneity is unclear. Publication bias was not detected in this analysis. Both dosing arms of the trial by Schnabel and colleagues showed a similar direction and magnitude of effect, suggesting a lack of dose-response relationship with rhGH therapy. In a single-arm, observational study (n=9), 12 months of rhGH therapy resulted in nonsignificant decreases in percent predicted FVC (baseline 85.6±17.9 percent; 12 months 80.7±19.7 percent, p-value not reported).[41] In another single-arm observational study of nine patients over 12 months, the percent predicted FVC improved in seven patients and remained stable in 2 patients, but quantifiable data was not reported.[44]

Four trials reported the change from baseline in absolute FEV_1 suitable for quantitative synthesis.[15, 25, 33, 34] Statistical pooling showed patients treated with rhGH experiencing significantly greater improvements in absolute FEV_1 versus control (WMD 0.23 L, 95 percent CI 0.01 to 0.46 L). (Figure 7) A moderate degree of statistical heterogeneity was detected (I^2=43.2 percent) and all trials showed similar direction of effect. Assessment for publication bias was nonsignificant. In one single-arm, observational study (n=9), 12 months of rhGH therapy resulted in nonsignificant increases in absolute FEV_1 (baseline 1.16±0.3 L; 12 months 1.20±0.52 L, p-value not reported).[41]

Four trials reported the change in percent predicted FEV_1 from baseline and were amenable to quantitative synthesis.[4, 23, 26, 34] Upon statistical pooling, there was a nonsignificant greater improvement in the rhGH group compared to control (WMD 2.43 percent, 95 percent CI -3.99 to 8.85 percent). (Figure 8) No statistical heterogeneity or publication bias was detected. Three single arm observational studies also evaluated the impact of rhGH therapy on percent predicted FEV_1. In the first study evaluating patients over the age of 6 years, five patients had baseline and 6 months data and four patients had baseline and 12 month data. The percent predicted FEV_1 after 6 months of rhGH therapy was nonsignificantly reduced (baseline 74±2.17 percent; 6 months 70±11.41, p=0.43) but at 12 months was nonsignificantly increased (baseline 75±1.41 percent; 12 months 81.5±21.76 percent, p=0.59).[40] In the second study (n=9), there was a nonsignificant decrease in percent predicted FEV_1 after 12 months of rhGH therapy (baseline 83.0±25.0 percent; 12 months 71.9±25.2 percent, p-value not reported).[41] In the final study, the percent predicted FEV_1 improved in seven of nine patients and remained stable in two of nine patients, but quantifiable data was not reported.[44]

Only one trial reported the change in FEV_1 Z-score from baseline.[4] Upon statistical pooling of the lower and higher dose rhGH arms versus placebo, there was no significant effect on FEV_1 Z-score (WMD -0.005, 95 percent CI -0.22 to 0.21).(Figure 9) There were too few trials to conduct evaluations of statistical heterogeneity and publication bias. Both dosing arms of rhGH showed similar null effects on FEV_1 Z-score.

Anthropometrics

<u>Height</u>

Seven trials reported the effect of rhGH on height-related outcomes in patients with CF, including absolute height, height velocity, height Z-score, and height percentile.[4, 15, 23, 32-34, 38] (Table 10) Six observational studied also reported on the effect of rhGH on height-related outcomes.[39-44]

Three trials reported on the change from baseline in height, permitting quantitative synthesis.[23, 25, 33] Upon statistical pooling, there was significant improvement in height from

930 baseline in the rhGH group compared to control (WMD 3.13 cm, 95 percent CI 0.88 to 5.38 cm).
931 (Figure 10) A high degree of statistical heterogeneity was detected (I^2=77.3 percent), but all
932 studies showed the same direction of effect. The individual point estimate for one trial[25] was
933 lesser than the other two trials[23, 33] which were conducted by the same investigator. Although the
934 doses of rhGH used in all three trials were similar, the trial by Hutler and colleagues was only
935 conducted for 6 months.[25] There were too few studies to assess the presence of publication bias.
936 In a single-arm observational study of 24 patients, therapy with rhGH yielded sustained increases
937 in height over several years of treatment, but quantifiable data was not reported.[42]

938 Three trials reported the change from baseline in height velocity after treatment with rhGH,
939 which was amenable to quantitative synthesis.[4, 15, 23] Statistical pooling of these trials showed a
940 significant improvement from baseline in height velocity in the rhGH group compared to control
941 (WMD 3.27 cm/year, 95 percent CI 2.33 to 4.21 cm/year). (Figure 11) A moderate degree of
942 statistical heterogeneity was detected (I^2=38.2 percent), though all studies exhibited the same
943 direction of effect. The statistical heterogeneity was most likely related to a more profound effect
944 in the trial by Hardin and colleagues in 2001[23] and the less profound effect in the lower dosing
945 arm of the trial by Schnabel and colleagues.[4] When evaluating the two dosing arms of the study
946 by Schnabel and colleagues, there was a nonsignificantly greater improvement in the higher
947 dosing arm, suggesting a potential dose-response relationship. The higher dose arm from the
948 Schnabel trial had a similar magnitude of effect as the Hardin trial, which had the greatest weight
949 in the meta-analysis. No publication bias was detected.

950 In a case report of a 9-year-old female with CF, height velocity increased from 3.2 cm/year to
951 12 cm/year, yielding a 2 cm increase in height within the first 2 months of rhGH therapy.[39] In a
952 single-arm observational study, the first 6 months of rhGH yielded increases in height velocity in
953 all seven patients studied (range 0.33 to 4.14 cm/year), with four patients experiencing clinically
954 significant increases (defined as a greater than 2 cm/year increase).[40] In another single-arm
955 observational trial (n=9), height velocity significantly increased after 12 months of rhGH
956 therapy, from 5.7±0.2 cm/year before therapy to 7.8±0.4 cm/year after therapy ($p<0.05$).[41] Upon
957 discontinuation of rhGH, height velocity declined to 4.5±0.6 cm/year in the year without rhGH
958 therapy and was significantly lower than the year prior to therapy ($p<0.05$).[41] Height velocity
959 also significantly increased in 7 patients out of the 24 evaluated in another single-arm evaluation
960 after 1 year of rhGH therapy ($p<0.05$) but other data was not provided.[42] The last single-arm
961 observational study (n=9) showed significant increases in height velocity from baseline over 12
962 months of rhGH treatment ($p=0.01$) but other data was not provided.[44]

963 Three trials reported the change from baseline in height Z-score, allowing for quantitative
964 synthesis.[23, 34, 38] Statistical pooling resulted in a significantly greater improvement from baseline
965 in rhGH-treated patients than control (WMD 0.51, 95 percent CI 0.35 to 0.66).(Figure 12) No
966 statistical heterogeneity was detected. Publication bias could not be evaluated because there were
967 too few trials. One additional trial did not report the change from baseline and could not be
968 included in the quantitative synthesis, but found that at the end of 12 months of treatment, the
969 height Z-score was nonsignificantly higher in the rhGH group than the control group (-1.09±0.8
970 versus -1.99±0.89, p-value not reported).[32]

971 In a single-arm observational trial (n=9), height Z-score significantly improved from -
972 1.3±0.23 to -0.76±0.23 ($p<0.05$) after 12 months of rhGH treatment.[41] Discontinuation of rhGH
973 resulted in height Z-scores returning to pretreatment values during the year after therapy, but
974 quantifiable data was not reported.[41] Another single-arm evaluation (n=5) found that height Z-

score significantly improved after 12 months of rhGH therapy (baseline -2.80±0.60; 12 months -1.56±0.60, p<0.01).[43] There was also a significant improvement at 24 months of therapy (-0.94±0.40, p<0.02 versus baseline and versus 12 months).[43] In another nine patients treated with rhGH in a single-arm evaluation, the height Z-score also significantly improved from baseline (baseline-1.86±0.7; 12 months -1.31±0.9, p=0.03).[44]

One trial reported on the effect of rhGH on height percentile.[23] After 12 months of therapy, the rhGH group experienced significant improvement from baseline in height percentile (baseline 7.5±1.2; 12 months 20.0±1.4, p=0.032).[23] Changes in the control group were not significant (baseline not reported; 12 months 7.8±1.6, p=0.64).[23]

Weight

Ten trials reported outcomes on weight in CF patients treated with rhGH, including absolute weight, weight velocity, weight Z-score, weight percentile, body mass index (BMI), BMI Z-score, percent of ideal body weight, and lean body mass (LBM).[4, 15, 23, 25, 26, 29, 32-34, 38] (Table 11) Four observational studies also reported results on weight outcomes.[40, 41, 43, 44]

Five trials reported the change from baseline in body weight, permitting quantitative synthesis.[4, 23, 25, 33, 38] Upon statistical pooling, there was significantly greater improvement in the rhGH group than the control group from baseline (WMD 1.48 kg, 95 percent CI 0.62 to 2.33 kg). (Figure 13) A moderate degree of statistical heterogeneity was detected (I^2=49 percent), but all studies showed the same direction of effect, and all but one[33] showed a similar magnitude of effect. The trial by Hardin and colleagues in 2005 evaluated adolescent patients exclusively,[33] who may have shown different responses to rhGH than the remaining trials. No publication bias was detected. The two dosing arms of the study by Schnabel and colleagues showed similar magnitude and direction of effect, suggesting a lack of dose-response relationship on body weight. In one single-arm observational trial (n=9), body weight was significantly increased after 1 year of rhGH therapy (baseline 21.5±3.1 kg, 12 months 24.9±4.2, p=0.007).[44]

Two trials reported the change in weight velocity from baseline, allowing for quantitative synthesis.[15, 23] Upon statistical pooling, the rhGH group showed significantly greater improvements in weight velocity from baseline compared to control (WMD 2.15 kg/year, 95 percent CI 1.52 to 2.78 kg/year). (Figure 14) There were too few studies to evaluate for statistical heterogeneity or publication bias, but both studies showed similar direction and magnitude of effect.

In a single-arm observational trial evaluating rhGH, the weight velocity nonsignificantly increased from baseline in seven patients treated for 6 months (baseline 1.84±2.52 kg/year; 6 months 3.15±1.69, p=0.24).[40] The p-value derived from comparing the 6 month time period to baseline was reported by the authors as being 0.03, but statistical analysis by our group using the raw data yielded a p-value of 0.24 using a paired t-test (Primer of Biostatistics: The Program, Dubeque, IA). Only four patients were treated for 12 months and their weight velocity nonsignificantly increased compared to baseline (6.58±3.46 kg/year versus 2.81±1.03 kg/year, p=0.07).[40] Another single-arm evaluation reported that weight velocity did not significantly change during or after rhGH therapy (quantifiable data and p-value not reported).[41] After 12 months of rhGH therapy in a third observational study (n=9), weight velocity significantly improved from baseline (1.7±0.9 to 3.8±1.6 kg/year, p=0.03).[44]

Four trials reported the change in weight Z-score from baseline, which was amenable to quantitative synthesis.[23, 26, 32, 34] Upon statistical pooling, there was a trend towards greater

improvements in weight Z-score in the rhGH group compared to control (WMD 0.49, 95 percent CI -0.02 to 1.00). (Figure 15) A moderate degree of statistical heterogeneity was detected (I^2=63.8 percent), though all but one trial[26] showed similar direction and magnitude of effect. The dose of rhGH and the duration evaluated in the trial by Schibler and colleagues[26] was the same as what was studied by Hardin and colleagues,[23, 32, 34] so this heterogeneity is not readily explained. No significant publication bias was noted.

In one single-arm observational study, weight Z-score significantly improved after 12 months of rhGH therapy (baseline -1.95±0.51; 12 months -0.97±0.56, p<0.01).[43] Weight Z-score was additionally improved at 24 months of therapy (-0.11±0.11, p<0.02 versus baseline and versus 12 months).[43]

One trial reported on the effect of rhGH on weight percentile.[23] After 12 months of therapy, the rhGH group experienced a significant improvement in weight percentile (baseline 4.0±1.5; 12 months 9.0±1.3, p=0.042).[23] There were no significant changes in the control group (baseline not reported; 12 months 3.5±1.9, p-value not reported).[23]

Two trials reported the change from baseline in BMI, permitting quantitative synthesis.[33, 34] Statistical pooling resulted in significantly greater improvements from baseline in BMI in the rhGH group compared to control (WMD 2.08 kg/m^2, 95 percent CI 1.20 to 2.96 kg/m^2). (Figure 16) There were too few studies to evaluate statistical heterogeneity or publication bias, but both studies showed similar direction and magnitude of effect.

One single-arm observational study (n=7) reported that there was no significant change in BMI from baseline, but quantifiable data was not reported.[40]

One trial reported the effect of rhGH on the change from baseline in BMI Z-score.[4] This trial evaluated two dosing arms of rhGH and was amenable to quantitative synthesis. After pooling the two dosing arms of the trial, there was no significant difference between the rhGH group and placebo group on BMI Z-score (WMD -0.05, 95 percent CI -0.30 to 0.20). (Figure 17) There were too few studies to evaluate statistical heterogeneity or publication bias, but both dosing arms of the trial showed similar direction and magnitude of effect. This suggests a lack of a dose-response relationship.

Two trials reported the effect of rhGH therapy on change from baseline in percent of IBW, permitting quantitative synthesis.[23, 33] Upon statistical pooling, there was a significantly greater improvement from baseline in percent IBW in the rhGH group compared to control (WMD 12.57, 95 percent CI 7.01 to 18.12). (Figure 18) There were too few studies to evaluate statistical heterogeneity or publication bias, but both studies showed similar direction and magnitude of effect.

Eight trials reported the change in LBM from baseline in patients treated with rhGH, and were amenable to quantitative synthesis.[4, 15, 23, 25, 26, 32, 34, 38] Upon statistical pooling, the rhGH group showed significantly greater improvements from baseline in LBM compared to control group (WMD 1.92 kg, 95 percent CI 1.47 to 2.37 kg). (Figure 19) A low degree of statistical heterogeneity was detected (I^2=20.9 percent) and all studies showed similar direction and magnitude of effect. Publication bias was unlikely. In a crossover trial not included in quantitative synthesis that evaluated rhGH, glutamine, or the combination of the two (n=9), there was no significant difference between the treatment groups at the end of the 4 week treatment period in LBM as measured by DEXA (rhGH 22.3±5.7 kg; rhGH and glutamine combination 22.4±4.2 kg; glutamine 21.4±4.5 kg, p-value not reported).[29] This trial was not included in

quantitative synthesis because it evaluated rhGH either alone or in combination with glutamine versus a glutamine control, rather than a nonactive control like in the other trials.[29]

Protein Markers

Two trials reported results on markers of protein catabolism subsequent to treatment with rhGH.[24, 29] (Table 12) One observational study also reported the effect of rhGH on markers of protein catabolism.[41]

In a parallel, randomized controlled trial, there was no significant change in leucine rate of appearance (LeuRa) from baseline in either the rhGH (-44±15 µmol/kg/hr) or control group (10±28 µmol/kg/hr) after 12 months of treatment, although qualitative improvements were seen.[24]Treatment with rhGH for 12 months significantly improved LeuOx, NOLD, and LeuOx/NOLD ratio (change from baseline: -19±7 µmol/kg/hr, -30±16 µmol/kg/hr, and -0.06±0.02, respectively, $p<0.05$ for all comparisons to baseline).[24] The control group experienced no significant changes from baseline in any of these parameters.[24] (Table 12) Data was not reported in a manner that we could calculate the intergroup p-values.

In a crossover trial, Darmaun and colleagues evaluated the effects of rhGH, glutamine, or their combination on LeuRa, LeuOx, and NOLD.[29] The LeuRa concentration at baseline was 2.89±0.22 µmol/kg of LBM/min.[29] Treatment with glutamine alone resulted in a nonsignificant decrease in LeuRa (2.82±0.18 µmol/kg of LBM/min, p=0.48 versus baseline), while rhGH alone (2.96±0.27 µmol/kg of LBM/min, p-value not reported) and rhGH and glutamine combination (2.98±0.30 µmol/kg of LBM/min, p=0.69) yielded nonsignificant increases in LeuRa.[29] Treatment with either rhGH alone (0.49±0.09 µmol/kg of LBM/min versus 0.72±0.05 µmol/kg of LBM/min, p=0.004) or the rhGH plus glutamine combination 0.46±0.08 µmol/kg of LBM/min versus 0.70±0.05 µmol/kg of LBM/min, p=0.01) significantly improved LeuOx versus baseline, while there was a nonsignificant change for glutamine alone (0.64±0.10 µmol/kg of LBM/min versus 0.71±0.05 µmol/kg of LBM/min, p=0.36).[29] For the NOLD endpoint, the rhGH alone (2.41±0.22 µmol/kg of LBM/min versus 2.13±0.22 µmol/kg of LBM/min, p=0.01) and the rhGH plus glutamine combination (2.52±0.21 µmol/kg of LBM/min versus 2.13±0.22 µmol/kg of LBM/min, p=0.05) groups showed statistically significant improvements from baseline, while the glutamine alone group remained unchanged (2.18±0.18 µmol/kg of LBM/min versus 2.18±0.22 µmol/kg of LBM/min, p-value not reported).[29]

In one single-arm observational study (n=9) which evaluated markers of protein metabolism, nitrogen balance was negative in all patients prior to beginning rhGH, but became less negative in five patients after treatment.[41] After 12 months of rhGH therapy, protein turnover changed from 5.6±0.5 g/kg/day before treatment to 5.2±0.5 g/kg/day (p-value not reported).[41] Protein synthesis remained unchanged over 12 months of rhGH therapy (3.9±0.3 g/kg/day before treatment to 3.9±0.4 g/kg/day at 12 months, p-value not reported).[41] In patients who achieved positive net protein anabolism (n=5), net protein anabolism changed from -0.6±0.1 g/kg/day before treatment to 0.317±0.07 g/kg/day at 12 months (p-value not reported).[41]

Exercise Tolerance

Three randomized controlled trials[4, 25, 26] evaluated exercise tolerance, all using a bicycle ergometer test, and reporting endpoints including exercise work rate, oxygen consumption, maximal oxygen consumption, oxygen pulse, and peak ventilation rate. (Table 13)

Two trials reported the change from baseline in exercise work rate, allowing for quantitative analysis.[4, 26] Upon statistical pooling, the exercise work rate was nonsignificantly improved in the rhGH group compared to control (WMD 11.80 W, 95 percent CI -0.44 to 24.04 W). (Figure 20) A low degree of statistical heterogeneity was detected (I^2=23.7 percent), but all studies exhibited the same direction of effect. Publication bias could not be evaluated because there were too few studies. The two dosing arms of the trial by Schnabel and colleagues showed similar direction and magnitude of effect, suggesting a lack of dose-response relationship with rhGH therapy.

The remaining endpoints were sparsely reported and thus not amendable to quantitative analysis. The trial by Hutler and colleagues was a crossover trial comparing rhGH therapy to control, and their data was reported as both separate time periods and as combined treatment groups.[25] When looking at only the first period of data, there appeared to be a greater improvement from baseline in those treated with rhGH in peak oxygen uptake ($VO_{2\text{-peak}}$) (change from baseline in rhGH 201±161 mL versus control -18±117 mL, p-value not reported).[25] There were also improvements from baseline in the rhGH group during the first period of treatment compared to control in oxygen pulse peak (rhGH 1.0±0.7 ml/beat versus control -0.1±0.5 ml/beat, p-value not reported) and in ventilation peak (rhGH 5.3±6.6 versus control -0.4±5.5, p-value not reported).[25] From the crossover data in which data from the same treatment groups were combined, there were significantly greater improvements from baseline in rhGH group compared to control in exercise power (p=0.008), VO_2 (p=0.009), and oxygen pulse (p=0.008).[25] In the study by Schibler and colleagues, the maximal oxygen consumption (VO_{2max}) remained unchanged in the rhGH group (baseline 40.7±2.7 ml/kg/min; 12 months 38.2±2.1 ml/kg/min, p-value not reported) but the control group showed significant decreases in VO_{2max} (baseline 44.1±3.5 ml/kg/min; 12 months 35.5±2.5 ml/kg/min, p=0.003).[26] Schnabel and colleagues found that maximal oxygen consumption (in ml/min) increased from baseline in both doses of rhGH treatment groups and that this change was significantly greater than the change from baseline in the placebo group ($p<0.05$ for both dose groups versus placebo).[4] During the open-label treatment of all patients following the double-blind study, patients originally treated with placebo showed improvements in work rate (6.1±16.6 W) and maximal oxygen consumption (86.9±220.4 ml/min) after being treated with rhGH.[4]

One single-arm observational study reported a decline in exercise endurance time in all five patients studied during the first 6 months of treatment (p-value not reported), but this resolved in the four patients who completed the study at 12 months (p-value not reported).[40]

Bone Mineralization

Five trials reported bone mineralization outcomes in CF patients being treated with rhGH, including bone age, bone mineral content, and bone mineral content Z-score.[15, 23, 32-34] (Table 14) Three observational studies also reported on changes in bone age subsequent to rhGH therapy.[40, 41, 43]

Two trials reported change from baseline in bone age.[23, 32] While this data is amenable to quantitative synthesis, the clinical implication of the value attained from statistical pooling is uncertain. Therefore, this endpoint is reported qualitatively. After 12 months of treatment, Hardin and colleagues reported that the change in bone age from baseline in the rhGH group was 1.1±0.9 years and the control group was 0.9±1.2 years.[23] The p-value was reported as nonsignificant, but it is unclear if it refers to the comparison from the end of 12 months to

baseline, or the comparison between treatment groups.[23] In adolescent patients with CF studied by Hardin and colleagues, bone age was similar between groups at baseline (rhGH 14.4±1.9 years versus control 14.1±1.2 year, p>0.05) and there was no significant differences in bone age after 1 year of treatment (rhGH 15.2±1.9 year versus control 14.9±0.9 years, p=0.7).[33]

In a single-arm observational study (n=7), bone age advanced faster than chronological age in four patients. The mean change in bone age in all patients was 0.79±0.42 years, but this was not significantly different from the change in chronological age (0.62±0.10 years, p=0.28).[40] Another single-arm observational study showed changes in bone age from baseline to be similar to change in chronological age (1.0±0.3 years over 12 months of rhGH therapy).[41] A third single-arm observational study found that bone age was not significantly improved over the first 12 months of therapy (baseline 2.0±1.0 versus 12 months 2.9±1.05, p-value not reported), nor at 24 months of therapy (24 months 3.6±1.3, p-value not reported).[43]

Four trials reported change from baseline in bone mineral content, permitting quantitative synthesis.[15, 32-34] Pooling the data resulted in a significant improvement in bone mineral content in the rhGH group compared to control (WMD 192 g, 95 percent CI 110 to 273 g). (Figure 21) A high degree of statistical heterogeneity was detected, likely due to differences in the magnitude of effect, though the direction of effect was similar in all studies. One trial by Hardin and colleagues in 2005[33] exhibited a more profound effect than the other trials, possibly due to it being comprised exclusively of adolescent patients, who may have accumulated a greater bone mass due to their pubertal status and presence of sex hormones. No significant publication bias was seen in this analysis.

Bone mineral content (BMC) Z-score was reported in one trial[15] and found to have significantly improved in patients treated with rhGH compared to control. At baseline, BMC Z-score was -2.1±0.6 in the rhGH group compared to -1.7±0.9 in the control group; at 12 months, the rhGH group had a value of -1.4±0.8 versus -1.7±0.8 in control.[15] The authors provided a p-value of 0.04 at the end of this statement, but it is unclear for which comparison it refers.[15] The rhGH group had a statistically significant increase in BMC Z-score from baseline compared to control (Table 14, p=0.001). In a 1 year open-label extension in which patients originally assigned to the control group received rhGH therapy, there was also an improvement in BMC Z-score up to -1.3±0.7 at the end of the study.[15]

Sexual Maturation

Pubertal status was reported in seven trials.[15, 23, 25, 29, 32-34] (Table 15) In five trials,[15, 25, 29, 32, 34] all patients were prepubertal (Tanner stage 1) and did not progress over the randomized controlled portion of the trials. In the trial by Hardin and colleagues in 2001, all patients started at Tanner stage 1; at the end of 12 months of therapy, none of the males progressed in Tanner stage, and three and two females in the rhGH and control groups progressed to Tanner stage 2, respectively.[23] The trial by Hardin and colleagues in 2005 evaluated pubertal patients exclusively and reported the mean Tanner stage at baseline (rhGH 3.6±0.4; control 3.4±0.6) and study end in both groups (rhGH 4.5±0.6; control 4.1±0.9, p=not significant).[33]

One publication[37] reported new data on sexual maturation by pubertal status and gender on patients who were enrolled in three prospective trials (including the Hardin 2001/2001 trial noted above).[15, 23, 33] More prepubertal females treated with rhGH exhibited breast development in the first 6 months than females in the control group (50 percent vs 23 percent, p<0.02).[37] In prepubertal males, nonsignificant improvements in testicular development was seen in the first 6

months of rhGH treatment compared to control (25 percent vs 12.8 percent, p=0.14).[37] Pubertal onset with respect to chronological age was normalized in both prepubertal females and males treated with rhGH.[37] In patients who had already reached puberty before initiating rhGH, treatment did not significantly alter further pubertal development compared to control.[37]

Discussion

Treatment with rhGH improved in pulmonary function as measured by absolute FVC (0.67 L improvement), percent predicted FVC (9.34 percent improvement), and absolute FEV_1 (0.23 L improvement). There were no significant effects on percent predicted FEV_1 and FEV_1 Z-score upon statistical pooling of trials from 6 to 12 months of duration. The nonsignificant effects on percent predicted FEV_1 in the face of significant improvements in absolute FEV_1 are likely due to the concurrent improvements in height. Since predicted values of FEV_1 are hinged upon a patient's height,[11] concurrent clinical improvements in both absolute FEV_1 and height may attenuate or nullify improvements in percent predicted FEV_1. It seems that pulmonary function improves with rhGH therapy but may not markedly improve above that which is caused by height improvements. The Cystic Fibrosis Foundation (CFF) pulmonary guidelines currently do not contain recommendations regarding the use of rhGH to improve pulmonary function.[103] In CF patients with moderate to severe lung disease, the CFF strongly recommends the use of inhaled tobramycin and recombinant human DNase based at least partially upon the ability to improve percent predicted FEV_1 by 7.8 to 12 percent (with tobramycin) and absolute FEV_1 11.2 to 15.4 percent (with DNase).[103] Although rhGH was unable to provide similar benefits on percent predicted FEV_1, inhaled tobramycin and DNase do not affect linear growth and assert effects on pulmonary function independently.[103]

Most of the anthropometrics evaluated in CF patients treated with rhGH significantly improved over a treatment range of 6 to 12 months. Significant improvements in height outcomes were detected with a 3.13 cm greater height gain in rhGH-treated patients than control, and a 3.27 cm/year greater height velocity than control. Height Z-score was also improved by 0.51. Similarly, body weight was significantly improved upon statistical pooling, with improvements of 1.48 kg in patients treated with rhGH. Treatment was associated with improvements in weight velocity by 2.15 kg/year and weight Z-score by 0.49. Treatment with rhGH provided significant improvements in BMI (with a gain of 2.08 kg/m^2), though BMI Z-score was not affected. Percent of IBW and LBM were significantly improved by 12.57 percent and 1.92 kg, respectively. There is some evidence to suggest that low anthropometric values are associated with decreases in pulmonary function. In the Epidemiologic Study of Cystic Fibrosis, multivariate analysis showed a significant decline in percent predicted FEV_1 with low weight-for-age percentile in CF patients aged 9 to 12 years (n=1696, p=0.029) and CF patients aged 13 to 17 years (n=1359, p=0.021).[104] Lower values of weight-for-age and height-for-age are also associated with low levels of percent predicted FEV_1 later in life, with anthropometrics ate age 3 years being correlated with pulmonary function at age 6 years.[7]

To provide clinical context to the absolute changes in height and weight, we calculated the height and weight percentiles and Z-scores for a hypothetical CF patient with typical characteristics. Based on unpublished data by Hardin and colleagues, we determined that a typical prepubertal CF patient at baseline is aged 9.33 years, is 125 cm tall, and weights 25 kg. Using the WHO AnthroPlus software for a male patient, this typical patient at baseline has a height percentile of 6.4, height Z-score of -1.52, weight percentile of 15.4, and weight Z-score of

1237 -1.02. Without the use of rhGH, the patient would gain 1 kg of body weight and 0.2 cm of height
1238 in 1 year, and would have height percentile 1.4, height Z-score -2.21, and incalculable weight
1239 percentile and weight Z-score. If rhGH were administered for 1 year with additional height
1240 increases of 3.13 cm and weight gain of 1.48 kg over control, this patient at 1 year would have
1241 height percentile 4.2, height Z-score -1.72, and incalculable weight percentile and Z-score. While
1242 the rhGH-treated patient has not achieved population norms, his values are closer to normal than
1243 without rhGH therapy.

1244 In both trials evaluating protein turnover, rhGH therapy significantly improved two protein
1245 markers (LeuOx and NOLD) but did not significantly impact LeuRa, although qualitative
1246 improvements in this marker were seen in both trials. In the observational, single arm trial,
1247 nitrogen balance was less negative but protein synthesis was unaltered. LeuRa is based on the
1248 rate of isotopically-labeled leucine release from tissues (due to protein breakdown) into the
1249 intracellular space.[105] Since leucine can be oxidized in muscle tissue,[105] LeuOx is measured to
1250 aid in the calculation of NOLD, which represents whole body protein synthesis.[24] Although there
1251 are no standard published values that correlate with a clinically significant change, improvement
1252 in protein kinetics can be helpful due to the catabolic condition of CF.[24] Given the small sample
1253 sizes, different comparators in the three studies (no treatment, glutamine treatment, and no
1254 control group), different study types (parallel trial, crossover trial, observational study), and
1255 different means of comparison, the strength of evidence for this endpoint is very low.

1256 Measures of exercise tolerance were also improved with rhGH therapy, with maximal work
1257 rate improving by 11.80 W in patients treated with rhGH compared to control. Maximal work
1258 rate is measured by setting up a bicycle ergometer at an initial work rate, increasing the work rate
1259 at predetermined increments per unit of time (either with Conconi protocol or Borg scale),[4, 26]
1260 and halting the exam at subjective physical exhaustion. The work rate at the time of exam
1261 completion is recorded as the maximal work rate, representing the point at which a patient cannot
1262 tolerate physical activity any further. Other endpoints related to exercise tolerance were sparsely
1263 reported and thus quantitative synthesis was not performed. One study reported improvements in
1264 peak oxygen uptake, oxygen pulse peak, and ventilation peak. Another study showed no changes
1265 in maximal oxygen consumption.

1266 Bone mineralization was another intermediate outcome of interest. After 1 year of therapy,
1267 there was no difference in bone age between rhGH-treated patients and control. Bone mineral
1268 content was significantly improved by 192 g in rhGH-treated patients versus control upon
1269 statistical pooling. In the one trial evaluating the endpoint, bone mineral content Z-score was also
1270 found to have significantly improved by 0.7 in rhGH-treated patients after 1 year of therapy.
1271 Bone mineralization deficiencies are problems in patients with CF for several underlying
1272 reasons: vitamin D malabsorption, poor nutrition, physical inactivity, or delayed pubertal
1273 development.[106] Several small randomized controlled trials may support the use of
1274 bisphosphonates in CF patients, showing increases in bone mineral density (BMD) up to 5.8
1275 percent in the lumbar spine versus control ($p<0.001$) with pamidronate.[107] However, the
1276 bisphosphonate trials were conducted in adult patients and presented results in percent change in
1277 bone mineral density, making comparisons difficult with the mostly pediatric population studied
1278 with rhGH and the results presented as absolute change in total body BMC. Therefore, the
1279 relevance of the changes seen in BMC with rhGH therapy is unclear.

1280 rhGH therapy does not seem to improve sexual maturation in males with CF and the impact
1281 in females with CF cannot be determined at this time. In five controlled trials, rhGH therapy did

1282 not improve sexual maturation regardless of gender. In one controlled trial, mean Tanner stage
1283 regardless of gender improved in all patients and in an analysis of three controlled trials, rhGH
1284 therapy significantly improved sexual maturation in females but not in males.

1285 While improvements in intermediate outcomes with rhGH therapy may be beneficial to the
1286 patient, it is essential to determine the effect of rhGH on important health outcomes. Key
1287 Question 2 seeks to evaluate the effect of rhGH on important health outcomes in CF patients,
1288 while Key Question 3 seeks to elucidate the linkages between intermediate and important health
1289 outcomes.

1290

Table 4. Study design and population of controlled trials which evaluated rhGH

Study, year	Study Design	Country	Study Funding	Quality Rating	Product	Dose	Follow-up	Inclusion Criteria	Exclusion Criteria
Hardin, 2001[23, 24]	RCT	United States	Government, Industry	Fair	Nutropin AQ	0.3 mg/kg/wk given daily	1 year	Any child who was ≤ 10th percentile for both height and weight, Tanner stage 1, and evaluated by nutritional staff and reported to have adequate caloric intake on at least two evaluations.	History of glucose intolerance or previous diagnosis of cystic fibrosis-related diabetes (CFRD); infection with *Burkholderia cepacia*; weight loss greater than 3% during 3 months before study; hospitalization within 6 weeks before the first study visit; treatment with systemic or oral steroids within 6 weeks of the study; or questionable adherence to previous dietary recommendations designed to provide adequate nutrition.
Hutler, 2002[25]	RCT	Germany	Foundation, Industry	Fair	Genotropin	0.27 to 0.35 mg/kg/wk given daily	6 months	CF confirmed by positive sweat test.	Not specified
Schibler, 2003[26]	RCT	Switzerland	Industry	Fair	Saizen	0.3 mg/kg/wk given daily	1 year	CF confirmed by positive sweat test and analysis of mutated CFTR gene.	Insulin dependent diabetes mellitus, hepatic disease, evidence of portal hypertension, and patients with clinically evident congestive heart failure.

Table 4. Study design and population of controlled trials which evaluated rhGH

Study, year	Study Design	Country	Study Funding	Quality Rating	Product	Dose	Follow-up	Inclusion Criteria	Exclusion Criteria
Darmaun, 2004[29b]	RCT	United States	Foundation, Industry	Fair	Not specified	0.3 mg/kg/wk given daily	1 month	CF confirmed by positive sweat test and analysis of mutated CFTR gene; age between 7 and 13 years; Tanner stage I; significant growth delay (as defined by height less than 5th percentile or below –2 SD for age) and/or undernutrition (weight for height less than 50th percentile); stable lung disease over the last 3 months, defined as unchanged pulmonary function tests; documented growth rate over the previous 2 years.	Clinically significant liver disease (bilirubin outside of normal limits and/or serum glutamine-pyruvate transaminase or serum glutamine-oxaloacetate transaminase over twice the upper limit of normal); diabetes; or other organic disease.
Hardin, 2005a[32]	RCT	United States	Government, Foundation, Industry	Fair	Nutropin AQ	0.3 mg/kg/wk given daily	1 year	Prepubertal children with CF.	Not specified
Hardin, 2005b[33]	Retro cohort	United States	Not specified	Fair	Nutropin AQ	0.3-0.35 mg/kg/wk given daily	1 year	Adolescents referred to pediatric endocrinologist for clinical evaluation of poor growth during years 1999-2003. Referral criteria: height less than 5th percentile for age despite “good” nutrition and Tanner III sexual maturity.	Reasons patients not referred were secondary to medical instability (frequent pulmonary infections, rapid weight loss and systemic corticosteroid use).

Table 4. Study design and population of controlled trials which evaluated rhGH

Study, year	Study Design	Country	Study Funding	Quality Rating	Product	Dose	Follow-up	Inclusion Criteria	Exclusion Criteria
Hardin, 2005c[34]	RCT	United States	Industry	Fair	Nutropin AQ	0.3 mg/kg/wk given daily	1 year	Height and weight less than 10th percentile for age; Tanner stage I; enteral nutritional supplementation for at least 2 years before study enrollment; and adherence to nutritional therapy, as assessed by repeated dietary evaluation.	Treatment with sustained systemic corticosteroid therapy within 6 weeks of study and colonization with Burkholderia cepacia.
Hardin, 2006[15]	RCT	United States	Industry	Fair	Nutropin AQ	0.3 mg/kg/wk given daily	1 year	Age 7-12 years; height and weight in the 25th percentile or lower for age; Tanner I breast in females; and testicular development 3 cc or less in males.	Pre-existing diabetes; systemic corticosteroid use within 6 months; colonization with Burkholderia cepacia; and/or addition of oral, enteral, or parenteral caloric supplements within the previous year.
Schnabel, 2007[4]	RCT	Germany	Industry	Good	Genotropin	0.07 or 0.039 mg/kg/day (equals 0.49 or 0.273 mg/kg/wk, respectively)	6 months	CF confirmed by positive sweat test and analysis of mutated CFTR gene; bone age 8-18 years; dystrophy defined as BMI <10th and/or body weight <3rd percentile despite high caloric intake (>120% of the recommended dietary allowance) according to a 3-day food-intake diary.	Acute pulmonary exacerbation in the 4 weeks before entering the trial; diabetes (fasting plasma glucose >126 mg/dl); liver cirrhosis with hypoalbuminemia; serum creatinine > 120umol/L; inability to perform exercise and lung function testing; history of malignancy; suspected noncompliance; participation in any other clinical trial during the active treatment phase; pregnancy or lactation; and treatment with growth hormone, anabolic steroids, or systemic corticosteroids within 12 months.

Table 4. Study design and population of controlled trials which evaluated rhGH

Study, year	Study Design	Country	Study Funding	Quality Rating	Product	Dose	Follow-up	Inclusion Criteria	Exclusion Criteria
Stalvey, 2008[38]	RCT	United States	NR	Fair	NR	0.3 mg/kg/wk given daily	1 year	Prepubertal children with CF and height ≤10th percentile.	NR

Legend: BMI=body mass index; CF=cystic fibrosis; CFTR=cystic fibrosis transmembrane regulator; NR=not reported; RCT=randomized controlled trial; SD=standard deviation

Table 5. Baseline characteristics of patients in controlled trials evaluating rhGH

Study, year	Group	Dose/wk (mg/kg)	N	Mean Age (SD)	Male (%)	Height (cm)	Height Z-score	Weight (kg)	Weight Z-score
Hardin, 2001[23, 24]	rhGH	0.3	10	10.2 (1.7)	50	137.8 (1.5)	-0.5 (1.4)	27.3 (2.8)	-1.6 (0.4)
	No treatment	NA	9	11.4 (1.3)	56	138.2 (1.7)	-0.6 (0.6)	28.5 (3.5)	-1.6 (0.3)
Hutler, 2002[25a]	rhGH	0.27 to 0.35	10	12.1 (1.7)	70	137.4 (9.2)	-	27.8 (4.2)	-
	No treatment	NA							
Schibler, 2003[26]	rhGH	0.35	10	15.4 (Range 11-22)	80	-	-	Median 42.5 (IQR 35.8 - 45.0)	-
	No treatment	NA	9	16.8 (Range 10-23)	78	-	-	Median 44.0 (IQR 40-45.5)	-
Darmaun, 2004[29b]	rhGH	0.3	9	9.7 (1.8)	78	-	-1.4 (0.6)	-	-0.7 (0.3)
	rhGH+GLN	0.3/0.7[c]							
	GLN	0.7[c]							
Hardin, 2005a[32]	rhGH	0.3	16	10.9 (1.8)[m] 11.2 (1.9)[f]	53	-	-0.12[m] -2.32[f]	-	-1.6 (1.0)
	No treatment	NA	16						-1.7 (1.1)
Hardin, 2005b[33]	rhGH	0.3 to 0.35	13	13.8 (1.4)	69	152.2 (4.6)	-1.9 (0.7)	38.8 (5.1)	-1.8 (0.8)
	No treatment	NA	12	14.3 (1.1)	67	149.5 (4.4)	-1.9 (0.6)	37.3 (3.9)	-2.0 (0.8)
Hardin, 2005c[34]	rhGH	0.3	9	11.6 (2.2)	-	129.6 (9.2)	-1.7 (1.0)	26.1 (6.2)	-2.0 (1.7)
	No treatment	NA	9	11.1 (1.9)	-	133.1 (6.7)	-1.7 (1.0)	27.5 (6.7)	-1.9 (0.8)
Hardin, 2006[15]	rhGH	0.3	32	10.3 (2.2)	50	-	-1.8 (0.7)	-	-1.7 (0.9)
	No treatment	NA	29	9.7 (1.7)	55	-	-1.9 (0.6)	-	-1.6 (0.8)
Schnabel, 2007[4]	Higher dose	0.49	20	14.3 (2.6)	62	151.7 (12.5)	-2.1 (1.1)	36.5 (7.7)	-
	Lower dose	0.273	22	13.8 (2.7)		151.3 (10.5)	-1.8 (1.3)	35.4 (7.5)	-
	Placebo	NA	21	14.6 (2.9)		149.8 (11.7)	-2.5 (1.2)	34.6 (6.7)	-
Stalvey, 2008[38]	rhGH	0.3	29	-	-	-	-1.8 (0.4)	24.1 (5.1)	-
	No treatment	NA	27	-	-	-	-1.9 (0.6)	24.7 (4.0)	-

Legend: All values given as mean (standard deviation), except where noted; - =not reported; [f]=value for females; GLN=glutamine; IQR=interquartile range; [m]=value for males; N=sample size; NA=not applicable; rhGH=recombinant human growth hormone; SD=standard deviation

[a]Hutler et al was a crossover study – baseline characteristics are before treatment with any of the interventions

[b]Darmaun et al was a crossover study – baseline characteristics are before treatment with any of the interventions

[c]Glutamine dosing is 0.7 g/kg per day

Table 6. Baseline characteristics of patients in controlled trials evaluating rhGH, continued

Study, year	Group	Dose/wk (mg/kg)	N	BMI (kg/m^2)	BMI Z-score	LBM (kg)	FVC (L)	%FVC	FEV_1 (L)	%FEV_1
Hardin, 2001[23, 24]	rhGH	0.3	10	-	-	23.3 (0.9) 22.6 (0.9)[m] 24 (0.8)[f]	-	66 (24)	-	70 (9)
	No treatment	NA	9	-	-	23.6 (0.8) 23.5 (0.7)[m] 23.6 (0.9)[f]	-	83 (18)	-	72 (15)
Hutler, 2002[25a]	rhGH	0.27 to 0.35	10	14.6 (0.8)	-	22.7 (2.5)	1.6 (0.4)	73 (20)	1.2 (0.3)	68 (22)
	No treatment	NA								
Schibler, 2003[26]	rhGH	0.35	10	-	-	-	-	-	-	-
	No treatment	NA	9	-	-	-	-	-	-	-
Darmaun, 2004[29b]	rhGH	0.3	9	-	-	-	-	-	-	84(18)
	rhGH+GLN	0.3/0.7[c]								
	GLN	0.7[c]								
Hardin, 2005a[32]	rhGH	0.3	16	-	-	23.1 (2.9)	-	-	-	-
	No treatment	0	16	-	-	24.2 (1.7)	-	-	-	-
Hardin, 2005b[33]	rhGH	0.3 to 0.35	13	15.7 (0.6)[d]	-	23.5 (2.5)	2.5 (0.7)	-	1.9 (0.8)	-
	No treatment	NA	12	15.8 (0.6)[d]	-	26.9 (2.1)	2.3 (0.4)	-	1.7 (0.5)	-
Hardin, 2005c[34]	rhGH	0.3	9	-	-	-	2.4 (0.8)[d]	78 (17)	1.9 (0.8)[d]	68 (15)
	No treatment	NA	9	-	-	-	2.1 (0.6)[d]	80 (14)	1.7 (0.6)[d]	66 (22)
Hardin, 2006[15]	rhGH	0.3	32	15.2 (1.4)	-	20.2 (4.1)	1.7 (0.5)	-	1.4 (0.4)	-
	No treatment	NA	29	15.4 (1.2)	-	18.7 (3.6)	1.6 (0.4)	-	1.3 (0.4)	-
Schnabel, 2007[4]	Higher dose	0.49	20	-	-2.0 (1.0)	-	-	66 (15)	-	52 (20)
	Lower dose	0.273	22	-	-2.0 (1.0)	-	-	68 (15)	-	54 (22)
	Placebo	NA	21	-	-2.2 (0.8)	-	-	67 (15)	-	55 (19)
Stalvey, 2008[38]	rhGH	0.3	29	-	-	18.4 (3.9)	-	-	-	-
	No treatment	NA	27	-	-	19.1 (4.0)	-	-	-	-

Legend: All values given as mean (standard deviation); - =not reported; BMI=body mass index; [f]=value for females; %FEV_1=percent predicted forced expiratory volume in one second; FEV_1=forced expiratory volume in one second; %FVC=percent predicted forced vital capacity; FVC=forced vital capacity; GLN=glutamine; LBM=lean body mass; [m]=value for males; N=sample size; NA=not applicable rhGH=recombinant human growth hormone; SD=standard deviation

[a]Hutler et al was a crossover study – baseline characteristics are before treatment with any of the interventions

[b]Darmaun et al was a crossover study – baseline characteristics are before treatment with any of the interventions

[c]Glutamine dosing is 0.7 g/kg per day

[d]Value extrapolated from figure

Table 7. Study design and population of single-arm observational studies evaluating rhGH

Study, year	Study Design	Quality Rating	Product and Dose	Duration of Treatment	Population	Reported Results
Mullis, 1991[39] N=1	Case Report	Poor	Grorm Dose NR	8 months	9 year old female with CF and classic presentation of growth hormone deficiency, delayed psychomotor development, and extremely short stature.	Improved height velocity and height Z-score for 2 months followed by complete growth arrest, which was probably due to anti-hGH antibodies.
Sackey, 1995[40] N=7	Prospective Single-group, all receiving rhGH	Fair	Humatrope 0.16 mg/kg/week given daily	6 months in 3 patients. 12 months in 4 patients.	Prepubertal patients with CF aged older than 3 years, height velocity below 75th percentile, with normal serum thyroxin levels. Patients were excluded if they had severe respiratory impairment (FEV_1<40% predicted), liver enzymes 20% over ULN, diabetes mellitus, receiving oral steroids, with significant steatorrhea, or asymptomatic gallstones.	Improved height velocity, height velocity Z-score, and height Z-score for bone age. Improved bone age. Improved weight velocity, but no significant changes in body mass index or lean body mass. Decreased exercise endurance in 6 months, but effect was reversed by 12 months. Pulmonary function improved, but was not significant, and the number of pulmonary exacerbations was reduced. **ADEs** Minor bruising at injection sites was reported by patients. There were no changes in glucose parameters. Transient increases in liver enzymes in 2 patients, but resolved over time.

Table 7. Study design and population of single-arm observational studies evaluating rhGH

Study, year	Study Design	Quality Rating	Product and Dose	Duration of Treatment	Population	Reported Results
Huseman, 1996[41] N=9	Prospective Single-group, all receiving rhGH	Fair	Product NR 0.3 mg/kg/wk given three times weekly	9 months in 1 patient. 12 months in 8 patients.	Prepubertal patients with CF aged 5.5 to 9.8 years, seen in outpatient clinic for at least the year before, during and the year after rhGH therapy.	Improved height velocity and height Z-scores. No significant changes in weight, but increased arm muscle area and decreased arm fat area. Improved bone age. Pulmonary function improved, but was not significant. Positive nitrogen balance, suggesting improved muscle mass. ADEs NR No significant change in routine chemistries including glucose values
Hardin, 1997[42] N=24	Retrospective Observational registry database	Fair	NR	Mean±SD 1.9±1.3 years	Patients with CF in the National Cooperative Growth Study database who had not been previously treated with rhGH.	Improved height and height velocity. Improved weight-for-height Z-scores. ADEs: Two patients (both females who had progressed from Tanner stage 1 to 2) reported glucose intolerance.
Alemzadeh, 1998[43] N=5	Prospective Single-group, all receiving rhGH	Fair	Humatrope 0.3 mg/kg/wk given daily six days of the week	2 years	Prepubertal patients with CF aged 6 months to 5.2 years, with pancreatic insufficiency and marked growth failure.	Improved height and height Z-scores. Improved weight and weight Z-scores. Increased levels of IGF-1 and IGFBP-3.

Table 7. Study design and population of single-arm observational studies evaluating rhGH

Study, year	Study Design	Quality Rating	Product and Dose	Duration of Treatment	Population	Reported Results
Hardin, 1998[44] N=9	Prospective Single-group, all receiving rhGH	Fair	Somatotropin 0.35 mg/kg/wk given daily	1 year	Prepubertal (Tanner Stage 1) patients with CF aged 5.4 to 12.2 years.	Improved height velocity and height Z-scores. Improved weight velocity and lean body mass. Pulmonary function trended towards improvement. ADEs: No changes in glucose parameters.
Petrowsky, 2006[45] N=1	Case Report	Poor	Norditropin 2.2 mg/day	3 years	18 year old female with CF having prior lung transplantation and developed growth retardation.	Developed pancreatic cancer, underwent pancreatic transplant. Developed diabetes mellitus. Died of metastases to liver.
Stalvey, 2008[46] N=2	Case Report	Poor	Product NR 0.3-0.35 mg/kg/wk	7-10 months	5 year old female and 5 month old male with CF and liver disease.	5 year old female: Improved height and weight. Increased levels of IGF-1 and IGFBP-3. Liver transaminases normalized. 5 month old male: Improved height, weight, muscle mass, and tone. Transitioned from total parenteral nutrition to enteral feeds.

Legend: ADE=adverse drug event; CF=cystic fibrosis; FEV_1=forced expiratory volume in one minute; IGF-I=insulin-like growth factor-I; IGFBP-3=insulin-like growth factor binding protein-3; N=sample size; NR=not reported; rhGH=recombinant human growth hormone; SD=standard deviation ULN=upper limit of normal

Table 8. Baseline characteristics of patients in single-arm observational studies evaluating rhGH

Study, year	Age Range or Mean Age (SD)	Male (%)	Height (cm)	Height Z-score	Weight (kg)	Weight Z-score	FVC (L)	%FVC	FEV_1 (L)	$\%FEV_1$
Mullis, 1991[39] N=1	9	0	99	-5.8	16.6	-4.8	-	-	-	-
Sackey, 1995[40] N=7	7.9 (2.8)	5 (72%)	-	-0.37 (1)	-	-	-	-	-	74 (2.16)
Huseman, 1996[41] N=9	5.5 to 9.8	6 (67%)	-	-1.3 (0.69)	-	-	1.33 (0.32)	85.6 (17.9)	1.16 (0.3)	83 (25)
Hardin, 1997[42] N=24	10.3 (4.3)	16 (67%)	-	-3.2 (1)	-	-	-	-	-	-
Alemzadeh, 1998[43] N=5	3.2 (1.9)	3 (60%)	-	-2.8 (0.60)	-	-1.95 (0.51)	-	-	-	-
Hardin, 1998[44] N=9	5.4 to 12.2	3 (33%)	-	-1.86 (0.7)	-	-1.62 (0.55)	-	-	-	-
Petrowsky, 2006[45] N=1	18	-	-	-	-	-	-	-	-	-
Stalvey, 2008[46] N=2	5	0	-	-4	-	-3.9	-	-	-	-
	0.4	1	62.5	-1.3	6.04	-1.8	-	-	-	...

Legend: - =not reported; $\%FEV_1$=percent predicted forced expiratory volume in one second; FEV_1=forced expiratory volume in one second; %FVC=percent predicted forced vital capacity; FVC=forced vital capacity; N=sample size; SD=standard deviation

Table 9. Change from baseline in pulmonary outcomes in controlled trials evaluating rhGH

Study, year	Group	Dose/wk (mg/kg)	N	FVC (L)	%FVC	FEV_1	$\%FEV_1$ (L)	FEV_1 Z-score
Hardin, 2001[23, 24]	rhGH	0.3	10	-	25 (21)[d]	-	-1 (15.6)[d]	-
	No treatment	NA	9	-	-5 (17)[d]	-	-5 (17.4)[d]	-
Hutler, 2002[25108a]	rhGH	0.27 to 0.35	6			0.0 (0.1)		-
	No treatment	NA	4			-0.0 (0.2)		-
Schibler, 2003[26]	rhGH	0.35	10	-	4 (11)	-	0.8 (12.3)	-
	No treatment	NA	9	-	0 (8)	-	-0.4 (12.3)	-
Darmaun, 2004[29b]	rhGH	0.3	9	-	-	-	-	-
	rhGH+GLN	0.3/0.7[c]	9	-	-	-	-	-
	GLN	0.7[c]	9	-	-	-	-	-
Hardin, 2005a[32]	rhGH	0.3	16	-	-	-	-	-
	No treatment	0	16	-	-	-	-	-
Hardin, 2005b[33]	rhGH	0.3 to 0.35	13	0.8 (1.0)[d]	6 (2)	0.7 (0.8)[d]	-	-
	No treatment	NA	12	-0.2 (0.7)[d]	-7 (2)	0.06 (0.7)[d]	-	-
Hardin, 2005c[34]	rhGH	0.3	9	0.9 (0.8)[e]	3 (19)[d]	0.6 (0.8)[e]	2 (19.5)[d]	-
	No treatment	NA	9	0 (0.6)[e]	-2 (17)[d]	0 (0.6)[e]	0 (22)[d]	-
Hardin, 2006[15]	rhGH	0.3	30	0.3 (0.4)	-	0.2 (0.4)	-	-
	No Treatment	NA	27	-0.1 (0.4)	-	0.0 (0.4)	-	-
Schnabel, 2007[4]	Higher dose	0.49	20	-	6 (11)	-	4.3 (13.4)	-0.04 (0.3)
	Lower dose	0.273	22	-	3 (13)	-	3.5 (12.3)	-0.03 (0.32)
	Placebo	NA	21	-	-1 (15)	-	1.0 (23)	-0.03 (0.44)
Stalvey, 2008[38]	rhGH	0.3	29	-	-	-	-	-
	No treatment	NA	27	-	-	-	-	-

Legend: All values given as mean (standard deviation); - =not reported; $\%FEV_1$=percent predicted forced expiratory volume in one second; FEV_1=forced expiratory volume in one second; %FVC=percent predicted forced vital capacity; FVC=forced vital capacity; GLN=glutamine; N=sample size; NA=not applicable; rhGH=recombinant human growth hormone

[a]Hutler et al was a crossover study which published values for each period separately – all values presented are change from baseline to the end of the first period

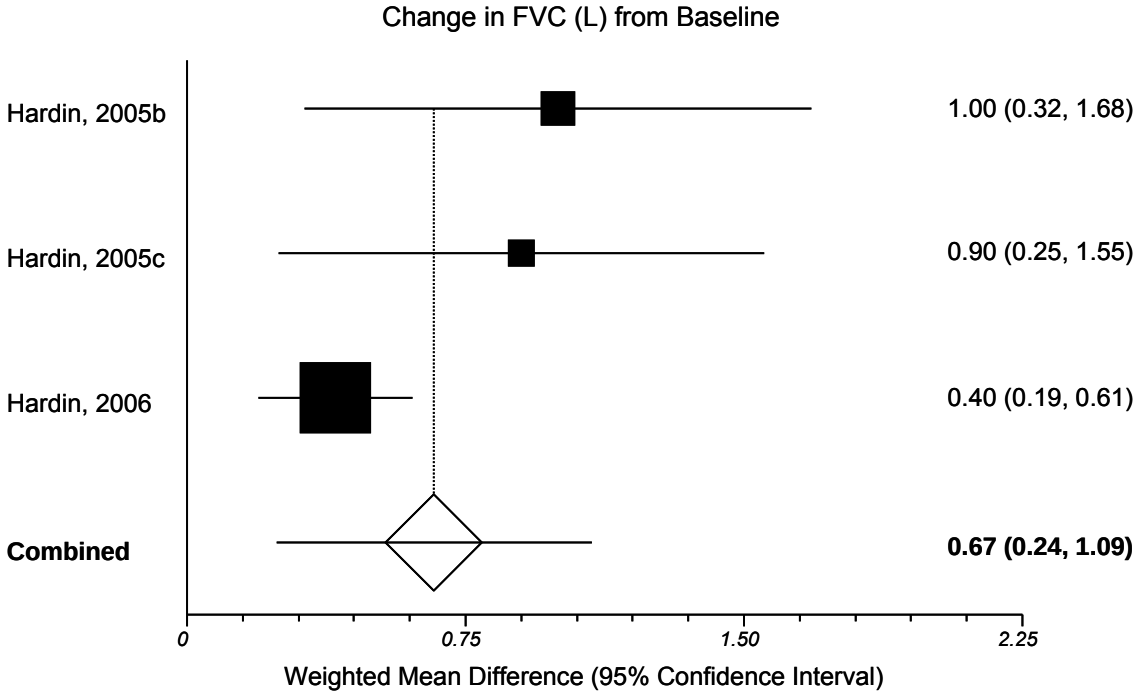
[b]Darmaun et al was a crossover study – all values presented are end values for that treatment period

[c]Glutamine dosing is 0.7 g/kg per day

[d]Change from baseline calculated from published baseline and final values

[e]Change from baseline calculated from extrapolated values from figure

Figure 5. KQ1 Pulmonary Function - Meta-analysis of change from baseline in absolute FVC in CF patients treated with rhGH



I^2 = 55%
Egger's p-value = NA

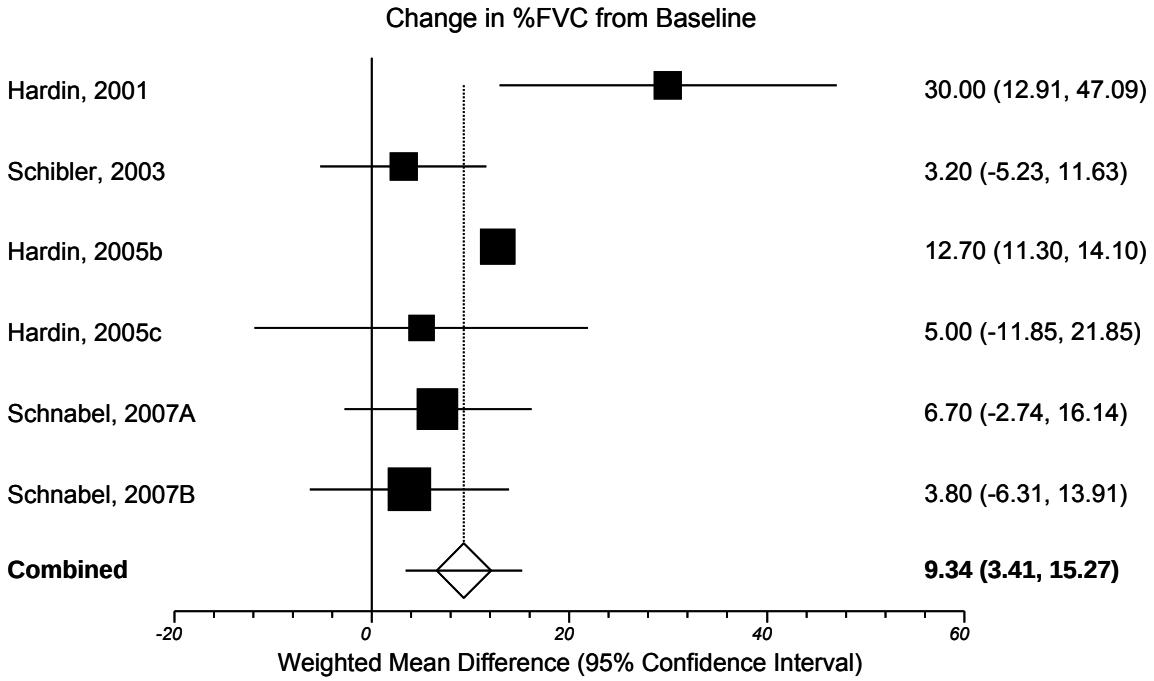
Legend: CF=cystic fibrosis; FVC=forced vital capacity; rhGH=recombinant human growth hormone

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Lowercase letters following a study year represent unique trials conducted within the same year.

Narrative: This figure depicts the meta-analysis of change from baseline in absolute FVC. The first trial by Hardin and colleagues in 2005 provided a mean difference of 1.00 L with 95 percent confidence interval of 0.32 to 1.68 L. The second trial by Hardin and colleagues, also in 2005, provided a mean difference of 0.90 L with a 95 percent confidence interval of 0.25 to 1.55 L. The third trial by Hardin and colleagues in 2006 provided a mean difference of 0.40 L with a 95 percent confidence interval of 0.19 to 0.61 L. The combined effect of the three studies showed a weighted mean difference of 0.67 L with a 95 percent confidence interval of 0.24 to 1.09 L. The I-squared value was 55 percent and the Egger's p-value was not applicable.

Figure 6. KQ1 Pulmonary Function - Meta-analysis of change from baseline in percent predicted FVC in CF patients treated with rhGH



I^2 = 62.9%
Egger's p-value = 0.39

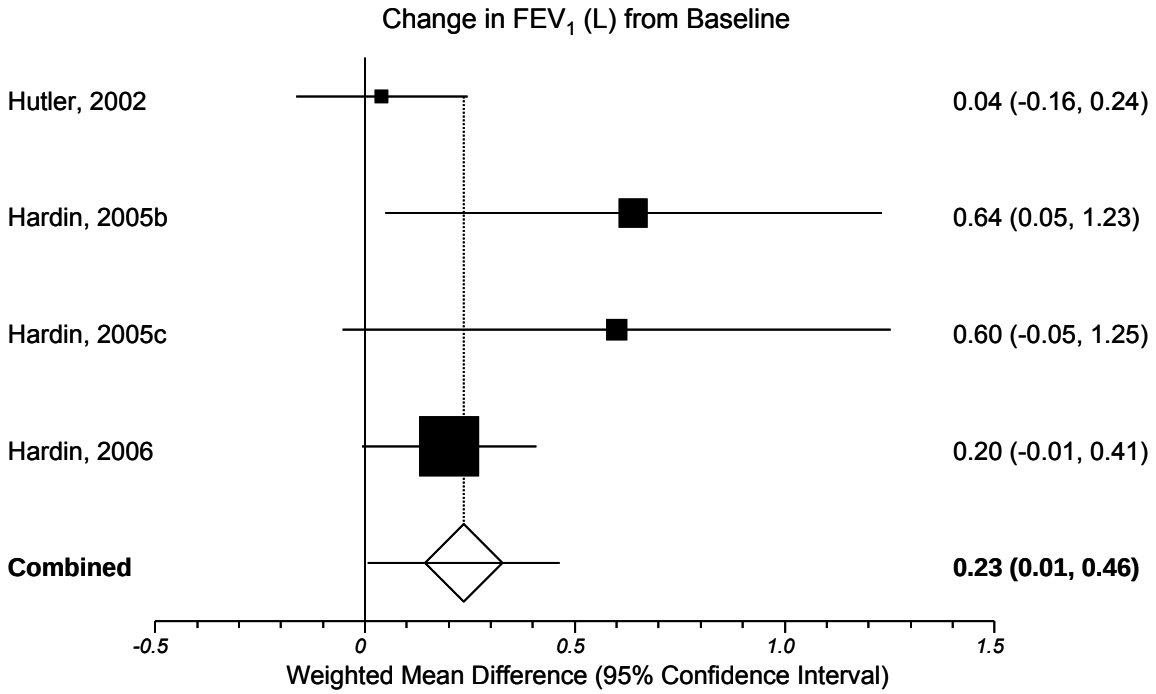
Legend: CF=cystic fibrosis; %FVC=percent predicted forced vital capacity; rhGH=recombinant human growth hormone

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Lowercase letters following a study year represent unique trials conducted within the same year. Uppercase letters represent study arms within the same trial.

Narrative: This figure depicts the meta-analysis of change from baseline in percent predicted FVC. The first trial by Hardin and colleagues in 2001 provided a mean difference of 30.00 percent with 95 percent confidence interval of 12.91 to 47.09. The second trial by Schibler and colleagues in 2003 provided a mean difference of 3.20 percent with a 95 percent confidence interval of -5.23 to 11.63. The third trial by Hardin and colleagues in 2005 provided a mean difference of 12.70 percent with a 95 percent confidence interval of 11.30 to 14.10. The fourth trial by Hardin and colleagues, also in 2005, provided a mean difference of 5.00 percent with a 95 percent confidence interval of -11.85 to 21.85. The fifth trial by Schnabel and colleagues in 2007 provided a mean difference of 6.70 percent with a 95 percent confidence interval of -2.74 to 16.14 with the higher dose of rhGH and a mean difference of 3.80 percent with a 95 percent confidence interval of -6.31 to 13.91 with the lower dose of rhGH. The combined effect of the studies showed a weighted mean difference of 9.34 percent with a 95 percent confidence interval of 3.41 to 15.27. The I-squared value was 62.9 percent and the Egger's p-value was 0.39.

Figure 7. KQ1 Pulmonary Function - Meta-analysis of change from baseline in absolute FEV_1 in CF patients treated with rhGH



I^2 = 43.2%
Egger's p-value = 0.11

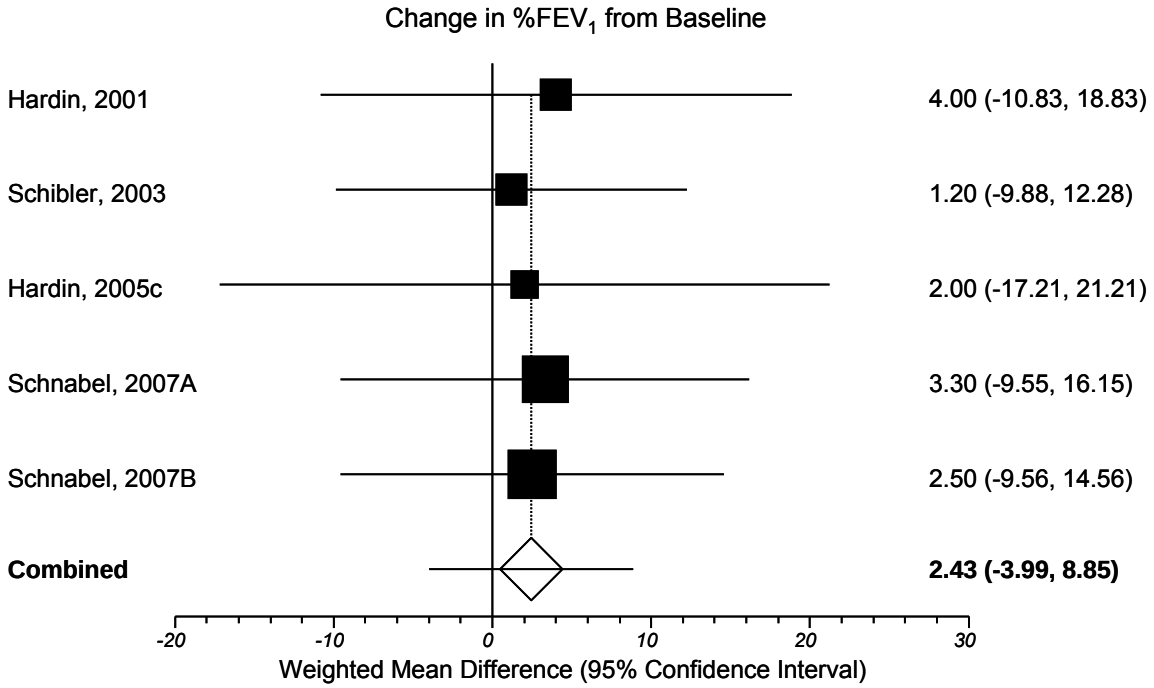
Legend: CF=cystic fibrosis; FEV_1=forced expiratory volume in one second; rhGH=recombinant human growth hormone

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Lowercase letters following a study year represent unique trials conducted within the same year.

Narrative: This figure depicts the meta-analysis of change from baseline in absolute FEV_1. The first trial by Hutler and colleagues in 2002 provided a mean difference of 0.04 L with 95 percent confidence interval of -0.16 to 0.24 L. The second trial by Hardin and colleagues in 2005 provided a mean difference of 0.64 L with a 95 percent confidence interval of 0.05 to 1.23 L. The third trial by Hardin and colleagues, also in 2005, provided a mean difference of 0.60 L with a 95 percent confidence interval of -0.05 to 1.25 L. The fourth trial by Hardin and colleagues in 2006 provided a mean difference of 0.20 L with a 95 percent confidence interval of -0.01 to 0.41. The combined effect of the four studies showed a weighted mean difference of 0.23 L with a 95 percent confidence interval of 0.01 to 0.46 L. The I-squared value was 43.2 percent and the Egger's p-value was 0.11.

Figure 8. KQ1 Pulmonary Function - Meta-analysis of change from baseline in percent predicted FEV_1 in CF patients treated with rhGH



I^2 = 0%
Egger's p-value = 0.56

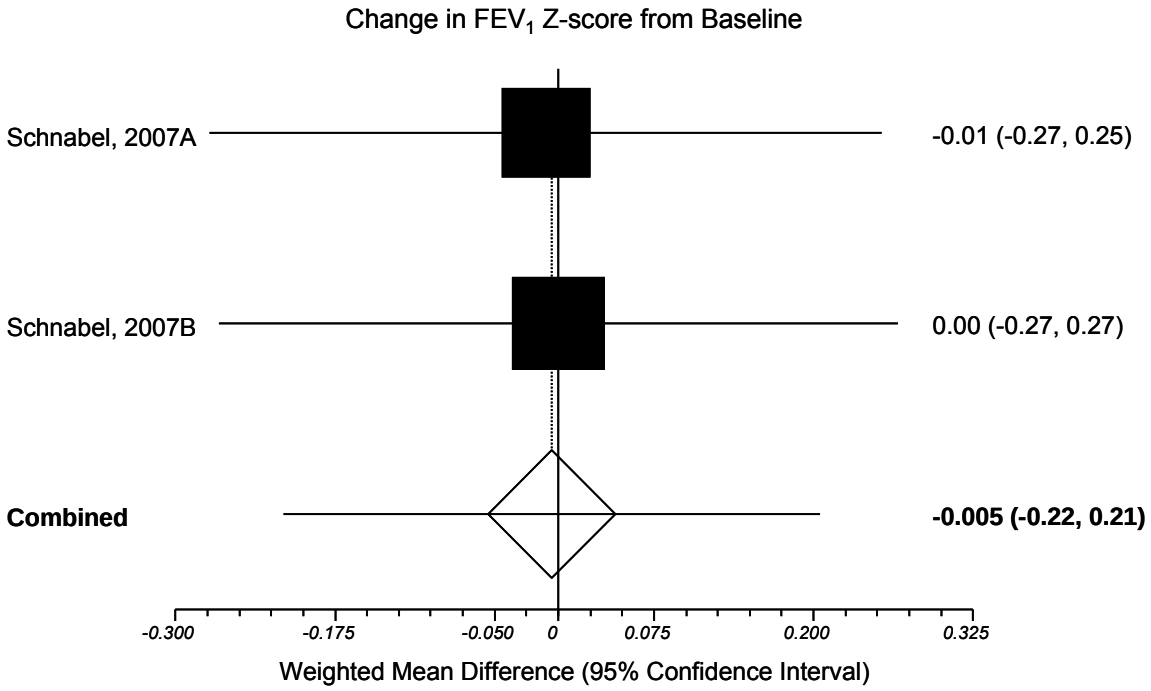
Legend: CF=cystic fibrosis; $\%FEV_1$=percent predicted forced expiratory volume in one second; rhGH=recombinant human growth hormone

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Lowercase letters following a study year represent unique trials conducted within the same year. Uppercase letters represent study arms within the same trial.

Narrative: This figure depicts the meta-analysis of change from baseline in percent predicted FEV_1. The first trial by Hardin and colleagues in 2001 provided a mean difference of 4.00 percent with 95 percent confidence interval of -10.83 to 18.83. The second trial by Schibler and colleagues in 2003 provided a mean difference of 1.20 percent with a 95 percent confidence interval of -9.88 to 12.28. The third trial by Hardin and colleagues in 2005 provided a mean difference of 2.00 percent with a 95 percent confidence interval of -17.21 to 21.21. The fourth trial by Schnabel and colleagues in 2007 provided a mean difference of 3.30 percent with a 95 percent confidence interval of -9.55 to 16.15 with the higher dose of rhGH and a mean difference of 2.50 percent with a 95 percent confidence interval of -9.56 to 14.56 with the lower dose of rhGH. The combined effect of the studies showed a weighted mean difference of 2.43 percent with a 95 percent confidence interval of -3.99 to 8.85. The I-squared value was 0 percent and the Egger's p-value was 0.56.

Figure 9. KQ1 Pulmonary Function - Meta-analysis of change from baseline in FEV_1 Z-score in CF patients treated with rhGH



I^2 = NA
Egger's p-value = NA

Legend: CF=cystic fibrosis; FEV_1=forced expiratory volume in one second; rhGH=recombinant human growth hormone

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Uppercase letters represent study arms within the same trial.

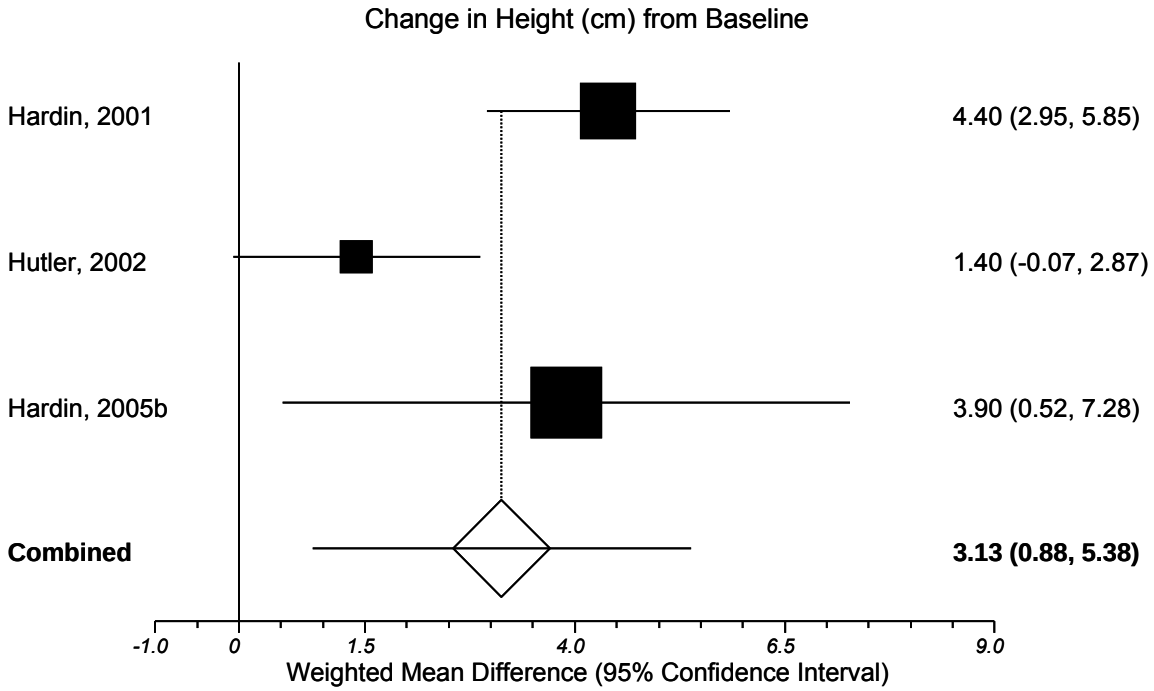
Narrative: This figure depicts the meta-analysis of change from baseline in FEV_1 Z-score. The trial by Schnabel and colleagues in 2007 provided a mean difference of -0.01 with 95 percent confidence interval of -0.27 to 0.25 with the higher dose of rhGH and a mean difference of 0.00 with a 95 percent confidence interval of -0.27 to 0.27 with the lower dose group. The combined effect of the two trial arms showed a weighted mean difference of -0.005 with a 95 percent confidence interval of -0.22 to 0.21. The I-squared value was not applicable and the Egger's p-value was not applicable.

Table 10. Change from baseline in height outcomes in controlled trials evaluating rhGH

Study, year	Group	Dose/wk (mg/kg)	N	Height (cm)	Height velocity (cm/yr)	Height Z-score	Height percentile
Hardin, 2001[23, 24]	rhGH	0.3	10	8.2 (2.0)	4.5 (2.0)[e]	0.23 (1.21)[d]	12.5 (1.3)[d]
	No treatment	NA	9	3.8 (1.0)	0 (1.0)[e]	-0.27 (0.56)[d]	-
Hutler, 2002[25108a]	rhGH	0.27 to 0.35	6	4.1 (1.2)	-	-	-
	No treatment	NA	4	2.7 (1.1)	-	-	-
Schibler, 2003[26]	rhGH	0.35	10	-	-	-	-
	No treatment	NA	9	-	-	-	-
Darmaun, 2004[29b]	rhGH	0.3	9	-	-	-	-
	rhGH+GLN	0.3/0.7[c]	9	-	-	-	-
	GLN	0.7[c]	9	-	-	-	-
Hardin, 2005a[32]	rhGH	0.3	16	-	-	-	-
	No treatment	0	16	-	-	-	-
Hardin, 2005b[33]	rhGH	0.3 to 0.35	13	8.9 (4.4)[d]	-	-	-
	No treatment	NA	12	5.0 (4.2)[d]	-	-	-
Hardin, 2005c[34]	rhGH	0.3	9	-	-	0.63 (1.02)[d]	-
	No treatment	NA	9	-	-	-0.08 (0.99)[d]	-
Hardin, 2006[15]	rhGH	0.3	30	-	8.0 (1.9)	-	-
	No Treatment	NA	27	-	5.0 (1.5)	-	-
Schnabel, 2007[4]	Higher dose	0.49	20	-	6.8 (4.3)	-	-
	Lower dose	0.273	22	-	5.6 (2.9)	-	-
	Placebo	NA	21	-	3.5 (2.3)	-	-
Stalvey, 2008[38]	rhGH	0.3	29	-	-	0.5 (0.4)	-
	No treatment	NA	27	-	-	0.0 (0.2)	-

Legend: All values given as mean (standard deviation); - =not reported; GLN=glutamine; N=sample size; rhGH=recombinant human growth hormone
[a]Hutler et al was a crossover study which published values for each period separately – all values presented are change from baseline to the end of the first period
[b]Darmaun et al was a crossover study – all values presented are end values for that treatment period
[c]Glutamine dosing is 0.7 g/kg per day
[d]Change from baseline calculated from published baseline and final values
[e]Change from baseline calculated from values extrapolated from figure

Figure 10. KQ1 Anthropometrics - Meta-analysis of change from baseline in height in CF patients treated with rhGH



I^2 = 77.3%
Egger's p-value = NA

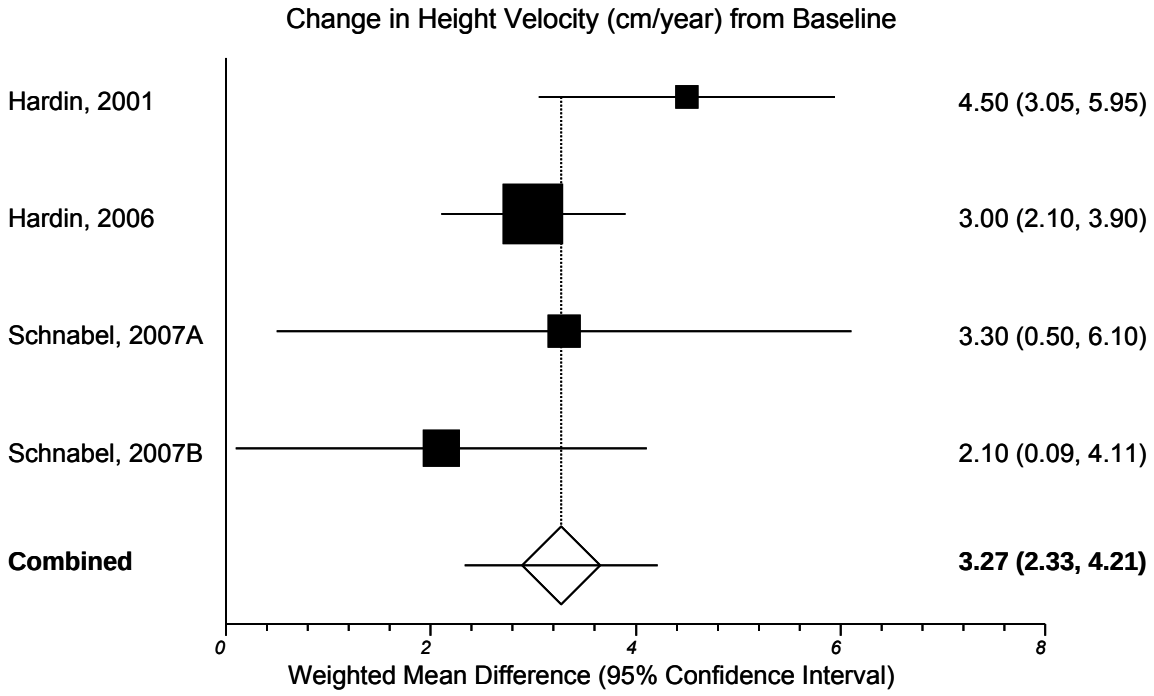
Legend: CF=cystic fibrosis; rhGH=recombinant human growth hormone

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Lowercase letters following a study year represent unique trials conducted within the same year.

Narrative: This figure depicts the meta-analysis of change from baseline in height. The first trial by Hardin and colleagues in 2001 provided a mean difference of 4.40 cm with 95 percent confidence interval of 2.95 to 5.85 cm. The second trial by Hutler and colleagues in 2002 provided a mean difference of 1.40 cm with a 95 percent confidence interval of -0.07 to 2.87 cm. The third trial by Hardin and colleagues in 2005 provided a mean difference of 3.90 cm with a 95 percent confidence interval of 0.52 to 7.28 cm. The combined effect of the three studies showed a mean difference of 3.13 cm with a 95 percent confidence interval of 0.88 to 5.38 cm. The I-squared value was 77.3 percent and the Egger's p-value was not applicable.

Figure 11. KQ1 Anthropometrics - Meta-analysis of change from baseline in height velocity in CF patients treated with rhGH



I^2 = 38.2%
Egger's p-value = 0.97

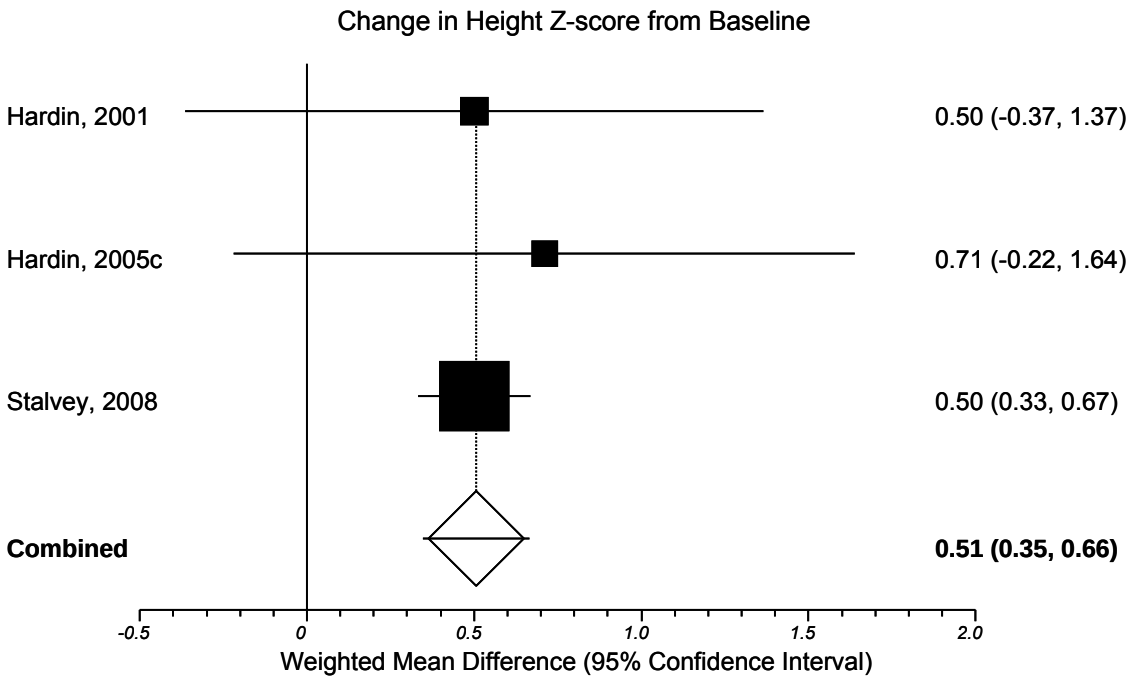
Legend: CF=cystic fibrosis; rhGH=recombinant human growth hormone

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Uppercase letters represent study arms within the same trial.

Narrative: This figure depicts the meta-analysis of change from baseline in height velocity. The first trial by Hardin and colleagues in 2001 provided a mean difference of 4.50 cm/year with 95 percent confidence interval of 3.05 to 5.95 cm/year. The second trial by Hardin and colleagues in 2006 provided a mean difference of 3.00 cm/year with a 95 percent confidence interval of 2.10 to 3.90 cm/year. The third trial by Schnabel and colleagues in 2007 provided a mean difference of 3.30 cm/year with a 95 percent confidence interval of 0.50 to 6.10 cm/year with the higher dose of rhGH and a mean difference of 2.10 cm/year with a 95 percent confidence interval of 0.09 to 4.11 cm/year with the lower dose of rhGH. The combined effect of the studies showed a weighted mean difference of 3.27 cm/year with a 95 percent confidence interval of 2.33 to 4.21 cm/year. The I-squared value was 38.2 percent and the Egger's p-value was 0.97.

Figure 12. KQ1 Anthropometrics - Meta-analysis of change from baseline in height Z-score in CF patients treated with rhGH



I^2 = 0%
Egger's p-value = NA

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

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Lowercase letters following a study year represent unique trials conducted within the same year.

Narrative: This figure depicts the meta-analysis of change from baseline in height Z-score. The first trial by Hardin and colleagues in 2001 provided a mean difference of 0.50 with 95 percent confidence interval of -0.37 to 1.37. The second trial by Hardin and colleagues in 2005 provided a mean difference of 0.71 with a 95 percent confidence interval of -0.22 to 1.64. The third trial by Stalvey and colleagues in 2008 provided a mean difference of 0.50 with a 95 percent confidence interval of 0.33 to 0.67. The combined effect of the studies showed a weighted mean difference of 0.51 with a 95 percent confidence interval of 0.35 to 0.66. The I-squared value was 0 percent and the Egger's p-value was not applicable.

Table 11. Change from baseline in weight outcomes in controlled trials evaluating rhGH

Study, year	Group	Dose/wk (mg/kg)	N	Weight (kg)	Weight velocity (kg/yr)	Weight Z-score	Weight percentile	BMI (kg/m^2)	BMI Z-score	%IBW	LBM (kg)
Hardin, 2001[23, 24]	rhGH	0.3	10	5.2 (1.7)	2.7 (1.0)[e]	0.46 (0.69)[d]	5 (1.4)[d]	-	-	3 (5)[d]	4.9 (1.2)
	No treatment	NA	9	2.4 (1.7)	0.4 (1.0)[e]	-0.26 (0.44)[d]	-	-	-	-7 (4.4)[d]	2.2 (1.4)
Hutler, 2002[25108a]	rhGH	0.27 to 0.35	6	1.7 (1.9)	-	-	-	-	-	-	3.1 (0.3)
	No treatment	NA	4	0.7 (1.0)	-	-	-	-	-	-	0.9 (1.1)
Schibler, 2003[26]	rhGH	0.35	10	-	-	-0.02 (0.32)	-	-	-	-	4.1 (2.4)
	No treatment	NA	9	-	-	-0.03 (0.39)	-	-	-	-	1.6 (2.0)
Darmaun, 2004[29b]	rhGH	0.3	9	-	-	-	-	-	-	-	22.3 (5.7)
	rhGH+GLN	0.3/0.7[c]	9	-	-	-	-	-	-	-	22.4 (4.2)
	GLN	0.7[c]	9	-	-	-	-	-	-	-	21.4 (4.5)
Hardin, 2005a[32]	rhGH	0.3	16	-	-	0.49 (1.0)	-	-	-	-	5.2 (2.7)
	No treatment	0	16	-	-	-0.17 (1.01)	-	-	-	-	1.7 (1.8)
Hardin, 2005b[33]	rhGH	0.3 to 0.35	13	8.6 (5.0)[d]	-	-	-	2.5 (0.5)[e]	-	13.6 (5.1)	-
	No treatment	NA	12	3.1 (4.5)[d]	-	-	-	0.0 (0.6)[e]	-	-2.1 (8.4)	-
Hardin, 2005c[34]	rhGH	0.3	9	-	-	1.28 (2.14)[d]	-	1.2 (0.8)	-	-	3.8 (1.0)
	No treatment	NA	9	-	-	-0.06 (1.21)[d]	-	-0.4 (0.6)	-	-	2.4 (1.1)
Hardin, 2006[15]	rhGH	0.3	30	-	4.2 (1.9)	-	-	-	-	-	3.9 (2.0)
	No Treatment	NA	27	-	2.2 (1.5)	-	-	-	-	-	2.1 (1.1)
Schnabel, 2007[4]	Higher dose	0.49	20	2.2 (2.3)	-	-	-	-	0.1 (0.6)	-	2.3 (2.5)
	Lower dose	0.273	22	2.4 (1.9)	-	-	-	-	0 (0.6)	-	2.5 (2.4)
	Placebo	NA	21	1.4 (1.7)	-	-	-	-	0.1 (0.4)	-	1.5 (2.3)
Stalvey, 2008[38]	rhGH	0.3	29	3.8 (1.8)	-	-	-	-	-	-	3.8 (1.8)
	No treatment	NA	27	2.8 (1.5)	-	-	-	-	-	-	2.1 (1.4)

Legend: All values given as mean (standard deviation); - =not reported; BMI=body mass index; GLN=glutamine; IBW=ideal body weight; LBM=lean body mass; N=sample size; NA=not applicable; rhGH=recombinant human growth hormone

[a]Hutler et al was a crossover study which published values for each period separately – all values presented are change from baseline to the end of the first period

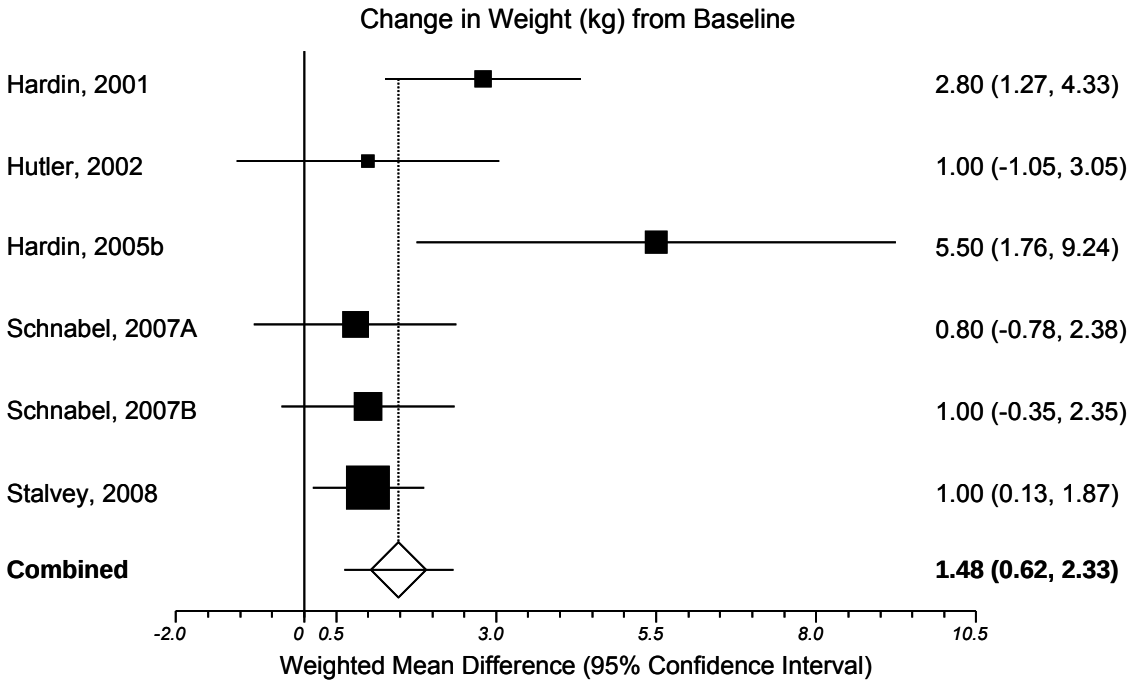
[b]Darmaun et al was a crossover study – all values presented are end values for that treatment period

[c]Glutamine dosing is 0.7 g/kg per day

[d]Change from baseline calculated from published baseline and final values

[e]Change from baseline calculated from extrapolated values from figure

Figure 13. KQ1 Anthropometrics - Meta-analysis of change from baseline in weight in CF patients treated with rhGH



I^2 = 49%
Egger's p-value = 0.18

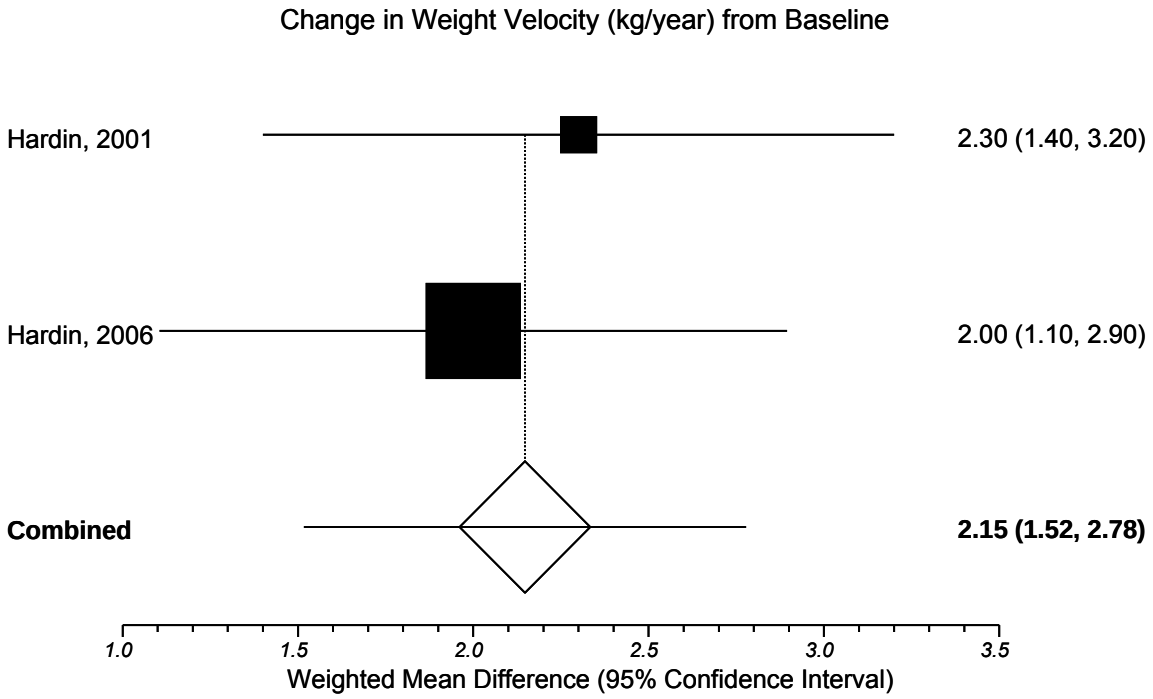
Legend: CF=cystic fibrosis; rhGH=recombinant human growth hormone

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Lowercase letters following a study year represent unique trials conducted within the same year. Uppercase letters represent study arms within the same trial.

Narrative: This figure depicts the meta-analysis of change from baseline in weight. The first trial by Hardin and colleagues in 2001 provided a mean difference of 2.80 kg with 95 percent confidence interval of 1.27 to 4.33 kg. The second trial by Hutler and colleagues in 2002 provided a mean difference of 1.00 kg with a 95 percent confidence interval of -1.05 to 3.05 kg. The third trial by Hardin and colleagues in 2005 provided a mean difference of 5.50 kg with a 95 percent confidence interval of 1.76 to 9.24 kg. The fourth trial by Schnabel and colleagues in 2007 provided a mean difference of 0.80 kg with a 95 percent confidence interval of -0.78 to 2.38 kg with the higher dose of rhGH and a mean difference of 1.00 kg with a 95 percent confidence interval of -0.35 to 2.35 kg with the lower dose of rhGH. The fifth trial by Stalvey and colleagues in 2008 provided a mean difference of 1.00 kg with a 95 percent confidence interval of 0.13 to 1.87 kg. The combined effect of the studies showed a weighted mean difference of 1.48 kg with a 95 percent confidence interval of 0.62 to 2.33 kg. The I-squared value was 49 percent and the Egger's p-value was 0.18.

Figure 14. KQ1 Anthropometrics - Meta-analysis of change from baseline in weight velocity in CF patients treated with rhGH



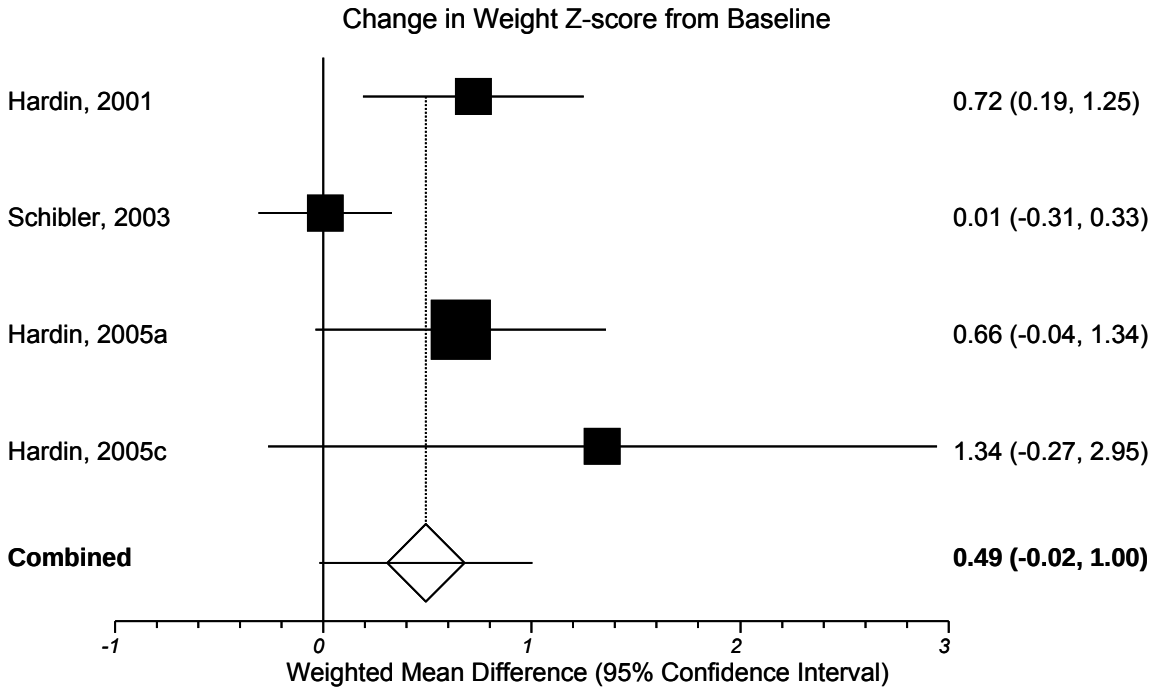
I^2 = NA
Egger's p-value = NA

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

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Narrative: This figure depicts the meta-analysis of change from baseline in weight velocity. The first trial by Hardin and colleagues in 2001 provided a mean difference of 2.30 kg/year with 95 percent confidence interval of 1.40 to 3.20 kg/year. The second trial by Hardin and colleagues in 2006 provided a mean difference of 2.00 kg/year with a 95 percent confidence interval of 1.10 to 2.90 kg/year. The combined effect of the studies showed a weighted mean difference of 2.15 kg/year with a 95 percent confidence interval of 1.52 to 2.78 kg/year. The I-squared value was not applicable and the Egger's p-value was not applicable.

Figure 15. KQ1 Anthropometrics - Meta-analysis of change from baseline in weight Z-score in CF patients treated with rhGH



I^2 = 63.8%
Egger's p-value = 0.15

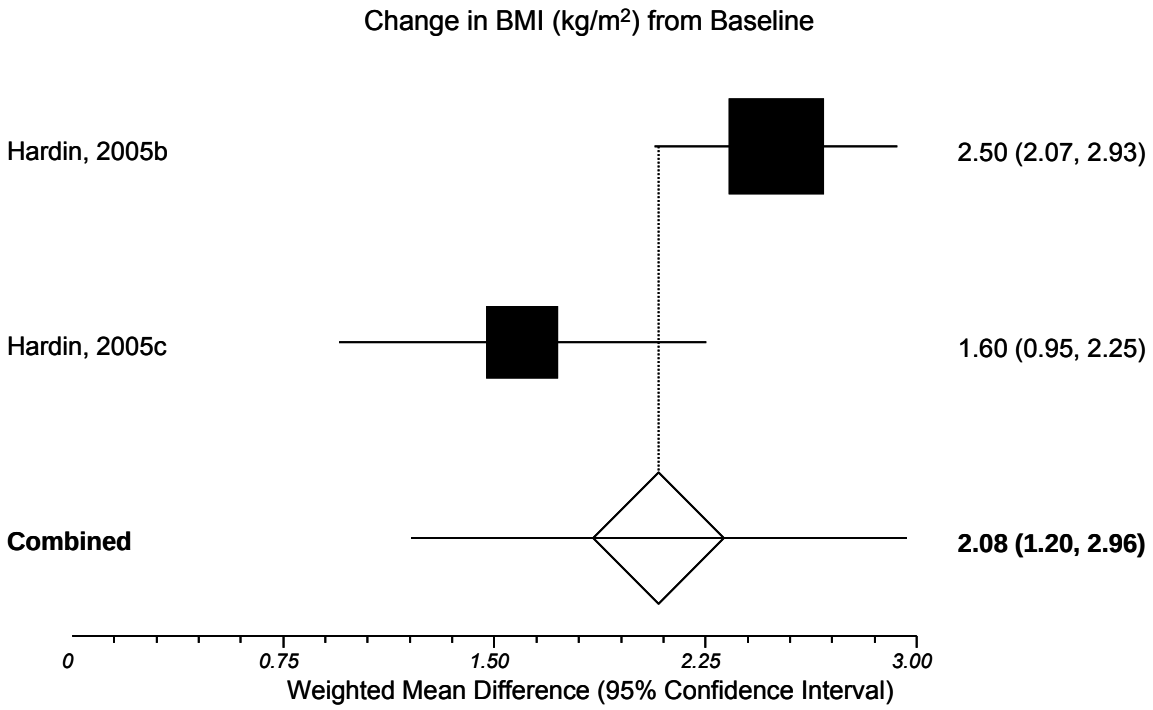
Legend: CF=cystic fibrosis; rhGH=recombinant human growth hormone

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Lowercase letters following a study year represent unique trials conducted within the same year.

Narrative: This figure depicts the meta-analysis of change from baseline in weight Z-score. The first trial by Hardin and colleagues in 2001 provided a mean difference of 0.72 with 95 percent confidence interval of 0.19 to 1.25. The second trial by Schibler and colleagues in 2003 provided a mean difference of 0.01 with a 95 percent confidence interval of -0.31 to 0.33. The third trial by Hardin and colleagues in 2005 provided a mean difference of 0.66 with a 95 percent confidence interval of -0.04 to 1.34. The fourth trial by Hardin and colleagues, also in 2005, provided a mean difference of 1.34 with a 95 percent confidence interval of -0.27 to 2.95. The combined effect of the studies showed a weighted mean difference of 0.49 with a 95 percent confidence interval of -0.02 to 1.00. The I-squared value was 63.8 percent and the Egger's p-value was 0.15.

Figure 16. KQ1 Anthropometrics - Meta-analysis of change from baseline in BMI in CF patients treated with rhGH



I^2 = NA
Egger's p-value = NA

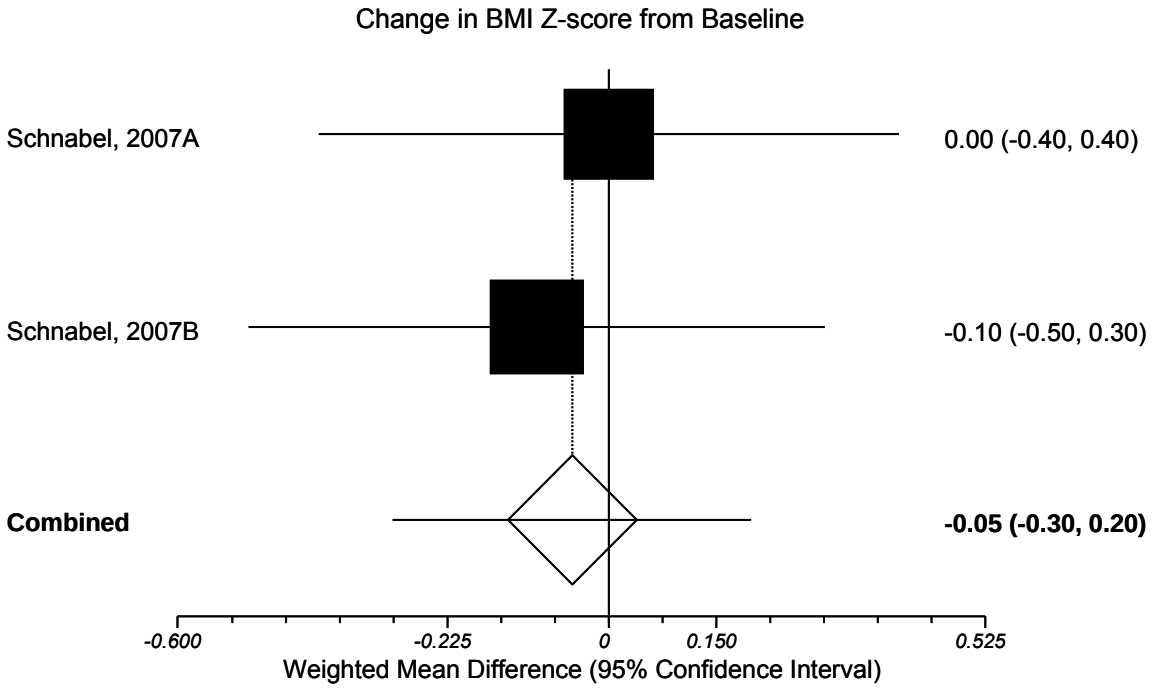
Legend: BMI=body mass index; CF=cystic fibrosis; rhGH=recombinant human growth hormone

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Lowercase letters following a study year represent unique trials conducted within the same year.

Narrative: This figure depicts the meta-analysis of change from baseline in BMI. The first trial by Hardin and colleagues in 2005 provided a mean difference of 2.50 kg/m^2 with 95 percent confidence interval of 2.07 to 2.93 kg/m^2. The second trial by Hardin and colleagues, also in 2005, provided a mean difference of 1.60 kg/m^2 with a 95 percent confidence interval of 0.95 to 2.25 kg/m^2. The combined effect of the studies showed a weighted mean difference of 2.08 kg/m^2 with a 95 percent confidence interval of 1.20 to 2.96 kg/m^2. The I-squared value was not applicable and the Egger's p-value was not applicable.

Figure 17. KQ1 Anthropometrics - Meta-analysis of change from baseline in BMI Z-score in CF patients treated with rhGH



I^2 = NA
Egger's p-value = NA

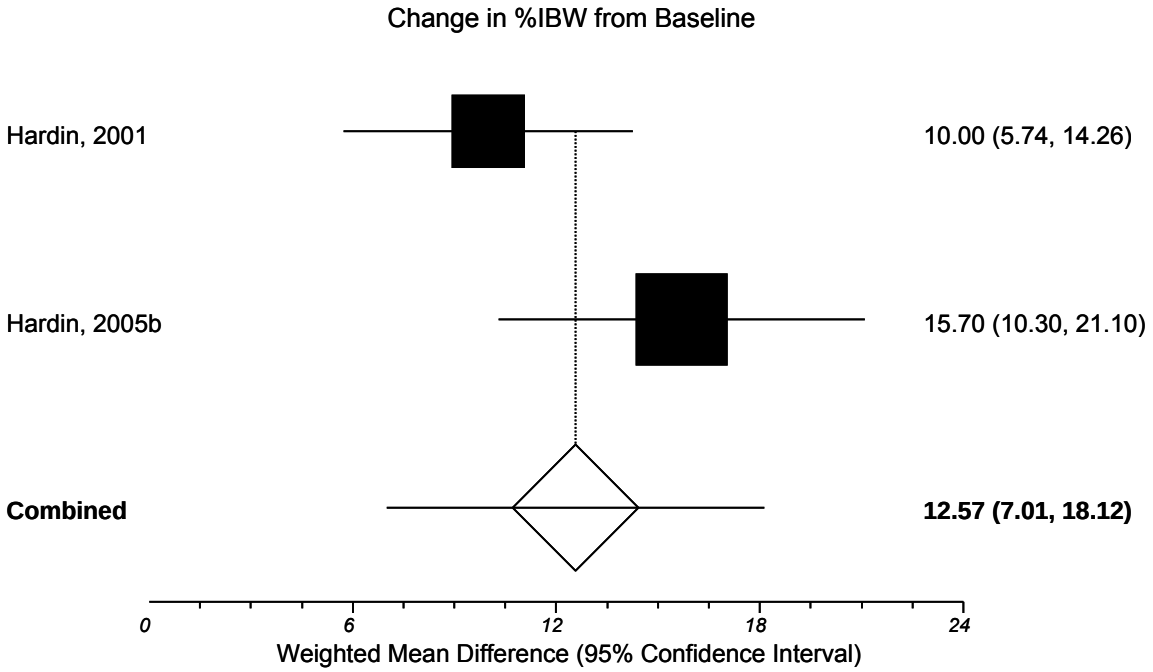
Legend: BMI=body mass index; CF=cystic fibrosis; rhGH=recombinant human growth hormone

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Uppercase letters represent study arms within the same trial.

Narrative: This figure depicts the meta-analysis of change from baseline in BMI Z-score. The trial by Schnabel and colleagues in 2007 provided a mean difference of 0.00 with 95 percent confidence interval of -0.40 to 0.40 with the higher dose of rhGH and a mean difference of -0.10 with a 95 percent confidence interval of -0.50 to 0.30 with the lower dose of rhgh. The combined effect of the two trial arms showed a weighted mean difference of -0.05 with a 95 percent confidence interval of -0.30 to 0.20. The I-squared value was not applicable and the Egger's p-value was not applicable.

Figure 18. KQ1 Anthropometrics - Meta-Analysis of change from baseline in percent IBW in CF patients treated with rhGH



I^2 = NA
Egger's p-value = NA

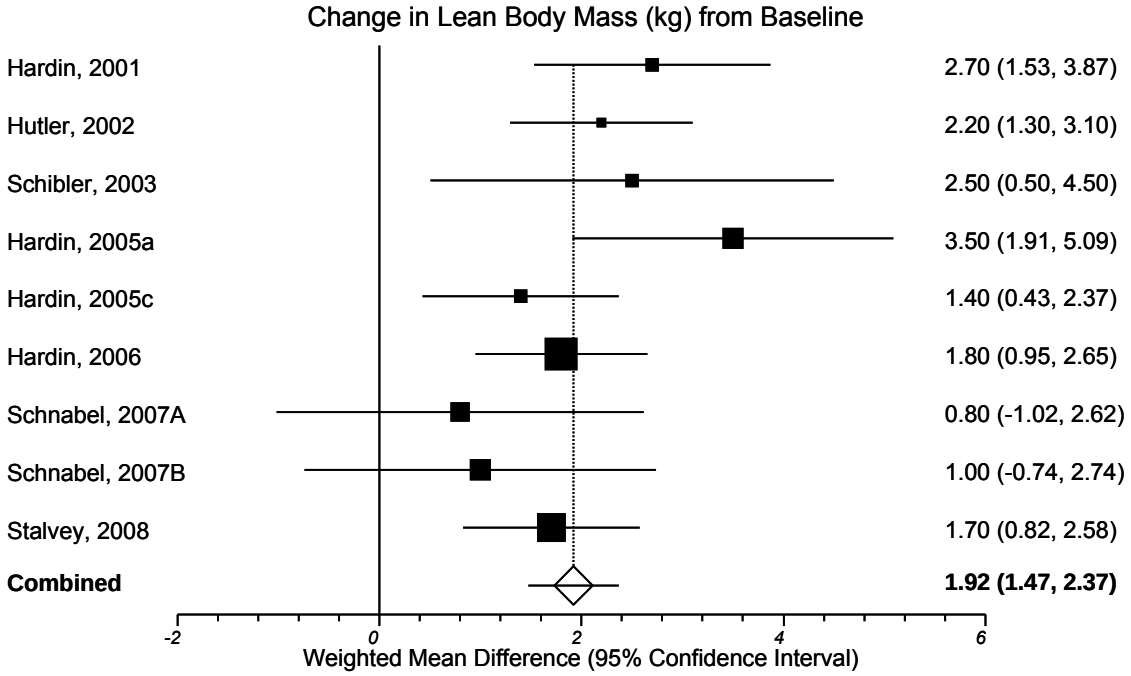
Legend: CF=cystic fibrosis; %IBW=percent ideal body weight; rhGH=recombinant human growth hormone

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Lowercase letters following a study year represent unique trials conducted within the same year.

Narrative: This figure depicts the meta-analysis of change from baseline in percent IBW. The first trial by Hardin and colleagues in 2001 provided a mean difference of 10.00 percent with 95 percent confidence interval of 5.74 to 14.26. The second trial by Hardin and colleagues in 2005 provided a mean difference of 15.70 percent with a 95 percent confidence interval of 10.30 to 21.10. The combined effect of the studies showed a weighted mean difference of 12.57 percent with a 95 percent confidence interval of 7.01 to 18.12. The I-squared value was not applicable and the Egger's p-value was not applicable.

Figure 19. KQ1 Anthropometrics - Meta-analysis of change from baseline in lean body mass in CF patients treated with rhGH



I^2 = 20.9%
Egger's p-value = 0.80

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

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Lowercase letters following a study year represent unique trials conducted within the same year. Uppercase letters represent study arms within the same trial.

Narrative: This figure depicts the meta-analysis of change from baseline in lean body mass. The first trial by Hardin and colleagues in 2001 provided a mean difference of 2.70 kg with 95 percent confidence interval of 1.53 to 3.87 kg. The second trial by Hutler and colleagues in 2002 provided a mean difference of 2.20 kg with a 95 percent confidence interval of 1.30 to 3.10 kg. The third trial by Schibler and colleagues in 2003 provided a mean difference of 2.50 kg with a 95 percent confidence interval of 0.50 to 4.50 kg. The fourth trial by Hardin and colleagues in 2005 provided a mean difference of 3.50 kg with a 95 percent confidence interval of 1.91 to 5.09 kg. The fifth trial by Hardin and colleagues, also in 2005 provided a mean difference of 1.40 kg with a 95 percent confidence interval of 0.43 to 2.37 kg. The sixth trial by Hardin and colleagues in 2006 provided a mean difference of 1.80 kg with a 95 percent confidence interval of 0.95 to 2.65 kg. The seventh trial by Schnabel in 2007 provided a mean difference of 0.80 kg with a 95 percent confidence interval of -1.02 to 2.62 kg with the higher dose of rhGH and a mean difference of 1.00 with a 95 percent confidence interval of -0.74 to 2.74 kg with the lower dose of rhGH. The eighth trial by Stalvey in 2008 provided a mean difference of 1.70 kg with a 95 percent confidence interval of 0.82 to 2.58 kg. The combined effect of the studies showed a weighted mean difference of 1.92 kg with a 95 percent confidence interval of 1.47 to 2.37 kg. The I-squared value was 20.9 percent and the Egger's p-value was 0.80.

Table 12. Change from baseline in protein markers in controlled trials evaluating rhGH

Study, year	Group	Dose/wk (mg/kg)	N	LeuRa (µmol/kg*h)	Leu Oxidation (µmol/kg*h)	NOLD (µmol/kg*h)	Oxidation/NOLD (µmol/kg*h)
Hardin, 2001[23, 24]	rhGH	0.3	10	-44 (15)	-19 (7)	-30 (16)[c]	-0.06 (0.02)[c]
	No treatment	NA	9	10 (28)[c]	5 (9.5)[c]	5 (16)[c]	0.03 (0.01)[c]
Hutler, 2002[25108]	rhGH	0.27 to 0.35	6	-	-	-	-
	No treatment	NA	4	-	-	-	-
Schibler, 2003[26]	rhGH	0.35	10	-	-	-	-
	No treatment	NA	9	-	-	-	-
Darmaun, 2004[29]	rhGH	0.3	9	169 (32)	38.4 (18)	131 (32)	-
	rhGH+GLN	0.3/0.7[b]	9	178 (49)	29.4 (16.2)	145 (40)	-
	GLN	0.7[b]	9	179 (54)	27.6 (14.4)	151 (38)	-
Hardin, 2005a[32]	rhGH	0.3	16	-	-	-	-
	No treatment	0	16	-	-	-	-
Hardin, 2005b[33]	rhGH	0.3 to 0.35	13	-	-	-	-
	No treatment	NA	12	-	-	-	-
Hardin, 2005c[34]	rhGH	0.3	9	-	-	-	-
	No treatment	NA	9	-	-	-	-
Hardin, 2006[15]	rhGH	0.3	30	-	-	-	-
	No Treatment	NA	27	-	-	-	-
Schnabel, 2007[4]	Higher dose	0.49	20	-	-	-	-
	Lower dose	0.273	22	-	-	-	-
	Placebo	NA	21	-	-	-	-
Stalvey, 2008[38]	rhGH	0.3	29	-	-	-	-
	No treatment	NA	27	-	-	-	-

Legend: - =not reported; GLN=glutamine; LeuRa=rate of appearance of leucine; N=sample size; NOLD=rate of nonoxidative leucine disappearance; rhGH=recombinant human growth hormone

[a]Darmaun et al was a crossover study – all values presented are end values for that treatment period

[b]Glutamine dosing is 0.7 g/kg per day

[c]Change from baseline calculated from published baseline and final values

Table 13. Change from baseline in exercise tolerance in controlled trials evaluating rhGH

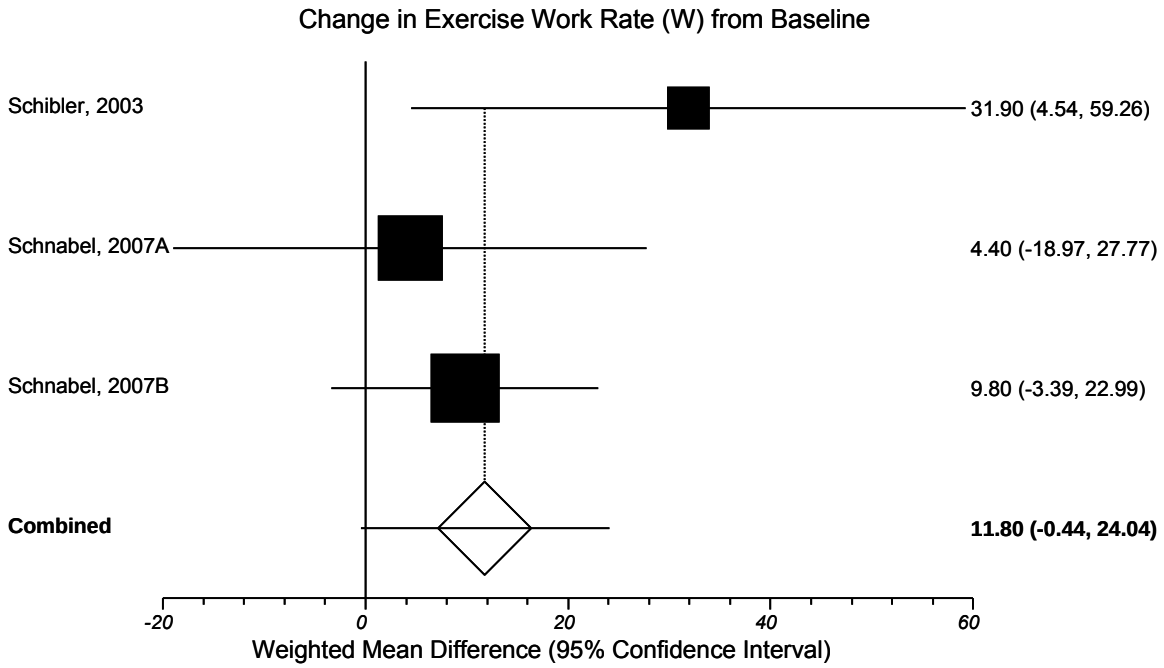
Study, year	Group	Dose/wk (mg/kg)	N	Test	Exercise Work Rate (W)	Vo_2 (ml/min)	Vo_{2peak} (ml)	Vo_{2max} (ml/kg/min)	Oxygen $pulse_{peak}$ (ml/beat)	$Ventilation_{peak}$ (L/min)
Hardin, 2001[23, 24]	rhGH	0.3	10	-	-	-	-	-	-	-
	No treatment	NA	9		-	-	-	-	-	-
Hutler, 2002[25108a]	rhGH	0.27 to 0.35	6	Bicycle ergometer	-	-	201 (161)	-	1.0 (0.7)	5.3 (6.6)
	No treatment	NA	4		-	-	-18 (117)	-	-0.1 (0.5)	-0.4 (5.5)
Schibler, 2003[26]	rhGH	0.35	10	Bicycle ergometer	21 (23.1)	-	-	-2.5 (7.3)	-	-
	No treatment	NA	9		-10.9 (36.9)	-	-	-8.6 (5.1)	-	-
Darmaun, 2004[29]	rhGH	0.3	9	-	-	-	-	-	-	-
	rhGH+GLN	0.3/0.7[b]	9		-	-	-	-	-	-
	GLN	0.7[b]	9		-	-	-	-	-	-
Hardin, 2005a[32]	rhGH	0.3	16	-	-	-	-	-	-	-
	No treatment	0	16		-	-	-	-	-	-
Hardin, 2005b[33]	rhGH	0.3 to 0.35	13	-	-	-	-	-	-	-
	No treatment	NA	12		-	-	-	-	-	-
Hardin, 2005c[34]	rhGH	0.3	9	-	-	-	-	-	-	-
	No treatment	NA	9		-	-	-	-	-	-
Hardin, 2006[15]	rhGH	0.3	30	-	-	-	-	-	-	-
	No Treatment	NA	27		-	-	-	-	-	-
Schnabel, 2007[4]	Higher dose	0.49	20	Bicycle ergometer	6.0 (36.2)	26.4 (77.2)	-	-	-	-
	Lower dose	0.273	22		11.4 (18.0)	12.5 (28.5)	-	-	-	-
	Placebo	NA	21		1.6 (17.8)	2.4 (17.0)	-	-	-	-
Stalvey, 2008[38]	rhGH	0.3	29	-	-	-	-	-	-	-
	No treatment	NA	27		-	-	-	-	-	-

Legend: All values given as mean (standard deviation); - =not reported; GLN=glutamine; N=sample size; NA=not applicable; rhGH=recombinant human growth hormone; VO_2= oxygen uptake; VO_{2max}= maximal oxygen uptake; VO_{2peak}= peak oxygen uptake

[a]Hutler et al was a crossover study which published values for each period separately – all values presented are change from baseline to the end of the first period

[b]Glutamine dosing is 0.7 g/kg per day

Figure 20. KQ1 Exercise Tolerance - Meta-analysis of change from baseline in exercise work rate in CF patients treated with rhGH



I^2 = 23.7%
Egger's p-value = NA

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

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Uppercase letters represent study arms within the same trial.

Narrative: This figure depicts the results of meta-analysis of change from baseline in exercise work rate. The first trial by Schibler and colleagues in 2003 provided a mean difference of 31.90 W with 95 percent confidence interval of 4.54 to 59.26 W. The second trial by Schnabel and colleagues in 2007 provided a mean difference of 4.40 W with a 95 percent confidence interval of -18.97 to 27.77 W with the higher dose of rhGH and a mean difference of 9.80 with a 95 percent confidence interval of -3.39 to 22.99 W with the lower dose of rhGH. The combined effect of the studies showed a weighted mean difference of 11.80 with a 95 percent confidence interval of -0.44 to 24.04 W. The I-squared value was 23.7 percent and the Egger's p-value was not applicable.

Table 14. Change from baseline in bone mineralization outcomes in controlled trials evaluating rhGH

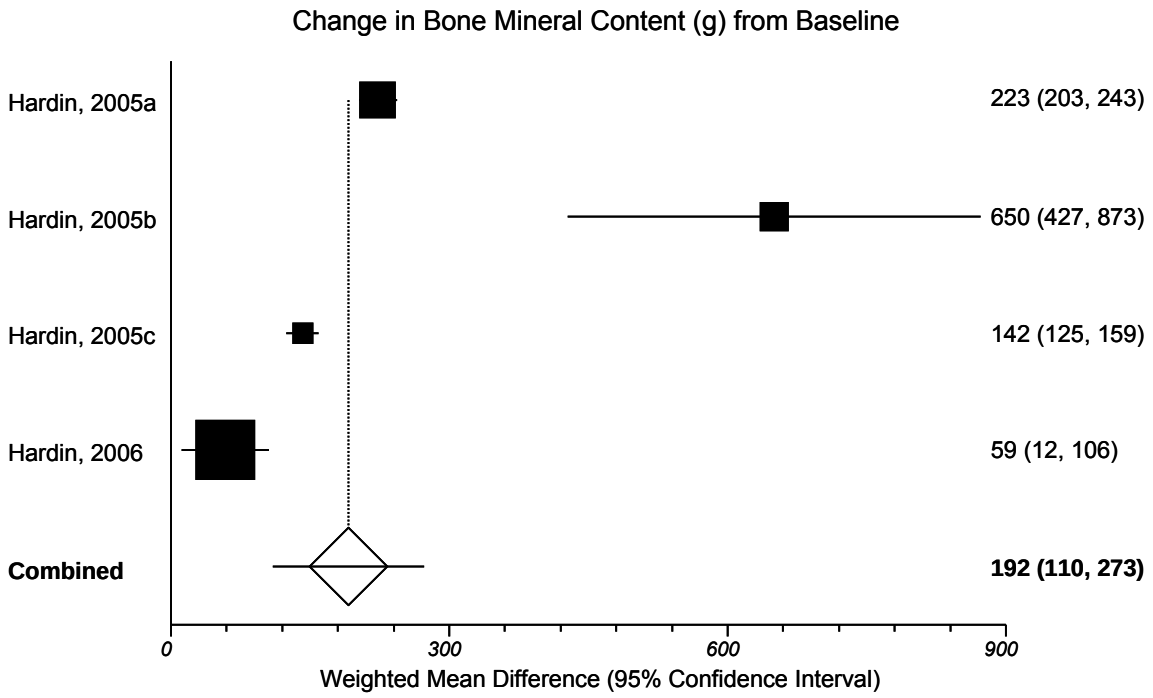
Study, year	Group	Dose/wk (mg/kg)	N	Bone Age	BMC (g)	BMC Z-score
Hardin, 2001[23, 24]	rhGH	0.3	10	1.1 (0.9)	-	-
	No treatment	NA	9	0.9 (1.2)	-	-
Hutler, 2002[25108]	rhGH	0.27 to 0.35	6	-	-	-
	No treatment	NA	4	-	-	-
Schibler, 2003[26]	rhGH	0.35	10	-	-	-
	No treatment	NA	9	-	-	-
Darmaun, 2004[29]	rhGH	0.3	9	-	-	-
	rhGH+GLN	0.3/0.7[a]	9	-	-	-
	GLN	0.7[a]	9	-	-	-
Hardin, 2005a[32]	rhGH	0.3	16	-	281 (34)	-
	No treatment	0	16	-	58 (23)	-
Hardin, 2005b[33]	rhGH	0.3 to 0.35	13	0.8 (1.9)	700 (312)[b]	-
	No treatment	NA	12	0.8 (1.1)	50 (250)[b]	-
Hardin, 2005c[34]	rhGH	0.3	9	-	176 (22)	-
	No treatment	NA	9	-	34 (15)	-
Hardin, 2006[15]	rhGH	0.3	30	-	169 (101)	0.70 (0.72)
	No Treatment	NA	27	-	110 (77)	0 (0.85)
Schnabel, 2007[4]	Higher dose	0.49	20	-	-	-
	Lower dose	0.273	22	-	-	-
	Placebo	NA	21	-	-	-
Stalvey, 2008[38]	rhGH	0.3	29	-	-	-
	No treatment	NA	27	-	-	-

Legend: All values given as mean (standard deviation); - =not reported; BMC=bone mineral content; GLN=glutamine; N=sample size; NA=not applicable; rhGH=recombinant human growth hormone

[a]Glutamine dosing is 0.7 g/kg per day

[b]Change from baseline calculated from extrapolated values from figure

Figure 21. KQ1 Bone Mineralization - Meta-analysis of change from baseline in BMC in CF patients treated with rhGH



I^2 = 96.1%
Egger's p-value = 0.82

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

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Lowercase letters following a study year represent unique trials conducted within the same year.

Narrative: This figure depicts the meta-analysis of change from baseline in BMC. The first trial by Hardin and colleagues in 2005 provided a mean difference of 223 g with 95 percent confidence interval of 203 to 243 g. The second trial by Hardin and colleagues, also in 2005, provided a mean difference of 650 g with a 95 percent confidence interval of 427 to 873 g. The third trial by Hardin and colleagues, also in 2005, provided a mean difference of 142 g with a 95 percent confidence interval of 125 to 159 g. The fourth trial by Hardin and colleagues in 2006 provided a mean difference of 59 g with a 95 percent confidence interval of 12 to 106 g. The combined effect of the four studies showed a weighted mean difference of 192 g with a 95 percent confidence interval of 110 to 273 g. The I-squared value was 96.1 percent and the Egger's p-value was 0.82.

Table 15. Outcomes of sexual maturation in controlled trials evaluating rhGH

Study, year	Group	Dose/wk (mg/kg)	N	Baseline Staging	Follow-up Staging
Hardin, 2001[23, 24]	rhGH	0.3	10	All in Tanner Stage 1	3 females progressed to Tanner Stage 2; Males did not develop signs of puberty
	No treatment	NA	9		2 females progressed to Tanner Stage 2; Males did not develop signs of puberty
Hutler, 2002[25108]	rhGH	0.27 to 0.35	6	All Prepubertal	None progressed over the course of the study.
	No treatment	NA	4		
Schibler, 2003[26]	rhGH	0.35	10	-	-
	No treatment	NA	9		
Darmaun, 2004[29]	rhGH	0.3	9	All in Tanner Stage 1	None progressed over the course of the study.
	rhGH+GLN	0.3/0.7[a]	9		
	GLN	0.7[a]	9		
Hardin, 2005a[32]	rhGH	0.3	16	All in Tanner Stage 1	None progressed over the course of the study.
	No treatment	0	16		
Hardin, 2005b[33]	rhGH	0.3 to 0.35	13	Four T4, four T3 Mean (SD): 3.6 (0.4)	Mean (SD): 4.5 (0.6)
	No treatment	NA	12	Four T4, four T3 Mean (SD): 3.4 (0.6)	Mean (SD): 4.1 (0.9)
Hardin, 2005c[34]	rhGH	0.3	9	All in Tanner Stage 1	None progressed over the course of year 1.
	No treatment	NA	9		
Hardin, 2006[15]	rhGH	0.3	32	All in Tanner Stage 1	None progressed over the course of year 1.
	No Treatment	NA	29		
Schnabel, 2007[4]	Higher dose	0.49	20	-	-
	Lower dose	0.273	22		
	Placebo	NA	21		
Stalvey, 2008[38]	rhGH	0.3	29	-	-
	No treatment	NA	27		

Legend: - =not reported; GLN=glutamine; N=sample size; NA=not applicable; rhGH=recombinant human growth hormone; SD=standard deviation
[a]Glutamine dosing is 0.7 g/kg per day

Key Question 2

In patients with CF, does treatment with rhGH as an adjuvant to usual care improve health outcomes, including: frequency of required intravenous antibiotic treatments; frequency of hospitalization; quality of life; bone fracture or development of osteoporosis/osteopenia; or mortality, compared with usual care alone?

Key Points

- There is insufficient evidence to determine the effect of rhGH on IV antibiotic use during therapy but preliminary data is promising.
- There is insufficient evidence to determine the effect of rhGH on pulmonary exacerbations.
- There is moderate evidence to suggest that rhGH therapy reduces the rate of hospitalization.
- There is insufficient evidence to determine the effect of rhGH on HRQoL in patients with CF.
- There is insufficient evidence to determine the effect of rhGH on bone consequences or mortality.

Detailed Analysis

Study Design and Population Characteristics

Studies to answer Key Question 2 are derived from the same set of studies used to evaluate Key Question 1 and are summarized in Table 4-Table 8.

Outcome Evaluations

Antibiotic Usage

Three trials, summarized in Table 16, reported information about antibiotic usage in patients with CF.[23, 34, 102] The varying definitions of antibiotic usage precluded quantitative analysis. In the first trial, the number of outpatient IV antibiotic courses was similar between groups in the year preceding the study (rhGH group 0.9±0.7 versus control group 0.8±0.7, p-value not reported) and in the year during therapy (rhGH group 0.7±0.8 versus control group 0.9±0.7, p-value not reported).[23] In patients who were receiving enteral nutrition, rhGH therapy did not affect outpatient IV antibiotic use compared to control (rhGH 0.57±0.51 versus control 0.85±0.8, units not reported, p=0.05).[34] In the third trial, it was reported that no difference in IV antibiotic use occurred between the rhGH and the control groups but quantifiable data was not reported.[102]

Pulmonary Exacerbations

One trial reported the number of patients who experienced pulmonary exacerbations over the duration of the trial, but there was no difference between patients treated with rhGH and those treated with placebo (Table 17, p-value not reported).[4]

One single-arm observational study compared the number of pulmonary exacerbations during 6 or 12 months of rhGH therapy to the 6 to 12 months preceding rhGH therapy.[40] In patients treated with rhGH for 12 months (n=4), the number of exacerbations fell from 13 to 6; in patients

treated for 6 months (n=3), exacerbations fell from 10 to 4. The authors report a p-value of p=0.04 at the end of these results but it is not clear to which comparison it belongs.[40]

Hospitalizations

The rates of hospitalizations per year were reported consistently in four trials and were amendable to quantitative synthesis.[23, 33, 34, 102] (Table 18) Upon statistical pooling, the rate of hospitalization during the study was significantly less in those treated with rhGH than control (WMD -1.62 hospitalizations per year, 95 percent CI -1.98 to -1.26 hospitalizations per year). (Figure 22) No statistical heterogeneity or publication bias was detected upon analysis. One additional trial reported that there were no statistically significant differences in hospitalization days between treatment groups but quantifiable data was not reported.[4]

Health-Related Quality of Life

Two trials reported information regarding HRQoL, using the Cystic Fibrosis Questionnaire (CFQ).[4, 102] (Table 19) Quantifiable data was only reported in one trial,[15] precluding quantitative synthesis. Patients treated with rhGH experienced greater improvements in the weight domain than patients in the control group (change from baseline 0.4±0.8 versus 0.3±0.8, respectively, p=0.04) and in the body image domain (change from baseline 0.3±0.9 versus -0.2±0.9, p=0.03).[102] No differences were seen in the remaining CFQ domains (data not reported).[102] A second trial reported no major differences among treatment groups in HRQoL but quantifiable data was not reported.

Bone Consequences

Incidence of bone consequences such as development of osteoporosis, osteopenia, or fracture was not reported in trials or studies.

Mortality

Incidence of CF-related death or death from any cause was not reported in trials or studies. Through a review of the trials and studies, no apparent deaths were reported but there were patients who were lost to followup precluding firm conclusions of their dispensation.

Discussion

From the current body of evidence, the impact that rhGH therapy has on important health outcomes is difficult to quantify. Clearly, more research is needed to discern the impact of rhGH on health outcomes and trial authors need to be more forthcoming with quantifiable outcome data, even for underpowered analyses.

Upon statistical pooling of four trials, rhGH use was associated with a 1.6 fewer hospitalizations per year than those not receiving therapy. However, an additional trial reported that no significant reductions in hospitalizations occurred with rhGH therapy, but quantifiable data was not provided and the trial could not be pooled with the others. Whether the rhGH group had qualitatively fewer hospitalizations is not known.

Data on other endpoints were either sparsely or inconsistently reported, precluding quantitative analysis. One study found a 33 percent reduction in intravenous antibiotic use with borderline significance, one trial showed 22 percent nonsignificant reduction, and the third trial only provided a summary statement saying that no significant impact occurred. As such, we cannot determine the impact of rhGH on intravenous antibiotic use in CF patients but preliminary data is promising.

Only one trial evaluated the impact of rhGH therapy on pulmonary exacerbations. The numbers of pulmonary exacerbations were qualitatively higher in the low and high dose rhGH groups than the placebo group with no dose response relationship seen. While one trial found significant benefits on two aspects of health related quality of life, another trial found no substantial benefits but did not quantify the data. No data was available for bone consequences of CF or mortality.

Key Question 3 seeks to elucidate the linkages between intermediate and important health outcomes but it would have been valuable to see if preliminary data in a CF population receiving rhGH would be similar.

Table 16. Intravenous antibiotic usage in patients in controlled trials evaluating rhGH

Study, year	Group	Dose/wk (mg/kg)	N	Outcome Definition	Outcome
Hardin, 2001[23, 24]	rhGH	0.3	10	Courses of outpatient IV antibiotic use during year of therapy	0.7 (0.8)
	No treatment	NA	9		0.9 (0.7)
Hutler, 2002[25108]	rhGH	0.27 to 0.35	6	-	-
	No treatment	NA	4		-
Schibler, 2003[26]	rhGH	0.35	10	-	-
	No treatment	NA	9		-
Darmaun, 2004[29]	rhGH	0.3	9	-	-
	rhGH+GLN[a]	0.3/0.7	9		-
	GLN[a]	0.7	9		-
Hardin, 2005a[32]	rhGH	0.3	16	-	-
	No treatment	0	16		-
Hardin, 2005b[33]	rhGH	0.3 to 0.35	13	-	-
	No treatment	NA	12		-
Hardin, 2005c[34]	rhGH	0.3	9	Outpatient IV antibiotic use (unit of measure not reported)	0.6 (0.5)
	No treatment	NA	9		0.9 (0.8)
Hardin, 2006[15]	rhGH	0.3	32	Days of IV antibiotic use	-
	No Treatment	NA	29		-
Schnabel, 2007[4]	Higher dose	0.49	20	-	-
	Lower dose	0.273	22		-
	Placebo	NA	21		-
Stalvey, 2008[38]	rhGH	0.3	29	-	-
	No treatment	NA	27		-

Legend: All values given as mean (standard deviation); - =not reported; GLN=glutamine; N=sample size; NA=not applicable; rhGH=recombinant human growth hormone

[a]Glutamine dosing is 0.7 g/kg per day

Table 17. Pulmonary exacerbations in patients in controlled trials evaluating rhGH

Study, year	Group	Dose/wk (mg/kg)	N	Outcome Definition	Pulmonary Exacerbations
Hardin, 2001[23, 24]	rhGH	0.3	10	-	-
	No treatment	NA	9		-
Hutler, 2002[25108]	rhGH	0.27 to 0.35	6	-	-
	No treatment	NA	4		-
Schibler, 2003[26]	rhGH	0.35	10	-	-
	No treatment	NA	9		-
Darmaun, 2004[29]	rhGH	0.3	9	-	-
	rhGH+GLN[a]	0.3/0.7	9		-
	GLN[a]	0.7	9		-
Hardin, 2005a[32]	rhGH	0.3	16	-	-
	No treatment	0	16		-
Hardin, 2005b[33]	rhGH	0.3 to 0.35	13	-	-
	No treatment	NA	12		-
Hardin, 2005c[34]	rhGH	0.3	9	-	-
	No treatment	NA	9		-
Hardin, 2006[15]	rhGH	0.3	32	-	-
	No Treatment	NA	29		-
Schnabel, 2007[4]	Higher dose	0.49	20	Number of patients affected	7
	Lower dose	0.273	22		6
	Placebo	NA	21		4
Stalvey, 2008[38]	rhGH	0.3	29	-	-
	No treatment	NA	27		-

Legend: - =not reported; GLN=glutamine; N=sample size; NA=not applicable; rhGH=recombinant human growth hormone
[a]Glutamine dosing is 0.7 g/kg per day

Table 18. Rate of hospitalizations in patients in controlled trials evaluating rhGH

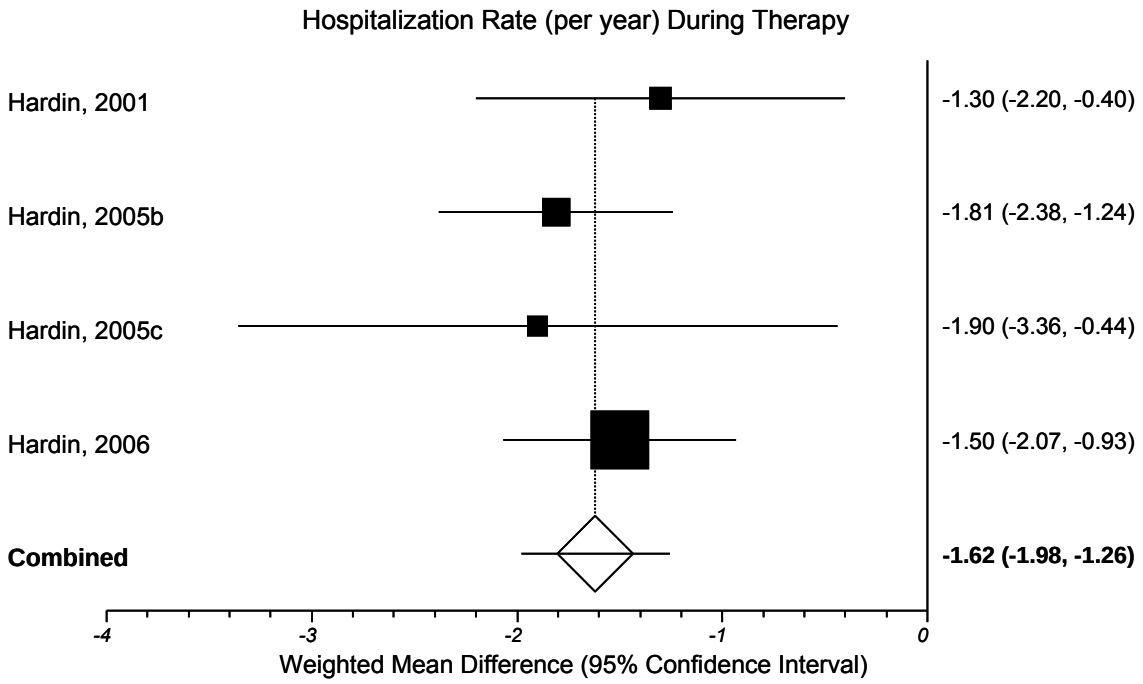
Study, year	Group	Dose/wk (mg/kg)	N	Hospitalizations per year
Hardin, 2001[23, 24]	rhGH	0.3	10	0.9 (0.9)
	No treatment	NA	9	2.2 (1.1)
Hutler, 2002[25108]	rhGH	0.27 to 0.35	6	-
	No treatment	NA	4	-
Schibler, 2003[26]	rhGH	0.35	10	-
	No treatment	NA	9	-
Darmaun, 2004[29]	rhGH	0.3	9	-
	rhGH+GLN[a]	0.3/0.7	9	-
	GLN[a]	0.7	9	-
Hardin, 2005a[32]	rhGH	0.3	16	-
	No treatment	0	16	-
Hardin, 2005b[33]	rhGH	0.3 to 0.35	13	0.7 (0.8)
	No treatment	NA	12	2.5 (0.7)
Hardin, 2005c[34]	rhGH	0.3	9	1.1 (1.0)
	No treatment	NA	9	3.0 (2.0)
Hardin, 2006[15]	rhGH	0.3	32	1.5 (0.5)[b]
	No Treatment	NA	29	3.0 (1.5)[b]
Schnabel, 2007[4]	Higher dose	0.49	20	-
	Lower dose	0.273	22	-
	Placebo	NA	21	-
Stalvey, 2008[38]	rhGH	0.3	29	-
	No treatment	NA	27	-

Legend: All values given as mean (standard deviation); - =not reported; GLN=glutamine; N=sample size; NA=not applicable; rhGH=recombinant human growth hormone

[a]Glutamine dosing is 0.7 g/kg per day

[b]Value extrapolated from figure

Figure 22. KQ2 - Meta-analysis of hospitalizations in CF patients treated with rhGH



I^2 = 0%
Egger's p-value = 0.98

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

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Lowercase letters following a study year represent unique trials conducted within the same year.

Narrative: This figure depicts the meta-analysis of hospitalization rate during therapy with rhGH. The first trial by Hardin and colleagues in 2001 provided a mean difference of -1.30 events per year with 95 percent confidence interval -2.20 to -0.40. The second trial by Hardin and colleagues in 2005 provided a mean difference of -1.81 events per year with 95 percent confidence interval -2.38 to -1.24. The third trial, also by Hardin and colleagues in 2005, provided a mean difference -1.90 events per year with 95 percent confidence interval -3.36 to -0.44. The last trial by Hardin and colleagues in 2006 provided a mean difference -1.50 events per year with 95 percent confidence interval -2.07 to -0.93. The combined weighted mean difference was -1.62 events per year with 95 percent confidence interval -1.98 to -1.26. The I-squared value was 0 percent and the Egger's p-value was 0.98.

Table 19. Change from baseline in health-related quality of life of patients in controlled trials evaluating rhGH

Study, year	Group	Dose/wk (mg/kg)	N	Scale Used	Overall score	Body image domain	Weight domain
Hardin, 2001[23, 24]	rhGH	0.3	10	-	-	-	-
	No treatment	NA	9		-	-	-
Hutler, 2002[25108]	rhGH	0.27 to 0.35	6	-	-	-	-
	No treatment	NA	4		-	-	-
Schibler, 2003[26]	rhGH	0.35	10	-	-	-	-
	No treatment	NA	9		-	-	-
Darmaun, 2004[29]	rhGH	0.3	9	-	-	-	-
	rhGH+GLN[a]	0.3/0.7	9		-	-	-
	GLN[a]	0.7	9		-	-	-
Hardin, 2005a[32]	rhGH	0.3	16	-	-	-	-
	No treatment	0	16		-	-	-
Hardin, 2005b[33]	rhGH	0.3 to 0.35	13	-	-	-	-
	No treatment	NA	12		-	-	-
Hardin, 2005c[34]	rhGH	0.3	9	-	-	-	-
	No treatment	NA	9		-	-	-
Hardin, 2006[15]	rhGH	0.3	32	CFQ	-	0.3 (0.9)	0.4 (0.8)
	No Treatment	NA	29		-	-0.2 (0.9)	0.3 (0.8)
Schnabel, 2007[4]	Higher dose	0.49	20	CFQ	-	-	-
	Lower dose	0.273	22		-	-	-
	Placebo	NA	21		-	-	-
Stalvey, 2008[38]	rhGH	0.3	29	-	-	-	-
	No treatment	NA	27		-	-	-

Legend: All values given as mean (standard deviation); - =not reported; CFQ=Cystic Fibrosis Questionnaire; GLN=glutamine; N=sample size; NA=not applicable; rhGH=recombinant human growth hormone

[a]Glutamine dosing is 0.7 g/kg per day

Key Question 3

In patients with CF, what is the strength of evidence that intermediate outcomes of pulmonary function, growth, and bone mineralization are associated with improvements in the health outcomes including quality of life, bone fracture, development of osteoporosis/osteopenia or mortality?

Key Points

- This key question evaluates the association between intermediate endpoints and important clinical outcomes in patients with CF.
- The association between pulmonary function and mortality in patients with CF was evaluated in 28 studies.
    - Only one of three studies which evaluated FVC at baseline and mortality found a univariate association and only two of five which evaluated percent predicted FVC at baseline and mortality found a univariate association. However, only one of the aforementioned studies performed multivariate analysis and found that percent predicted FVC at baseline was a multivariate predictor. Decreases in FVC were univariate and multivariate predictors of mortality in two trials, but not in two other trials.
    - Some studies using univariate analysis found an association between measures of absolute FEV_1 and mortality but other studies did not. In the only two multivariate analyses, an association was found between FEV_1 and mortality in one study but no association was seen between the decline in FEV_1 and mortality. The link between percent predicted FEV_1 and mortality is stronger with a majority of studies finding an association between percent predicted FEV_1 and mortality.
- The association between anthropometrics and mortality in patients with CF was evaluated in 26 studies.
    - The link between height and mortality is weak with only a minority of studies reporting an association.
    - The link between different measures of weight and mortality was supported in majority studies by univariate analysis. Only one study found a multivariate relationship between weight and mortality but another multivariate analysis did not. The link between BMI and mortality is controversial with some studies showing no association, others showing only a univariate association and very few showing no multivariate association. The link between IBW and mortality was supported by several univariate associations and in the only multivariate analysis that was performed.
    - The only study evaluating the association between percent predicted weight-for-height and mortality found a multivariate association.
- No studies evaluated the association between protein turnover and mortality.
- The association between exercise tolerance and mortality in patients with CF was evaluated in 10 studies. The link between walk testing and mortality is weak with some

studies finding no association, some finding only a univariate association and very few finding a multivariate association. The link between peak oxygen uptake during exercise testing and mortality was only supported by univariate analyses.

- No studies evaluated the association between bone mineralization and mortality.
- The association between pulmonary function and HRQoL in patients with CF was evaluated in 14 studies but using 10 different scales. All studies but one specified that they explored the association between percent predicted FEV_1 and HRQoL but rhGH has little to no impact on this parameter (see KQ1). The last study did not specify whether the FEV_1 was the absolute or percent predicted. Only four studies employed multivariate analyses (each using different questionnaires to rate HRQoL).
    - In multivariate analyses, higher percent predicted FEV_1 was associated with improvements in "ways of coping" but not subjective health perception in one study, but whether this is absolute or percent predicted FEV_1 is not specified. Higher percent predicted FEV_1 was associated with improvements in seven of nine health domains (including social and physical functioning and chest symptoms) in another study and general well being in another study, but no association was seen between FEV_1 and general health perception in the final study.
- The association between anthropometrics and HRQoL in patients with CF was evaluated in 10 studies but using nine different scales and different anthropometric parameters. Only five studies employed multivariate analyses (each using different questionnaires to rate HRQoL).
    - In multivariate analysis, greater percent IBW was not associated with subjective health perception or coping in one study, greater BMI was only associated with improvements in body image but not any other factor including social and physical functioning and chest symptoms in another study, adequate weight gain over 2 years was associated with improvements in physical functioning but not social or emotional functioning and BMI Z-score was not associated with any of the three dimensions in one study, greater BMI was associated with lower general health perception in one study, and BMI was not associated with life satisfaction.
- No studies evaluated the association between protein turnover and HRQoL.
- Two studies evaluated the impact between exercise tolerance and HRQoL using two different questionnaires. Greater exercise capacity (determined by VO_{2peak} or maximal workload) is associated with better measures of HRQoL scores in univariate analyses.
- No studies evaluated the association between bone mineralization and HRQoL.
- Only one study evaluated the association between pulmonary function or anthropometrics and bone consequences. In univariate analyses, there was no relationship between FEV_1, FVC, or BMI and bone fracture.
- No studies evaluated the association between protein turnover, exercise tolerance, or bone mineralization and bone consequences.

Detailed Analysis

Study Design and Population Characteristics

Thirty-four studies evaluated the relationship between intermediate outcomes and mortality.[8, 47-50, 52-79, 109, 110] (Table 20)

Patients in 24 studies were clinically stable.[8, 47-51, 54-56, 58-61, 63, 65-70, 72, 75, 78, 79] Three studies evaluated patients around the time of admission to the Intensive Care Unit.[73, 74, 77] Seven studies included patients that were evaluated for or received lung transplantation.[52, 53, 57, 62, 64, 71, 76] Nine studies only evaluated adult patients,[52, 57, 58, 62, 71, 73, 74, 77, 111] 4 studies evaluated a combination of adolescent and adult patients,[56, 60, 61, 78] only 1 study evaluated a combination of children and adolescents,[72] 4 studies evaluated only children,[47, 67, 75, 79] and 16 studies evaluated children, adolescents, and adults.[8, 49-51, 53-55, 59, 63-66, 68-70, 76] Seventeen studies followed patients from 1 to 25 years,[49-51, 55, 58-60, 63, 65, 67-70, 72, 74, 77, 78] 12 studies followed patients until death or the time of analysis,[8, 47, 48, 55, 56, 61, 64, 66, 71, 73, 75, 76] 4 studies followed patients until death or transplantation,[52, 53, 57, 79] and 1 study did not report the duration of followup.[62]

Fifteen studies evaluated the relationship between intermediate outcomes and HRQoL.[81-92, 94-96, 112, 113] (Table 21) Eight different generic health scales were used to rate HRQoL: Alltagsleben (Every Day Life),[85] Child Health Questionnaire (CHQ),[88, 91] EuroQoL 5D (EQ-5D),[86] Medical Outcomes Short Form 36 (SF-36),[86, 87] Nottingham Health Profile (NHP),[83] Quality of Well-Being (QWB),[82, 114] Questions on Life Satisfaction,[94] and the Sickness Impact Profile (SIP)[84] Two CF-specific scales were also used: Cystic Fibrosis Quality of Life Questionnaire (CFQoL),[89, 90] and Cystic Fibrosis Questionnaire (CFQ).[92, 93, 95-97] Descriptions of the different HRQoL measures and their interpretations are found in the Appendix Glossary.

Patients in all studies were clinically stable.[81-92, 94-97, 112] Six studies only evaluated adult patients,[83, 84, 86, 89, 90, 95-97] three studies evaluated a combination of adolescent and adult patients,[85, 92, 94] two studies only evaluated adolescents,[87, 88] two studies evaluated a combination of children and adolescents,[82, 91] one study only evaluated children,[91] and one study evaluated children, adolescents, and adults.[81] One study followed patients for up to 18 months,[94] one study was a cross-sectional survey with a 1 year followup survey,[86] and the remaining studies were all cross-sectional at a single timepoint.[81-85, 87-92, 95-97, 112]

One study evaluated the relationship between intermediate outcomes and bone consequences.[98] (Table 22) This was a retrospective cohort study which evaluated adult patients referred for lung transplantation between January 1994 and December 1996.[98] Patients were assessed retrospectively for the incidence of bone fracture.[98]

Outcome Evaluations

Mortality

<u>Pulmonary Function</u>

Twenty-eight studies evaluated the relationship between mortality and various measures of pulmonary function.[48-56, 58-66, 68, 70, 71, 73-79] (Appendix Table 1)

1901 *Forced Vital Capacity (FVC) at Baseline*

1902 Three studies evaluated the relationship between forced vital capacity at baseline and
1903 mortality using univariate but not multivariate analyses.[53, 62, 64] In two of the studies, there was no
1904 significant difference in FVC at baseline between those who lived and those who subsequently
1905 died. (Ciriaco: MD 0L, 95 percent CI -0.48 to 0.48; Venuta: MD 0 L, 95 percent CI -0.58 to
1906 0.58).[53, 62] In the third trial, the FVC was significantly higher in those who lived versus those
1907 who subsequently died (MD -0.27 L, p=0.006).[64]

1908 *Percent Predicted Forced Vital Capacity (FVC) at Baseline*

1909 Five studies evaluated the relationship between percent predicted FVC at baseline and
1910 mortality using univariate analysis,[53, 56, 62, 64, 111] and of the five, only one conducted multivariate
1911 analyses.[56] In two of the studies there was no significant difference in percent predicted FVC at
1912 baseline between those who lived and those who subsequently died (Ciriaco: MD -2 percent, 95
1913 percent CI -5.35 to 9.35; Venuta: MD -2 percent, 95 percent CI -6.89 to 10.89).[53, 62] In the third
1914 study, the FVC was significantly higher in those who lived versus those who subsequently died
1915 (MD -4 percent, p=0.031).[64] In the fourth study, no significant difference in percent predicted
1916 forced vital capacity occurred between those who survived and those who subsequently died but
1917 the effect sizes, p-values, and variance were not provided.[111] In the fifth study, those who
1918 survived had a significantly greater percent predicted FVC at baseline than those who died but
1919 the effect size was not reported (p<0.001). In multivariate analysis, increasing percent predicted
1920 FVC was significantly associated with a reduction in mortality (RR 0.963, p<0.0001).[56]

1921 *Ten Percent Decrease in Percent Predicted Forced Vital Capacity (FVC)*

1922 Two studies evaluated the risk of death associated with a 10 percent decrease in percent
1923 predicted forced vital capacity using both univariate and multivariate analysis.[50, 76] In the first
1924 study, for every 10 percent decrease in percent predicted FVC, the hazard of death was
1925 significantly increased (HR 2.1, 95 percent CI 1.5 to 3.0) in univariate analysis but a 10 percent
1926 decrease in percent predicted FVC was not a multivariate predictor of mortality.[76] In the second
1927 trial, for every 10 percent decrease in percent predicted forced vital capacity, the relative risk of
1928 death was significantly increased within two years in univariate (RR 1.9, 95 percent CI 1.8 to
1929 2.1) and multivariate analysis (RR 2.0, 95 percent CI 1.8 to 2.2).[50]

1930 *Decline in Percent Predicted Forced Vital Capacity (FVC)*

1931 Two studies performed univariate and multivariate analysis to evaluate the relationship
1932 between mortality and decline in percent predicted forced vital capacity.[55, 61] In the first study,
1933 the univariate results were not reported but upon multivariate analysis, there was a significant
1934 relationship between declines in percent predicted FVC and mortality.[55] In the second study,
1935 there was no significant difference in the rate of decline in percent predicted FVC per year in
1936 those who lived versus those who died in univariate (MD 0.39 percent, p=0.1) or multivariate
1937 analysis, but the effect size and measures of variance were not reported.[61]

1938 *Forced Expiratory Volume in One Minute (FEV_1) at Baseline*

1939 Six studies performed univariate, but not multivariate analysis to evaluate the relationship
1940 between FEV_1 at baseline and mortality.[52, 53, 62, 64, 66, 71] Upon univariate analysis, one study found
1941 that the hazard of death was significantly decreased (HR 0.999, 95 percent CI 0.998 to 0.999) in
1942 those with a higher FEV_1 at baseline.[66] In another study, univariate analysis revealed that the risk

of death was significantly decreased (RR 0.28, 95 percent CI 0.08 to 0.97) in those with a higher FEV_1 at baseline.[52] In four studies, patients who subsequently died had a lower FEV_1 at baseline (ranging from 0.04 to 0.149 liters less) than those who lived, but FEV_1 was not a significant univariate predictor of mortality in any of these studies.[53, 62, 64, 71]

One study used both univariate and multivariate analysis to evaluate the relationship between FEV_1 at baseline and mortality using data from the United States Cystic Fibrosis Foundation National Patient Registry in 1996.[68] A statistically significant univariate relationship between FEV_1 and mortality, but the effect size was not reported. Multivariate analysis revealed that each liter increase in FEV_1 decreased the odds of dying (OR 0.09, 95 percent CI 0.7 to 0.11).[68]

Decline in Forced Expiratory Volume in One Minute (FEV_1)

Three studies evaluated the relationship between decline in FEV_1 and mortality.[70, 74, 75] The first study did not report the results of univariate analysis, but a significant relationship was found between decline in FEV_1 and mortality upon multivariate analysis although no effect size was reported.[70] The second study found that a decline in FEV_1 before admission for a pulmonary exacerbation increased the hazard of death after pulmonary exacerbation (HR 0.70, 95 percent CI 0.49 to 1.00) but the results of multivariate analysis were not significant.[74] The third study found an increase in the hazard of death with decline in FEV_1 over the study period (HR 0.959, 95 percent CI 0.928 to 0.0991) upon univariate analysis, but did not a multivariate relationship.[75]

Percent Predicted Forced Expiratory Volume in One Minute (FEV_1) at baseline

Eleven studies[49, 52, 56, 58, 60, 62, 64-66, 71, 78] evaluated the univariate relationship between percent predicted forced expiratory volume in one minute at baseline, but only six evaluated the multivariate relationship.[56, 58, 60, 65, 66, 78] Using only univariate analysis, studies evaluating the relationship between percent predicted FEV_1 at baseline and mortality had conflicting findings.[49, 53] Two studies, one evaluating individuals in two different clinics, found percent predicted FEV_1 at baseline was significantly higher in those who lived versus those who subsequently died (Corey, Site 1: MD -40 percent, p=<0.05; Site 2: MD -40 percent, p<0.001, Ciriaco: MD -5 percent, p<0.02).[49, 53] In contrast, three studies found that percent predicted FEV_1 at baseline was not significantly higher in those who lived versus those who subsequently died (Venuta: MD 3.4 percent, 95 percent CI -1.53 to 8.33, Vizza: MD 0 percent, p=<0.823, Stanchina: MD 4.8 percent, 95 percent CI -0.78 to 10.38).[62, 64, 71] While another study found that there was not a significant decrease in the risk of death for individuals with a higher percent predicted FEV_1 at baseline compared to those with a lower percent predicted FEV_1 at baseline based on univariate analysis (RR 0.96, 95 percent CI 0.92 to 1.00).[52]

In studies using multivariate analyses, all six studies found a relationship between percent predicted FEV_1 at baseline and mortality.[56, 58, 60, 65, 66, 78] Upon univariate analysis, two studies found that percent predicted FEV_1 at baseline was significantly higher in those who lived compared to those who subsequently died (Moorcroft: MD -29.2 percent, p<0.001, Courtney: MD -28.3 percent, p<0.001) and for both studies percent predicted FEV_1 at baseline was a significant multivariate predictor of mortality but the effect size was not provided.[58, 78]Three studies found a statistically significant univariate relationship between percent predicted FEV_1 at baseline and mortality but did not report an effect size.[56, 60, 65] Bell and colleagues found a statistically significant multivariate relationship but did not report effect size.[60] Liou and colleagues found a decrease in the odds of dying upon multivariate analysis of percent predicted

1987 FEV_1 at baseline, but did not report statistical significance (OR 0.96, NR).[65] Belkin and
1988 colleagues found that there was a significant increase in the hazard of death for individuals with
1989 a percent predicted FEV_1 ≤30 percent at baseline compared to those with a percent predicted
1990 FEV_1 ≥30 percent in univariate (HR 3.8, 95 percent CI 2.0 to 7.5) and multivariate (HR 6.8, 95
1991 percent CI 2.4 to19.3) analysis.[76] One study found that individuals with a higher percent
1992 predicted FEV_1 at baseline have a decreased hazard of death than those with a lower percent
1993 predicted FEV_1 in univariate (HR 0.945, 95 percent CI 0.934, 0.956) and multivariate analysis
1994 (HR 0.953, 95 percent CI 0.931 to 0.975).[66]

1995 *Percent Predicted Forced Expiratory Volume in One Minute (FEV_1)*

1996 One study evaluated the relationship between the most recently recorded percent predicted
1997 FEV_1 values recorded in the Canadian Patient Data Registry for the period of 1985-1989 and
1998 mortality using univariate and multivariate analysis.[54] The study revealed a significant decrease
1999 in the hazard of death for those with a higher percent predicted FEV_1 upon univariate (HR 0.93,
2000 95 percent CI 0.92 to 0.94) and multivariate analysis (HR 0.93, 95 percent CI 0.92 to 0.94).[54]

2001 *Percent Predicted Forced Expiratory Volume in One Minute (FEV_1) Evaluated by Percent*

2002 Three studies evaluated the relationship between percent predicted FEV_1 evaluated by
2003 percent and mortality using both univariate and multivariate analysis.[51, 59, 66] The first study
2004 evaluated the relationship between mortality and percent predicted FEV_1 below and above 80
2005 percent of predicted using univariate and multivariate analysis and found that the hazard of death
2006 was significantly increased for those individuals with a percent predicted FEV_1 between 60 and
2007 80 percent when compared to those with a percent predicted FEV_1 greater than 80 percent in
2008 univariate (HR 2.7, 95 percent CI 1.4 to 5.5) but not in multivariate analysis (HR 1.8, 95 percent
2009 CI 0.7 to 4.3).[59] The hazard of death was significantly increased for those individuals with a
2010 percent predicted FEV_1 between 40 to 59 percent when compared to those with a percent
2011 predicted FEV_1 greater than 80 percent in univariate (HR 14.0, 95 percent CI 7.8 to 25.1) and
2012 multivariate analysis (HR 11.3, 95 percent CI 4.9 to 26.3).[59] Finally, the hazard of death was
2013 significantly increased for those individuals with a percent predicted FEV_1 below 40 percent
2014 when compared to those with a percent predicted FEV_1 greater than 80 percent in univariate (HR
2015 56.7, 95 percent CI 32.6to 98.5) and multivariate (HR 27.5, 95 percent CI 11.2 to 67.8)
2016 analysis.[59]

2017 In the second study, the risk of death was significantly increased for those with a percent
2018 predicted FEV_1 less than or equal to 50 percent when compared to those with a percent predicted
2019 FEV_1 greater than or equal to 65 percent in univariate analysis (RR 3.7, 95 percent CI 1.8 to 7.9),
2020 but not in multivariate analysis (RR 1.1, 95 percent CI 0.4 to 2.7).[51] In the third study, the risk of
2021 hazard of death was significantly higher for those with a percent predicted FEV_1 less than or
2022 equal to 30 percent compared to those with a percent predicted FEV_1 greater than 30 percent in
2023 univariate (HR 4.83, 95 percent CI 3.44,6.78), but not multivariate analysis.[66]

2024 *Percent Predicted Forced Expiratory Volume in One Minute (FEV_1) at the Last Recorded Visit*

2025 In one study, the relationship between the percent predicted FEV_1 at the last visit and
2026 subsequent mortality was evaluated using univariate analysis.[75] No relationship was seen
2027 between a one percent drop in percent predicted FEV_1 and mortality (HR 0.928, 95 percent CI
2028 0.894 to 0.968).[75]

2029 *Percent Predicted Forced Expiratory Volume in One Minute (FEV_1) Prior to Intensive Care Unit Admission*

2030 Three studies performed univariate, but not multivariate analysis, to evaluate the relationship
2031 between percent predicted FEV_1 prior to admission to the Intensive Care Unit for pulmonary
2032 exacerbation.[73, 74, 77] In the first study, the risk of death was significantly increased (RR 3.68, 95
2033 percent CI 1.11 to 16.33) for those with a percent predicted FEV_1 below 24 upon admission.[73]
2034 The second study found that there was not a significant hazard (HR 1.00, 95 percent CI 0.91 to
2035 1.02) of death for those patients with a stable percent predicted FEV_1 at the time of admission.[74]
2036 The third study found that there was a significant decrease in the hazard of death (HR 0.97, 95
2037 percent CI 0.93 to 1.02) associated with higher percent predicted FEV_1 values within 6 months
2038 preceding intensive care unit admission.[77]

2039 *Decline in Percent Predicted Forced Expiratory Volume in One Minute (FEV_1)*

2040 Four studies evaluated the relationship between mortality and a decline in percent predicted
2041 FEV_1; four performing only univariate analyses and three performing univariate and multivariate
2042 analyses.[55, 61, 63, 77] In the first study, the univariate results were not presented but there was a
2043 significant multivariate relationship between greater rates of decline in percent predicted FEV_1
2044 beginning at age 5 years and ending at age of death but the effect size was not reported.[55] The
2045 second study found that patients who died had a steeper percent predicted FEV_1 decline per year
2046 than those who lived (MD 1.07 percent per year, p=0.0001) upon univariate analysis and a
2047 significant increase in the hazard of death upon multivariate analysis (HR 1.3, p=0.0001).[61] The
2048 third study evaluated the univariate, but not the multivariate, relationship between the decline in
2049 percent predicted FEV_1 over the 4 years preceding death and found a significant difference in
2050 percent predicted FEV_1 decline per year in the 4 years preceding death (MD 6.1 percent, p<0.01)
2051 and the percent predicted FEV_1 decline per year in the 2 years preceding death (MD 9.7 percent,
2052 p<0.01), however the percent predicted FEV_1 decline per year between 2 and 4 years preceding
2053 death was not a significant predictor of death (MD 4.25 percent, p=0.22).[63] In the final study,
2054 univariate (HR 1.25, 95 percent CI 1.04 to 1.52) and multivariate (HR 1.47, 95 percent CI 1.18 to
2055 1.85) analysis revealed that a decline in percent predicted FEV_1 per year significantly increased
2056 the hazard of death.[77]

2057 *Ten Percent Decline in Percent Predicted Forced Expiratory Volume in One Minute (FEV_1)*

2058 Two studies performed univariate analysis to evaluate the relationship between a 10 percent
2059 decline in percent predicted FEV_1 and mortality, but only one evaluated the multivariate
2060 relationship.[50, 76] The first study found that there was a significant increase in the risk of death for
2061 those who had a decrease in percent predicted FEV_1 below 10 percent of the predicted value in
2062 univariate (RR 1.8, 95 percent CI 1.7 to 2.0) and multivariate (RR 2.0, 95 percent CI 1.9 to 2.2)
2063 analysis.[50] The second study found that there was a significant increase in the hazard of death for
2064 those with a 10 percent decrease in percent predicted FEV_1 in univariate (HR 2.1, 95 percent CI
2065 1.5 to 3.0) but not multivariate analysis.[76]

2066 *Forced Expiratory Volume in One Minute (FEV_1) Z-Score*

2067 In one study, the positive predictive value and sensitivity of having an FEV_1 Z-score below
2068 negative 2 versus a more normal value on the outcome of death or need for transplantation was
2069 evaluated.[79]The authors suggested a clinically relevant positive predictive value and sensitivity
2070 would be 70 percent and 90 percent.[79] The positive predictive values for children aged 8, 9, 10,
2071 11 and 12 ranged from 10 to 47 percent and the sensitivities ranged from 33 percent to 76

percent suggesting that having an FEV_1 Z-score at or below negative 2 is not a strong predictor of mortality or need for transplantation.[79] No differences were seen between those who subsequently died or had a need for transplantation versus those who survived on FEV_1 Z-score decline over the previous 2 years in children aged 10 to 12.[79]

Forced Expiratory Volume in One Minute/Forced Vital Capacity (FEV_1/FVC) at Baseline

Three studies evaluated the relationship between FEV_1/FVC and mortality in univariate but not multivariate analyses.[52, 64, 111] In the first study, there was no significant difference in FEV_1/FVC at baseline between those who lived versus those who subsequently died, but the effect size and measures of variance were not reported.[111] In the second study, a decline in FEV_1/FVC at baseline was not associated with the risk of death (RR 1.00, 95 percent CI 0.98 to 1.03).[52] In contrast, in the third trial the FEV_1/FVC ratio at baseline was significantly lower in those who survived versus those who subsequently died (MD 0.04, p=0.011).[64]

Anthropometrics

Twenty-seven studies evaluated the relationship between mortality and various anthropometric measurements and mortality.[8, 47, 49-52, 54, 56, 58-60, 62, 64-69, 71-74, 76-79, 111] (Appendix Table 2)

Height at Baseline

Five studies evaluated the relationship between height at baseline and mortality using univariate analysis,[56, 64, 68, 71, 76] while two of these studies used multivariate analysis.[56, 68] In the first study, those with greater height lived had a reduced risk of death than those with a lesser height based upon univariate analysis, but the effect size was not reported (ES NR, p<0.001) and multivariate analysis (RR 0.033, p<0.0001).[56] Like the first study, height was higher in those who lived versus those who subsequently died (MD -3 cm, p=0.073).[64] In the third study no significant difference in height at baseline occurred between those who subsequently died and those that lived (MD -0.6in, 95 percent CI -3.44 to 2.24).[71] Similar to the third trial and in contrast with the first two trials, the fourth study found that there was no significant difference in height at baseline between those who subsequently died and those who lived (MD -1cm, p=0.30).[76]

The final study used univariate and multivariate analysis to evaluate the relationship between mortality and the mean height in 1996, when the study began retrospectively reviewing data from the United States Cystic Fibrosis Foundation National Patient Registry in 1996.[68] There was a significant association between mean height at baseline and mortality upon univariate analysis but investigators did not report an effect size (ES NR, SS). Multivariate analysis revealed a significant increase in the risk of dying among patients with a higher mean height at baseline than those with a lower mean height at baseline (OR 1.04, 95 percent CI 1.03 to 1.05).[68]

Height-for-age at baseline

One study evaluated the relationship between mortality and calculated height-for-age at baseline using univariate but not multivariate analysis.[72] Those with a higher calculated height at baseline were not significantly more likely to die than those who lived (MD -1, p=0.8).[72]

2111 *Height Quartile*

2112 One study evaluated the relationship between mortality and height within the shortest height
2113 quartile.[76] The hazard of death was not significantly increased for those with a height in the
2114 shortest height quartile compared to those with a height above the shortest quartile in univariate
2115 (HR 1.4, 95 percent CI 0.9 to 2.4) or multivariate analysis.[76]

2116 *Height Percentile*

2117 Two studies evaluated the relationship between height percentile and mortality.[8, 49] The first
2118 study evaluated the baseline height percentile in patients seen in CF clinics in Boston, MA, and
2119 Toronto, Canada. Based on univariate analysis, there was not a significant difference in height
2120 percentile among those who lived versus those who died at the Boston clinic (MD -1 percent, 95
2121 percent CI -12.29 to 10.29), however those who died at the Toronto clinic had a significantly
2122 lower height percentile (MD -10 percent, $p<0.05$).[49] The second study found a significant
2123 increase in the hazard of death for males and females at age 5 (males: HR 2.9, 95 percent CI 1.23
2124 to 6.91 and females: HR 4.3, 95 percent CI 2.54 to 7.31) and age 7 (males: HR 6.3, 95 percent CI
2125 2.10 to 18.87 and females: HR 5.8, 95 percent CI 2.53 to 13.11) occurred if the height-for-age
2126 was below the 5th percentile.[8]

2127 *Height Z-score*

2128 Two studies evaluated the relationship between mortality and height Z-score using univariate
2129 analysis,[59, 69] but only one of the two studies performed multivariate analysis. One study
2130 performed univariate, but not multivariate analysis to evaluate relationship between height-for-
2131 age Z-score above and below -1.29. The study found that those who had a height-for-age Z-score
2132 less then -1.29 did not have a significant increase in the risk of death (RR 4.06, $p=0.06$).[69]

2133 The other study evaluated the hazard of death for individuals based on quartile of height Z-
2134 score with the lowest quartile further divided above and below the 10th percentile.[59] In this study,
2135 the hazard of death in the 2 years following Z-score measurement for those with a height Z-score
2136 ranging from -0.46 to -1.32 was not significantly increased compared to those with a height Z-
2137 score > -0.46 based on univariate (HR 1.4, 95 percent CI 0.9 to 2.1) or multivariate (HR 1.1, 95
2138 percent CI 0.6 to 1.9) analysis.[59] The hazard of death in the 2 years following Z-score
2139 measurement for those with a height Z-score ranging from -1.33 to -2.21 was significantly
2140 increased compared to those with a height Z-score > -0.46 on univariate (HR 1.6, 95 percent CI
2141 1.1 to 2.5) but not multivariate (HR 1.0, 95 percent CI 0.5 to 1.9) analysis.[59] The hazard of death
2142 in the 2 years following Z-score measurement for those with a height Z-score ranging from -2.22
2143 to -3.25 was significantly increased compared to those with a height z score > -0.46 based on
2144 univariate (HR 4.6, 95 percent CI 3.1 to 6.7) but not multivariate (HR 1.9, 95 percent CI 0.9 to
2145 4.1) analysis.[59] Finally, the hazard of death in the 2 years following Z-score measurement for
2146 those with a height Z-score ≤-3.26 was significantly increased compared to those with a height
2147 Z-score > -0.46 based on univariate (HR 8.8, 95 percent CI 5.9 to 13.1) and multivariate
2148 (HR=2.9, 95 percent CI 1.2 to 7.0) analysis.[59]

2149 *Weight*

2150 Two studies evaluated the relationship between weight and mortality at the time of
2151 evaluation for lung transplantation using univariate, but not multivariate analyses.[64, 71] The first
2152 study found that weight at the time of evaluation for transplant was not significantly different in
2153 those who lived compared to those who subsequently died (MD -2.4kg, $p=0.200$).[64] The second

study found that weight at the time of evaluation for transplant was not significantly different in those who lived compared to those who subsequently died (MD 6.5 lbs, 95 percent CI -26.61 to13.61).[71]

Birth Weight

One study evaluated the relationship between birth weight and mortality using univariate and multivariate analysis.[69] This study found that there was a significant reduction in the risk of death for those individuals with a birth weight greater than or equal to 3000 grams when compared to those with a birth weight less than 3000 grams upon univariate (RR 4.06, p=0.01) and multivariate (RR 7, p<0.001) analysis.[69]

Relative Underweight

One study evaluated the univariate, but not the multivariate relationship between being relatively underweight and mortality.[47] The study found that those who lived were less likely to be relatively underweight for age than those who subsequently died, but effect size was not reported (ES NR, p<0.05).[47]

Weight Percentile

Three studies evaluated the relationship between mortality and weight percentile[49, 67, 111] but only one performed multivariate analysis.[111] The first study that evaluated individuals in two different clinics found that there was a significant difference in weight percentile between those who lived and those that subsequently died at both sites (Site 1 MD -25 percent, p<0.001, Site 2: MD -25 percent, p<0.001).[49] The second study evaluated the relationship between mortality and weight percentile above and below the fiftieth percentile.[67] The hazard of death was significantly increased for those individuals with a weight less than or equal to the fifth percentile when compared to those with a weight greater than fiftieth percentile using univariate analysis (HR 3.9, 95 percent CI 2.1 to 7.3).[67] The hazard of death was significantly increased for those individuals with a weight from the fifth to the fifteenth percentile compared to those with a weight greater than the fiftieth percentile based on univariate analysis (HR 2.4, 95 percent CI 1.2 to 4.8).[67] Finally, the hazard of death was not significantly increased when those individuals with a weight from the fifteenth to the fiftieth percentile were compared to those with a weight greater than the fiftieth percentile using univariate analysis (HR 1.5, 95 percent CI 0.8 to 2.9).[67]

In the final study, the weight percentile was significantly lower in patients who died compared to those who lived based upon univariate analysis (MD -10.8 percent, p=0.0001) but lower weight percentile was not a multivariate predictor of mortality.[111] Patients who died were more likely to have a weight percentile less than the five at age 18 years than those who lived (MD -39 percent, p=0.0004) based upon univariate analysis, however weight percentile was a multivariate predictor of mortality but study did not report the effect size (ES NR, p<0.0001).[111]

Percent Predicted Weight

Three studies conducted univariate analysis to evaluate the relationship between percent predicted weight and mortality, [49, 56, 62] but only one of them performed multivariate analysis.[49] The first study found a significant univaraite relationship between percent predicted weight and mortality but did not report an effect size.[56] The second study did not find a significant difference in percent predicted weight between those who lived and those who subsequently died (MD -3.3 percent, 95 percent CI -6.25 to 12.85).[62]

The final study found a significant decrease in the hazard of death among those individuals with a higher percent predicted weight compared to those with a lower percent predicted weight in univariate (HR 0.95, 95 percent CI 0.93 to 0.96) but not multivariate analysis (HR 0.99, 95 percent CI 0.98 to 1.00).[49]

Weight-for-Height

Two studies evaluated the relationship between weight-for-height and mortality using univariate but not multivariate analysis.[52, 72] The risk of death was significantly decreased (RR 0.96, 95 percent CI 0.92 to 0.99) in those with a higher weight for height compared to those with a lower weight for height.[52] In the second study, the weight-for-height at baseline was significant greater for those who lived compared to those who subsequently died (MD -13, p=0.01). [72]

Percent Predicted Weight-for-Height

One study evaluated the relationship between percent predicted weight-for-height and mortality.[50] Both univariate (RR 1.4, 95 percent CI 1.3 to 1.5) and multivariate (RR 1.4, 95 percent CI 1.3 to 1.5) analyses revealed a significant increase in the risk of death for those individuals with a lower percent predicted weight-for-height compared to those individuals with a higher percent predicted weight for height.[50]

Weight Z-score

Two studies evaluated the relationship between weight Z-score and mortality using univariate and multivariate analyses.[59, 65] The first study evaluated the relationship between mortality and weight Z-score above and below -0.46 using univariate, but not multivariate analysis.[59] In this study, the hazard of death was not significantly increased for those with a weight Z-score between -0.49 and -1.25 when compared to those with a weight Z-score greater than -0.49 (HR 1.2, 95 percent CI -0.7 to 2.1).[59] The hazard of death was significantly increased in those with a weight Z-score between -1.26 and -1.98 when compared to those with a weight Z-score greater than -0.49 (HR 2.8, 95 percent CI 1.7 to 4.4).[59] The hazard of death was significantly increased in those with a weight Z-score between -1.98 and -2.74 when compared to those with a weight Z-score greater than -0.49 (HR=7.8, 95 percent CI 5.0 to 12.2).[59] Finally, the hazard of death was significantly increased in those with a Z-score ≤-2.75 when compared to those with a Z-score greater than -0.49. (HR 16.4, 95 percent CI 10.5 to 25.6).[59] The second study found a statistically significant univariate relationship between mortality and weight for age Z-score but did not report an effect size (ES NR, SS), while multivaratie analysis revealed a non-significant decrease in the odds of death for those with a higher weight for age Z-score compared to those with a lower weight for age Z-score (OR 0.75, NS).[65]

Body Mass Index (BMI) ≤ 16 versus ≥18.6

One study evaluated the relationship between mortality and a BMI less than or equal to 16 or greater than or equal to 18.6 using univariate, but not multivariate analysis.[51] In this study there was no significant difference in the risk of death for those with a BMI less than or equal to 16 when compared with those who had a BMI greater than or equal to 18.6 (RR 1.6, 95 percent CI 0.8 to 3.1).[51]

2235 *Body Mass Index (BMI) at Baseline*

2236 Three studies evaluated the relationship between BMI at baseline and mortality using
2237 univariate and multivariate analyses.[58, 60, 78] The first study found that BMI at baseline was
2238 significantly greater among those who lived compared to those who died using univariate
2239 analysis (MD -1.9 kg/m^2, p=0.001) but BMI at baseline was not a significant multivariate
2240 predictor of mortality (ES NR, NS).[58] The second study did not report an effect size for
2241 univariate or multivariate analysis, but did report a significant univariate (ES NR, p=0.05) and
2242 multivariate, but the effect size was not reported (ES NR, SS) relationship between BMI and
2243 mortality.[60] In the last study individuals who lived had a significantly higher BMI at baseline
2244 than those who died (MD -1.5kg/m^2, p=0.008), but baseline BMI was not a multivariate
2245 predictor of mortality, but the effect size was not reported (ES NR, p=0.31).[78]

2246 *Body Mass Index (BMI) Prior to Intensive Care Unit Admission*

2247 Three studies evaluated the relationship between mortality and BMI prior to admission to the
2248 intensive care unit for pulmonary exacerbation using univariate but not multivariate analyses.[73,
2249 74, 77] The first study found that there was a significant increase in the risk of death among those
2250 with a BMI less than 18 at the time of admission to the intensive care unit compared to those
2251 with a BMI greater than 18 at the time of admission (RR 3.25, 95 percent CI 1.27 to 3.25).[73] The
2252 second study found a non-significant decrease in the hazard of death for those individuals with a
2253 lower BMI at the time of admission to the Intensive Care Unit compared to those with a higher
2254 BMI at the time of admission (HR 0.87, 95 percent CI 0.69 to1.11).[74] A final study found that
2255 there was no significant increase in the hazard of death for those patients admitted to the
2256 intensive care unit that had a lower BMI when compared to those with a higher BMI (HR 0.95,
2257 95 percent CI 0.80 to 1.13).[77]

2258 *Body Mass Index (BMI) at Time of Transplant Evaluation*

2259 Two studies evaluated the relationship between mortality and BMI using univariate but not
2260 multivariate analysis.[71, 76] The first study found no significant difference in BMI at the time of
2261 evaluation for lung transplant when individuals who lived were compared to those who
2262 subsequently died using univariate analysis (MD -1.26 kg/m^2, 95 percent CI -3.91 to 1.39).[71] The
2263 second study found no significant increase in hazard of death for those with a lower BMI than
2264 those with a higher BMI at the time of evaluation for lung transplant (HR 1.0, 95 percent CI 0.9
2265 to 1.1).[76]

2266 *Percent Ideal Body Weight (IBW)*

2267 One study evaluated the relationship between percent ideal body weight in patients at the
2268 time of listing for lung transplant and mortality using univariate but not multivariate analysis,
2269 and found the percent IBW was not significantly higher in those who lived versus those who
2270 subsequently died (MD 1 percent, p=0.685).[64]

2271 *Percent Ideal Body Weight (IBW) at Baseline*

2272 One study evaluated the relationship between percent ideal body weight at baseline and
2273 mortality using univariate and multivariate analysis.[66] The study found that there was a
2274 significant decrease in the risk of death for those with a higher percent IBW at baseline
2275 compared to those with a lower percent IBW at baseline upon univariate (RR 0.955, 95 percent
2276 CI 0.944 to 0.967) and multivariate (RR 0.968, 95 percent CI 0.947 to 0.99) analysis.[66]

2277 *Percent Ideal Body Weight (IBW) ≤85 percent*

2278 One study evaluated the relationship between percent ideal body weight less than 85 percent
2279 and mortality.[66] In the study there was a significant increase in the hazard of death for those
2280 individuals with a percent IBW less than 85 percent when compared to those with a percent IBW
2281 greater than 85 percent (HR 2.64, 95 percent CI 1.85 to 3.75).[66]

2282 *Percent Ideal Body Weight (IBW) Evaluated by Percent*

2283 One study evaluated the relationship between percent ideal body weight and mortality using
2284 univariate, but not multivariate analysis.[59] The study found that the hazard of death was not
2285 significantly increased for individuals with a percent IBW between 98 and 104.9 when compared
2286 to those with a percent IBW greater than 105 (HR 0.9, 95 percent CI 0.6 to 1.5).[59] The hazard of
2287 death was significantly increased for individuals with a percent IBW between 90 and 97.9 when
2288 compared to those with a percent IBW greater than 105 (HR 1.6, 95 percent CI 1.1 to 2.3).[59] The
2289 hazard of death was significantly increased for individuals with a percent IBW between 84 and
2290 89.9 when compared to those with a percent IBW greater than 105 (HR 3.2, 95 percent CI 2.2 to
2291 4.7).[59] The hazard of death was significantly increased for individuals with a percent IBW less
2292 than 84 when compared to those with a percent IBW greater than 105 (HR 7.1, 95 percent CI 5.0
2293 to 10.2).[59]

2294 Protein Turnover

2295 No studies reported the relationship between protein turnover and mortality in CF patients.

2296 Exercise Tolerance

2297 A total of 10 studies evaluated the link between various measures of exercise tolerance and
2298 mortality. [51-53, 57, 58, 62, 64, 71, 75, 76] (Appendix Table 3)

2299 *Walk Testing*

2300 A total of nine studies evaluated the link between exercise tolerance and mortality.[52, 53, 57, 58,
2301 62, 64, 71, 75, 76]

2302 Five studies evaluated the link between 6 minute walk testing and mortality.[53, 57, 62, 64, 76]
2303 Three studies evaluated the relationship between distance walked in meters and mortality using
2304 univariate but not multivariate analyses. [53, 57, 62] In these studies, patients who subsequently died
2305 qualitatively walked a lesser distance (ranging from 43 to 137 meters less in distance walked)
2306 than those who survived, but walking distance was only a univariate predictor of mortality in one
2307 of the three studies (MD -137.4, p=0.016). In the fourth study, the univariate and multivariate
2308 relationship between distance walked, in 50 meter increments, and mortality were evaluated.[64]
2309 For each 50 meter increase in the six minute walk distance, the risk of death decreased by 27
2310 percent (RR 0.73, 95 percent CI 0.62 to 0.87) in univariate and 31 percent (RR 0.69, 95 percent
2311 CI 0.57 to 0.84) in multivariate analysis. In the same study, for every five percent incremental
2312 increase in distance walked, the risk of death decreased by 18 percent (RR 0.82, 95 percent CI
2313 0.72 to 0.94) but multivariate analysis was not conducted.[64] In the fifth study, individuals with a
2314 lesser six minute walk distance did not have an increased hazard of death than those with a
2315 greater six minute walk distance (HR 1.0, 95 percent CI 0.99 to 1.0) upon univariate analysis and
2316 no multivariate analysis was conducted.[76]

In a similar study, the univariate relationship between exercise tolerance after a 12 minute walk and mortality was explored but multivariate analysis was not conducted.[52] When comparing patients who walked a distance above the median of 540 meters against patients who walked a distance below the median, the relative risk of death was not significantly increased (RR 0.89, 95 percent CI 0.41 to 1.95).[52]

Percent Predicted Peak Oxygen Uptake ($VO_{2\text{-}peak}$)

Two studies evaluated the relationship between percent predicted peak oxygen uptake during exercise testing.[51, 58]

In the first study, those who lived had a significantly greater percent predicted peak oxygen uptake than those who subsequently died (MD -12.9 percent, p=0.022) but no significant multivariate relationship was seen.[58] Unfortunately, the effect size and measure of variance were not reported for the multivariate analysis.[58]

In the second study, both univariate and multivariate analysis were performed to evaluate the relationship between having a peak oxygen uptake less than or equal to 58 percent versus greater than or equal 82 percent during exercise testing and mortality.[51] The relative risk of death was higher subjects with peak oxygen uptake of less than or equal to 58 percent versus those with values greater than or equal to 82 percent during exercise testing in univariate (RR 6.4, 95 percent CI 2.6 to 15.7) and multivariate (RR 3.2, 95 percent CI 1.2 to 8.6) analysis, respectively.[51]

Peak Oxygen Uptake ($VO_{2\text{-}peak}$)

Two studies evaluated the relationship between maximum oxygen uptake ($VO_{2\text{-peak}}$) during exercise testing and mortality using univariate but not multivariate analysis.[71, 75] In the first study, there was no significant difference in maximum oxygen uptake during exercise testing between those who subsequently died and those who survived (MD - 0.171 L/min, 95 percent CI -1.85 to 2.19).[71] In the second study, no relationship was seen between increasing peak oxygen uptake and mortality (HR 0.953, 95 percent CI 0.865 to 1.051) in initial testing but a univariate relationship was seen during final testing where for every 1mL/min/kg increase in peak oxygen uptake, the hazard of death was (MD 0.845, 95 percent CI 0.757 to 0.944).[75]

Percent Predicted Peak Work Rate (W_{peak})

One study evaluated the relationship between the percent predicted peak work rate during exercise testing and mortality using both univariate and multivariate analysis.[58] Those patients who lived had a significantly greater percent predicted peak work rate during exercise testing than those who subsequently died (MD -18.1 percent, p=0.015) in univariate analysis but peak work rate was not a multivariate predictor of mortality.[58]

Minute Ventilation/Peak Oxygen Uptake (VE/VO_2)

One study evaluated the relationship between the ratio of minute ventilation to peak oxygen uptake during exercise testing and mortality using both univariate and multivariate analysis.[58] The study found that those who died had a statistically greater VE/VO_2 during exercise testing than those who lived (MD 6.3, p=0.002), and that VE/VO_2 was not a multivariate predictor of mortality.[58]

Peak Minute Ventilation (VE_{peak})

One study evaluated the relationship between the peak minute ventilation during exercise testing and mortality using both univariate and multivariate analysis.[58] The peak minute ventilation was greater in those who lived than those who subsequently died (MD -8.1 L/min, p=0.04) but peak minute ventilation was not a significant multivariate predictor of mortality.[58]

Bone Mineralization

No studies reported the relationship between bone mineralization and mortality in CF patients.

Health-Related Quality of Life

Pulmonary Function

A total of 14 studies evaluated the link between pulmonary function and various scales of HRQoL.[81-92, 94-97] (Appendix Table 4)

Alltagsleben (Every Day Life)

One study evaluated the link between pulmonary function and the Alltagsleben questionnaire, a scale developed for German-speaking patients.[85] Staab and colleagues evaluated 89 adolescents and adults with CF.[85] Staab and colleagues analyzed results in two different hierarchical regression analysis models, the first of which included subjective health perception variables and the other which included ways of coping variables.[85] In univariate analysis, there was a significant positive relationship between FEV_1 and Alltagsleben scores (r=0.31, p<0.01 for model 1 where n=83, and r=0.36, p<0.001 in model 2 where n=84).[85] From the publication, it is not specified whether the values for FEV_1 are absolute or percent predicted, as units of measure were not reported; however, in looking at the mean values of FEV_1 and their range in the patients studied, it appears to be percent predicted FEV_1.[85]

Upon multivariate analysis, FEV_1 was no longer statistically significant in model 1 (β=0.12, p-value not reported), but retained statistical significance in model 2 (β=0.24, p<0.05).[85]

Child Health Questionnaire

The univariate relationship between pulmonary function and CHQ was evaluated in two studies but multivariate analyses were not conducted.[88, 91] Powers and colleagues evaluated 24 adolescents with CF during a routine CF clinic visit.[88] In these patients, there was a significant positive univariate relationship between percent predicted FEV_1 and the domains of general health, role/social-physical, and bodily pain (r=0.73, 0.47, and 0.42 respectively, p<0.05 for all).[88] Nonsignificant positive correlations were found between percent predicted FEV_1 and domains of physical functioning, role/social-emotional, mental health, family activities, and self-esteem (range of r values were from 0.24 to 0.39, p-values not reported).[88] Nonsignificant negative univariate correlations were found between percent predicted FEV_1 and domains of role/social-behavior and behavior problems (range of r values were from -0.21 to -0.04, p-values not reported).[88]

In another evaluation of 36 patients, ranging in age from 10 to 15.5 years, there was no univariate relationship found between percent predicted FEV_1 to any of the 12 subscores of the CHQ (p-values not reported), with the exception of family cohesion subscore (r=0.37, p=0.05).[91]

2397 *Cystic Fibrosis Quality of Life Questionnaire*

2398 One study evaluated the link between pulmonary function and the CFQoL scale.[89, 90] Adults
2399 and adolescents with CF were surveyed.[89, 90] Univariate results are presented separately for males
2400 and females.[89] In females, there was a significant positive correlation between percent predicted
2401 FEV_1 and seven domains of the CFQoL (emotional functioning, relationships, physical
2402 functioning, body image, chest symptoms, career issues, and treatment issues; r values ranged
2403 from 0.17 to 0.60, $p<0.05$ for all), while there was no significant relationship between FEV_1 and
2404 the two domains of concerns for the future or social functioning (p-values not reported).[89] In
2405 males, there was a significant relationship between percent predicted FEV_1 in all domains (r
2406 values ranged from 0.22 to 0.50, $p<0.05$ for all) except the domain for relationships (p-value not
2407 reported).[89]

2408 Multivariate analysis combined data for participants regardless of gender.[90] Upon
2409 multivariate analysis, percent predicted FEV_1 was significantly associated with seven domains
2410 (physical functioning, social functioning, treatment issues, chest symptoms, emotional
2411 functioning, concerns for the future, and interpersonal relationships; β values ranged from 0.12 to
2412 0.29, (p-values not reported) and was not significantly associated with body image or career
2413 concerns (p-values not reported).[90]

2414 *Cystic Fibrosis Questionnaire*

2415 Three studies evaluated the univariate link between pulmonary function and CFQ but
2416 multivariate analyses were not conducted.[92, 95-97] All three studies found a significant positive
2417 univariate relationship between percent predicted FEV_1 and physical domain (r values ranged
2418 from 0.27 to 0.57, $p<0.05$ for all) and health perceptions domain (r values ranged from 0.38 to
2419 0.51, $p<0.05$ for all).[92, 95-97] Havermans and colleagues did not report results for any of the
2420 remaining domains of the CFQ.[96, 97] Both Quittner and colleagues and Riekert and colleagues
2421 found a significant positive univariate relationship between percent predicted FEV_1 and seven
2422 other CFQ domains (role, vitality, social, body image, eating, respiratory, and weight; r values
2423 ranged from 0.23 to 0.41, $p<0.01$ for all).[92, 95] Quittner and colleagues additionally found a
2424 significant positive univariate correlation between percent predicted FEV_1 and the emotion
2425 domain ($r=0.28$, $p<0.01$), while Riekert and colleagues did not ($r=0.20$, p-value not reported).[92]
2426 Percent predicted FEV_1 was also positively associated with the treatment domain in the study by
2427 Riekert and colleagues ($r=0.32$, $p<0.01$), but was not significantly correlated in the study by
2428 Quittner and colleagues ($r=0.11$, p-value not reported).[92, 95] The digestive domain was not
2429 associated with percent predicted FEV_1 in either study (r values ranged from 0.01 to 0.03, p-
2430 values not reported).[92, 95]

2431 *EuroQoL-5D*

2432 The link between pulmonary function and EQ-5D was reported in one study.[86] At baseline
2433 evaluation of 39 adults with CF, percent predicted FEV_1 was significantly positively associated
2434 with EQ-5D on univariate analysis (Spearman's $\rho=0.427$, $p=0.017$).[86]

2435 After 1 year, the EQ-5D was readministered to patients and there was a significant
2436 multivariate relationship between percent predicted FEV_1 at baseline and EQ-5D index after 1
2437 year ($\beta=0.000$, $p=0.005$).[86]

2438 *Medical Outcomes Short Form-36*

2439 Two studies evaluated the univariate link between pulmonary function and SF-36 but
2440 multivariate analyses were not conducted.[86, 87] In adults with CF (n=39), there was a significant
2441 positive univariate relationship between percent predicted FEV_1 and the physical composite
2442 score (Spearman's ρ=0.396, p=0.025).[86] Abbott and colleagues evaluated English CF patients
2443 aged 14-18 years (n=58) and German patients aged 13 to 17 years (n=26).[87] In both English and
2444 German patients, there was a significant positive univariate relationship between percent
2445 predicted FEV_1 and the physical functioning subscore (r=0.39, p<0.003 and r=0.43, p<0.03,
2446 respectively).[87] Neither population showed significant relationships between percent predicted
2447 FEV_1 and the remaining domains of the SF-36 (physical role limitation, social functioning,
2448 mental health, mental role limitation, energy and vitality, general health perceptions, changes in
2449 health; p-values not reported).[87]

2450 *Nottingham Health Profile*

2451 One study reported on the univariate link between pulmonary function and NHP but
2452 multivariate analysis was not conducted.[83] In clinically stable adults with CF (age over 16 years),
2453 there was a statistically significant negative univariate relationship between percent predicted
2454 FEV_1 and all subscores of NHP (r values ranged from -0.51 to -0.15, p<0.05 for all), with higher
2455 percent predicted FEV_1 indicating better HRQoL.[83]

2456 *Quality of Well-Being Scale*

2457 Two studies evaluated the univariate relationship between pulmonary function and QWB
2458 scores but multivariate analyses were not conducted.[81, 82] Orenstein and colleagues evaluated CF
2459 patients aged 7 to 36 years (n=44) and found a statistically significant positive relationship
2460 between absolute FEV_1 and QWB (r=0.55, p<0.0001) on univariate analysis.[81]

2461 Czyzewski and colleagues found no relationship between pulmonary function and QWB in
2462 their study of patients under age 18 (r= -0.07 and 0.001 for percent predicted FEV_1 and percent
2463 predicted FVC, respectively, p-values not reported).[82]

2464 *Questions on Life Satisfaction*

2465 The relationship between pulmonary function and the Questions on Life Satisfaction Scale
2466 was evaluated in one study.[94] Results of univariate analysis were not reported. Upon multivariate
2467 analysis of patients aged at least 15 years with CF, neither percent predicted FEV_1 at second
2468 clinic visit nor the change in percent predicted FEV_1 between two clinic visits were significantly
2469 associated with HRQoL scores (p-values not reported).[94]

2470 *Sickness Impact Profile*

2471 One study evaluated the univariate link between pulmonary function and SIP but multivariate
2472 analysis was not conducted.[84] Upon univariate analysis, percent predicted FEV_1 negatively
2473 correlated with overall SIP and physical subscores but was not statistically significant (r= -0.33
2474 and -0.40, respectively, p-values not reported), and was nonsignificantly positively correlated
2475 with psychosocial subscore (r=0.05, p-value not reported).[84]

2476 Anthropometrics

2477 A total of 10 studies evaluated the link between anthropometric measures and various scales
2478 of HRQoL.[83, 85-87, 89-94, 96, 97] (Appendix Table 5)

2479 *Alltagsleben (Every Day Life)*

2480 One study evaluated HRQoL using the "Alltagsleben" questionaire, a scale developed for
2481 German-speaking patients.[85] Staab and colleagues evaluated 89 adolescents and adults with CF.[85]
2482 Staab and colleagues analyzed results in two different hierarchical regression analysis models,
2483 the first of which included subjective health perception variables and the other which included
2484 ways of coping variables.[85] Univariate analysis showed no significant relationship between
2485 percent IBW and HRQoL (r=0.11 in model 1 where n=83, and r=0.10 in model 2 where n=84).[85]
2486 In multivariate analysis, no significant association between percent IBW and subjective health
2487 perception or ways of coping (β=0.05 and -0.11 in models 1 and 2, respectively, p-values not
2488 reported).[85]

2489 *Child Health Questionnaire*

2490 One study evaluated the univariate relationship between anthropometrics and the CHQ scale
2491 but multivariate analysis was not conducted.[91] In 36 patients ranging in age from 10 to 15.5
2492 years, there was no univariate relationship found between either height-for-age or weight-for age
2493 Z-scores and any of the 12 subscores of the CHQ (p-values not reported), with the exception of
2494 weight-for-age Z-score and the general health perception subscore (r=0.36, p=0.03).[91]

2495 *Cystic Fibrosis Quality of Life Questionnaire*

2496 One study evaluated the association between anthropometrics and the CFQoL scale. Adults
2497 and adolescents with CF were surveyed.[89, 90] Univariate results are presented separately for males
2498 and females.[89] The only domain that had a significant positive relationship in both males and
2499 females was the relationship between BMI and the CFQoL body image subscore (r=0.34 and
2500 0.55 respectively, p=0.001 for both).[89] Males additionally experienced a significant positive
2501 relationship between BMI and chest symptoms (r=0.21, p=0.02), while females did not (p-value
2502 not reported).[89] Females also showed a significant positive relationship between BMI and
2503 concerns for the future (r=0.20, p=0.02), while males did not (p-value not reported).[89] All other
2504 domains of CFQoL (physical functioning, social functioning, treatment issues, emotional
2505 functioning, social functioning, treatment issues, emotional functioning, interpersonal
2506 relationships, and career concerns) were not significant for both males and females (p-values not
2507 reported).[89]

2508 For multivariate analysis, all patients were analyzed as a single group, regardless of gender.[90]
2509 Higher BMI was associated with the body image subscore (β=3.4, 95 percent CI 2.1 to 4.6), but
2510 all other domains were not significantly associated (p-values not reported).[90]

2511 *Cystic Fibrosis Questionnaire*

2512 Three studies evaluated the link between anthropometrics and CFQ.[92, 96, 97] Two studies
2513 reported results on each of the twelve subscores of the CFQ in adults and adolescents with CF.[92,
2514 96, 97] Both studies found a significant positive univariate relationship between BMI and body
2515 image domain and eating domain, with higher BMI correlating with higher body image score (r
2516 values ranged from 0.28 to 0.38, p<0.05 for all) and higher eating domain scores (r values ranged
2517 from 0.16 to 0.44, p<0.05 for all).[92, 97] Higher BMI was also associated with higher weight

domain scores in both studies (r values ranged from 0.43 to 0.47, p<0.01 for all).[92, 97] Quittner and colleagues additionally found a significant relationship between BMI and health perceptions domain scores (r=0.14, p<0.05).[92] No other domains in Quittner's analysis were statistically significant [92], and results from the remaining domains in the study by Havermans and colleagues were not reported.[97]

Multivariate analysis was conducted in one study, which reported CFQ results in three dimensions (physical, emotion, and social).[93] Koscik and colleagues found that neither adequate weight gain within 2 years of diagnosis nor BMI Z-score greater than -1 were predictors of social or emotion dimension scores upon multivariate analysis of 45 CF patients aged 8 to 18 years.[93] However, adequate weight gain was associated with improvements in the CFQ physical dimension (model p=0.04 after adjusting for age), though BMI Z-score was not (model p=0.52 after adjusting for age).[93]

EuroQoL-5D

One study evaluated the relationship between anthropometrics and EQ-5D. [86] At the baseline evaluation of adults with CF (n=39), there was no significant univariate relationship between BMI and EQ-5D VAS (p-value not reported).[86]

After 1 year, the EQ-5D was re-administered to patients and there was a significant negative multivariate relationship between BMI at baseline and EQ-5D index after 1 year (β= -0.002, p=0.005).[86]

Medical Outcomes Short Form-36

Two studies evaluated the univariate association between anthropometrics and SF-36, multivariate analyses were not conducted.[86, 87] In one study comprised of adult patients with CF (n=39), there was no significant univariate relationship between BMI and either the SF-36 physical composite score or mental composite score (p-value not reported).[86]

Abbott and colleagues evaluated English CF patients aged 14-18 years (n=58) and German patients aged 13 to 17 years (n=26).[87] In both populations, there was no significant univariate relationship between BMI and any of the SF-36 subscores (physical functioning, physical role limitation, social functioning, mental health, mental role limitation, energy and vitality, general health perception, or changes in health) (p-values not reported).[87]

Nottingham Health Profile

One study evaluated the univariate association between anthropometrics and HRQoL, using the NHP, multivariate analysis was not conducted.[83] In 240 patients aged over 16 years, there was a significant univariate negative correlation between BMI and NHP energy subscore, NHP sleep subscore, and physical mobility subscore (p<0.001, p<0.05, p<0.0001, respectively), meaning that higher BMI represents better HRQoL.[83] The relationship between the remaining NHP subscores (pain, emotion, and social isolation) were not significant (p-values not reported).[83]

Questions on Life Satisfaction

One study reported on the relationship between anthropometrics and the Questions on Life Satisfaction scale.[94] In 108 adult and adolescent patients with CF, there was no relationship between BMI and HRQoL in multivariate analysis (p>0.15).[94]

Protein Turnover

No studies reported the relationship between protein turnover and HRQoL in CF patients.

Exercise Tolerance

Two studies evaluated the relationship between exercise tolerance and HRQoL.[81, 84] In pediatric and adult patients evaluated with bicycle ergometer testing and the Quality of Well-Being Scale (QWB), there was a statistically significant relationship between $Vo_{2\text{-peak}}$ and QWB scores, with higher exercise capacity relating to better QWB scores ($p<0.01$).[81, 84] (Appendix Table 6)

In adult patients evaluated with bicycle ergometer testing and the Sickness Impact Profile (SIP), maximal workload (W_{peak}) negatively correlated with SIP Overall Score and Physical Subscore ($p<0.05$ and $p<0.01$, respectively), indicating that greater exercise capacity related to better HRQoL.[84] There was no statistically significant relationship between W_{peak} and SIP Psychosocial Subscore.[84] (Appendix Table 6)

Bone Mineralization

No studies reported the relationship between bone mineralization and HRQoL in CF patients.

Bone Consequences

Pulmonary Function

One study evaluated the association between pulmonary function and important bone consequences.[98] There was no significant relationship between either FEV_1 or FVC and bone fracture, with patients who had experienced bone fracture showing no significant difference in pulmonary function than those who had not experienced fracture.[98] (Appendix Table 7)

Anthropometrics

The study by Aris and colleagues was also the only ones to evaluate the association between anthropometrics and bone fracture.[98] There was no significant difference in BMI between patients who has experienced bone fracture and those who did not.[98] (Appendix Table 8)

Protein Turnover

No studies reported the relationship between protein turnover and bone consequences in CF patients.

Exercise Tolerance

No studies reported the relationship between exercise tolerance and bone consequences in CF patients

Bone Mineralization

No studies reported the relationship between bone mineralization and bone consequences in CF patients.

Discussion

With the limited amount of evidence regarding the impact of rhGH on important health outcomes, it is important to determine if the outcomes affected by rhGH would ultimately predict final health outcomes like HRQoL, bone consequences, and mortality. Therefore, studies which follow the natural progression of CF were sought to determine these linkages. While univariate analysis provides some insight into the relationship between an intermediate and final health outcome, the associations can be greatly impacted by confounders and thus provides weaker evidence. Multivariate analysis allows the determination of a variable's predictive ability, independent of other possible confounding variables. As such, multivariate predictors of an outcome provide more compelling evidence of an association.

The relationship between absolute change in FVC and mortality is weak with one study showing an association but the majority of studies finding no association. The relationship between percent predicted FVC and mortality is also weak, with three studies showing an association, but the majority of studies showing no association. In contrast, half of the studies reported an association between decline in FVC and mortality. In KQ1, we found that rhGH significantly increased the absolute measures of FVC and percent predicted FVC. However, because there was not a strong link between measures of FVC and mortality in KQ3, we cannot be confident in our ability to extrapolate improvements in FVC associated with rhGH therapy to improvements in survival.

The relationship between absolute changes in FEV_1 and mortality is controversial with some limited studies showing an association and others not finding an association. The relationship between percent predicted FEV_1 and mortality is much stronger with many more trials evaluating this association and a majority finding an association between higher percent predicted FEV_1 and improved survival. In KQ 1, we found that rhGH significantly increased absolute measures of $FEV_{1,}$ but did not significantly increase percent predicted FEV_1. As such, we are not as confident in our ability to extrapolate improvements in FEV_1 associated with rhGH therapy to improvements in survival.

Only one of three studies found an association between the FEV_1/FVC ratio and mortality but none of the trials included in KQ1 evaluated the effects of rhGH on FEV_1/FVC.

Height at baseline was not strongly associated with mortality with only two studies reporting an association and the majority of studies reporting no association. One study evaluated the relationship between height for age at baseline and mortality and found no association with mortality. Only one study evaluated the relationship between height quartile and mortality and found no association with mortality. A single study evaluated the relationship between height quartile and mortality finding no association. There was a univariate association between mortality in two of the three studies that evaluated mortality and height percentile but there was no multivariate association. Three studies evaluated the relationship between height Z-score and mortality and found an association for those individuals with lower Z-scores compared to those with higher Z-scores in the majority of univariate and multivariate analyses. In KQ 1, we found that rhGH significantly increased measures of height from baseline, and change from baseline in Z-score. However, because there was not a strong link between measures of height and mortality in KQ3, we can not be confident in our ability to extrapolate improvements in height associated with rhGH therapy to improvements in survival.

2636 The relationship between being relatively underweight and mortality was only evaluated by
2637 one study with a univariate association reported. The relationship between weight percentile and
2638 mortality was evaluated by three studies and all three studies found a univariate association with
2639 mortality, while only one found a multivariate relationship. The majority of studies evaluating
2640 the relationship between mortality and percent predicted weight found a univariate relationship;
2641 however, none reported a multivariate relationship. Weight Z-score was a significantly
2642 associated with mortality in univariate analyses performed by two studies, but no multivariate
2643 associations were found. In the only study that evaluated percent predicted weight-for-height,
2644 there was an association upon univariate and multivariate analysis. Weight-for-height was
2645 associated with mortality in univariate analysis in two studies, but neither found a multivariate
2646 association. Finally, there was only an association between mortality and weight in one of the
2647 three studies evaluating weight as predictor of mortality. In KQ1, we found that rhGH
2648 significantly increased absolute measures of weight from baseline, weight percentile and trended
2649 toward improvements in Z-score. However, because there was not a strong link between
2650 measures of weight and mortality in KQ3, we cannot be confident in our ability to extrapolate
2651 improvements in weight associated with rhGH therapy to improvements in survival.

2652 One study comparing BMI below 16.0 and above 18.6 found no univariate or multivariate
2653 association with mortality. All of the studies evaluating change in BMI from baseline found a
2654 significant univariate association with mortality, but only one found a multivariate association. In
2655 studies evaluating BMI prior to intensive care unit admission, only one found a univariate
2656 association with mortality. Finally, none of the studies evaluating BMI at the time of evaluation
2657 for transplant found an association with mortality. In KQ 1, we found that rhGH significantly
2658 increased the absolute measures of BMI from baseline. As such, we are not as confident in our
2659 ability to extrapolate improvements in BMI associated with rhGH therapy to improvements in
2660 survival.

2661 The only study that evaluated the relationship between percent IBW found no association
2662 with mortality. In contrast, the only study that evaluated the relationship between percent IBW at
2663 baseline and mortality found a univariate and multivariate association with mortality. Percent
2664 IBW below 85 percent was associated with mortality on univariate, but not multivariate analysis.
2665 Similarly, when percent IBW ranging from 84 percent to 97.9 percent compared to <84 percent
2666 there was a significant univariate but not multivariate association with mortality. In KQ 1, we
2667 found that rhGH significantly improved percent of ideal body weight but we are not as confident
2668 in our ability to extrapolate improvements in ideal body weight associated with rhGH therapy to
2669 improvements in survival.

2670 Six-minute walk distance was associated with mortality in only one of the studies evaluating
2671 this outcome and none of the studies found a multivariate association. Additionally, there was no
2672 association between 12-minute walk distance and mortality when univariate analysis was
2673 conducted. In one study that evaluated exercise tolerance in 50 meter increments there was an
2674 association with mortality in univariate and multivariate analysis. There was a univariate
2675 association between 5 percent incremental increases in walk distance and mortality. However,
2676 the impact of rhGH therapy on exercise tolerance in CF patients has not been firmly
2677 established.[40]

2678 Two studies evaluating percent predicted peak oxygen uptake during exercise testing found a
2679 univariate association with mortality, but only one reported a multivariate association. In both
2680 studies, evaluating the relationship between mortality and peak oxygen during exercise testing

uptake there was no association between mortality and initial peak oxygen uptake, but there was a univariate association between final peak oxygen uptake and mortality. The study that evaluated the relationship between percent predicted work rate and during exercise testing and mortality found a univariate association with mortality, but was not associated on multivariate analysis. In KQ1, we found there was no significant improvement in work rate. As such, we are not as confident in our ability to extrapolate improvements in work rate associated with rhGH therapy to improvements in survival.

The study that evaluated the association between the ratio of VE to VO_2 and mortality found a univariate but not multivariate association. One study found that peak minute ventilation was associated with mortality in univariate but not multivariate analysis. None of the trials included in KQ1 evaluated the effects of rhGH on the ratio of VE to VO_2.

There are several limitations to the applicability of studies evaluating the link between intermediate outcomes and HRQoL to patients receiving rhGH therapy in CF. Most studies were cross-sectional and may not elucidate the relationship between clinical status at the time of rhGH administration and HRQoL throughout the patient's life. One study [112]did specifically evaluate this but the results are only available in abstract form even though the abstract was published in 2006. These studies evaluate the innate effect of FEV_1 or anthropometrics on HRQoL and do not account for the potential treatment burden of using rhGH that could attenuate HRQoL improvements. In many studies, relationships were made between intermediate outcomes and individual domains of HRQoL scales, not to the overall HRQoL scales. In these studies, an association between improvements in an intermediate outcomes and several HRQoL subscales may potentially be interpreted as an association with overall HRQoL, but this may be an erroneous conclusion. Finally, only eight studies explicitly state that determining the relationship between intermediate outcomes and HRQoL was an primary objective of their study[83, 84, 86, 88-90, 93-95] with other studies stating primary objectives such as validity assessment either of the tool in a CF population,[81, 82, 92] or comparing HRQoL in CF patients to generally healthy persons.[83, 87]

While numerous studies evaluated the association between higher FEV_1 and HRQoL, all of the trials where it was specified evaluated percent predicted FEV_1 instead of absolute FEV_1. This is problematic since our analysis in KQ 1 suggests that rhGH improved absolute FEV_1 but may not impact percent predicted FEV_1. As such, it makes it difficult to link the impact that rhGH has on absolute FEV_1 with HRQoL. That being said, three of four multivariate analyses found some link between improvements in FEV_1 and improvements in HRQoL.[85, 86, 90, 94]

The multivariate relationship between anthropometrics and HRQoL was assessed in five studies.[85, 89, 90, 94, 112, 115]Most studies showed no relationship between improved measures of weight and improvements in HRQoL. The lack of association may occur because adolescents and adults prefer being underweight.[83, 86] However, one study showed a positive correlation between adequate weight gain at diagnosis and the physical domain of CFQ [93]while another study showed a negative relationship between BMI and EQ-5D.[86] This seemingly contradictory information is difficult to interpret and may be attributable to several factors. Koscik and colleagues evaluated the impact of adequate weight gain within the first 2 years of CF diagnosis on HRQoL in later childhood,[93] while Johnson and colleagues evaluated adult patients in a cross-sectional survey with a 1 year followup.[86] It is possible that adults view their HRQoL differently than children and the impact body weight may have also differs between those populations. The difference might also be due to the specific use of a physical domain of a scale versus an assessment of overall HRQoL in the other study. Finally, an absolute measure of weight, the

2726 BMI, might not be as important in determining HRQoL as how a patient perceives their weight
2727 growth over a period of time.

2728 Only univariate evidence is available to evaluate the link between exercise tolerance and
2729 HRQoL. Both studies found that greater exercise tolerance is significantly related to
2730 improvements in HRQoL.[81, 84] Based on very limited data, the improvements in exercise
2731 tolerance may not impact psychosocial functioning. From the analysis in KQ1, rhGH
2732 qualitatively improved measures of exercise tolerance, although none of the results reached
2733 statistical significance.

2734 Patients with CF are inherently at risk for adverse bone consequences including osteopenia,
2735 osteoporosis, and fractures because of vitamin D malabsorption, poor nutritional status, delayed
2736 pubertal maturation, and physical inactivity.[106] In the one study to evaluate the association
2737 between either FEV_1, FVC, or BMI and bone fracture, no associations were found. This was a
2738 relatively small study and only evaluated bone fracture. Whether associations would have been
2739 seen between these factors and osteopenia or osteoporosis is not known.[98] In addition, aside from
2740 the impact of rhGH on pulmonary function and anthropometrics, rhGH does improve bone
2741 mineralization which might impact adverse bone consequences through another mechanism.
2742

Table 20. Characteristics of studies which report on the relationship between intermediate outcomes and mortality

Study, Year	Quality Rating	Population/Setting	Duration of Followup	Predictors Evaluated
Kraemer, 1978[47] N=117	Poor	Children with CF seen between Jan 1956 and Jun 1976, divided into three groups based on symptoms at diagnosis.	Until death or age 10	Relative underweight
Huang, 1987[48] N=142	Fair	Patients with CF seen at the clinic who had attained age 18 by the end of 1984.	Until death or Dec 1984	%FVC FEV_1/FVC Weight percentile Weight percentile <5 at age 18
Corey, 1988[49] N=1033	Poor	All patients with CF seen in established clinics for CF in Boston or Toronto in 1982.	1 year	%FEV_1 Height percentile Weight percentile
Kerem, 1992[50] N=673	Fair	Patients with CF followed between 1977 and 1989, whose pulmonary function was evaluated at least once before the end of 1987.	2 years	%FVC (10% decrease) %FEV_1 (10% decrease) %Weight-for-height
Nixon, 1992[51] N=109	Fair	Patients with CF aged 7 to 35, who underwent pulmonary function and exercise testing in the late 1970s.	8 years	%FEV_1 ≥50 versus ≥65 BMI ≤16 versus ≥18 $Vo_{2\text{-peak}}$ ≤58 versus ≥82%
Sharples, 1993[52] N=67	Fair	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	FEV_1 %FEV_1 FEV_1/FVC Weight-for-height 12 minute walk test
Ciriaco, 1995[53] N=67	Poor	All patients with CF listed for lung transplantation between Jan 1990 and July 1993.	Until death or transplant by July 1993	FVC %FVC FEV_1 %FEV_1 6 minute walk test
Corey, 1996[54] N=3795	Fair	Patients from the Canadian Patient Data Registry, operated from the Canadian Cystic Fibrosis Foundation, between 1970 and 1989.	Until death or 1989	%FEV_1 % Weight
Corey, 1997[55] N=366	Fair	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	FEV_1 decline FVC decline
Hayllar, 1997[56] N=403	Fair	Patients with CF seen between 1969 and 1987, followed until death or 1989.	Until death or 1989	%FVC %FEV_1 Height %Weight
Kadikar, 1997[57] N=41	Poor	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	6 minute walk test

Table 20. Characteristics of studies which report on the relationship between intermediate outcomes and mortality

Study, Year	Quality Rating	Population/Setting	Duration of Followup	Predictors Evaluated
Moorcroft, 1997[58] N=92	Fair	Patients with CF who underwent exercise testing between 1986 and 1989.	5 years	$\%FEV_1$ BMI $\%Vo_{2\text{-peak}}$ $\%W_{peak}$ VE/Vo_2 VE_{peak}
Rosenfeld, 1997[59] N=21,047	Fair	All patients with CF seen at a Cystic Fibrosis Foundation-accredited clinic between Jan 1988 and Dec 1992.	2 years	$\%FEV_1$ 60-80 versus >80 $\%FEV_1$ 40-59 versus >80 $\%FEV_1$ <40 versus >80 Height Z-score -0.46 to -1.32 versus >-0.46 Height Z-score -1.33 to -2.21 versus >-0.46 Height Z-score -2.22 to -3.25 versus >-0.46 Height Z-score ≤-3.26 versus >-0.46 Weight Z-score -0.49 to -1.25 versus >-0.49 Weight Z-score -1.26 to -1.98 versus >-0.49 Weight Z-score -1.99 to -2.74 versus >-0.49 Weight Z-score ≤-2.75 versus >-0.49 %IBW 98 to 104.9 versus ≥105 %IBW 90 to 97.9 versus ≥105 %IBW 84 to 89.9 versus ≥105 %IBW <84 versus ≥ 105
Bell, 1998[60] N=84	Fair	All patients with CF seen for routine clinic appointment within 3 months of Feb 1994.	4 years	$\%FEV_1$ BMI
Milla, 1998[61] N=61	Fair	All patients with CF followed up since 1975 in whom at least 3 years of followup 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	FEV_1 decline FVC decline
Venuta, 1998[62] N=22	Poor	Patients with CF evaluated for lung transplantation.	NR	FVC %FVC FEV_1 $\%FEV_1$ %Weight 6 minute walk test

Table 20. Characteristics of studies which report on the relationship between intermediate outcomes and mortality

Study, Year	Quality Rating	Population/Setting	Duration of Followup	Predictors Evaluated
Robinson, 2000[63] N=56	Poor	Patients with CF between 7-18 years of age, followed at the Children's Hospital in Boston, Massachusetts between 1980 and 1997.	4 years	%FEV_1 decline in 4 years preceding death %FEV_1 decline in 2 years preceding death %FEV_1 decline in 2 to 4 years preceding death
Vizza, 2000[64] N=146	Fair	Patients with CF listed for lung transplantation at Barnes-Jewish Hospital between Jan 1, 1989 and May 12, 1998.	Until death or Feb 1999	FVC %FVC FEV_1 %FEV_1 FEV_1/FVC Height Weight %IBW 6 minute walk test, 50 m increment 6 minute walk test percent predicted, 5% increment
Beker, 2001[8] N=2273	Fair	Patients from the Cystic Fibrosis Foundation registry, born between 1980 and 1989, who had a minimum of 4 records, were alive at age 7, and contained a recorded height measurement at age 7 to 8.	Until death or 1993	Height-for-age below 5th percentile, males at age 5 Height-for-age below 5th percentile, males at age 7 Height-for-age below 5th percentile, females at age 5 Height-for-age below 5th percentile, females at age 7
Liou, 2001[65] N=5820	Fair	Patients in the Cystic Fibrosis Foundation Patient Registry who were alive in Jan 1, 1993, and for whom followup data were available through Dec 31, 1997.	5 years	%FEV_1 Weight-for-age Z-score
Sharma, 2001[66] N=584	Fair	Patients with CF attending to Royal Brompton Hospital between 1985 and 1996.	Until death or 1996	FEV_1 %FEV_1 %FEV_1 ≤30 %IBW at baseline %IBW ≤85
Emerson, 2002[67] N=3213	Fair	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	Weight percentile ≤5 versus percentile >50 Weight percentile 5-15 versus percentile >50 Weight percentile 15-50 versus percentile >50

Table 20. Characteristics of studies which report on the relationship between intermediate outcomes and mortality

Study, Year	Quality Rating	Population/Setting	Duration of Followup	Predictors Evaluated
Mayer-Hamblett, 2002[68] N=14,572	Fair	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	Mean FEV_1 in 1996 Mean Height in 1996 Mean Weight in 1996
Oliveira, 2002[67] N=127	Fair	Patients with CF followed at the Hospital das Clinicas in Brazil between March 1977 and December 1997.	12 years	Height Z-Score Birth weight, kg
Schaedel, 2002[70] N=377	Fair	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	FEV_1 decline
Stanchina, 2002[71] N=44	Poor	Patients with CF who underwent evaluation for lung transplantation between Nov 1990 and Jan 1999 at Massachusetts General Hospital.	Until death or Jan 1999	FEV_1 at baseline $\%FEV_1$ Height Weight BMI $Vo_{2\text{-max}}$
Banjar, 2003[72] N=190	Poor	All CF patients referred to the CF clinic at the King Faisal Specialist Hospital and Research Center in Riyadh, Kingdom of Saudi Arabia during a 9 year period between Nov 1993 and Nov 2002.	9 years	Weight-for-height at baseline Height-for-age at baseline
Vedam, 2004[73] N=20	Poor	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	$\%FEV_1$ <24 upon admission BMI <18 upon admission
Ellaffi, 2005[74] N=69	Fair	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	$\%FEV_1$ in stable state FEV_1 decline BMI on admission
Pianosi, 2005[75] N=28	Poor	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	FEV_1 decline FEV_1 at last visit $Vo_{2\text{-peak}}$ $Vo_{2\text{-peak}}$ at last visit
Belkin, 2006[76] N=346	Fair	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	$\%FEV_1$ (10% decrease) %FVC (10% decrease) $\%FEV_1 \leq 30$ Shortest height quartile BMI Height, cm 6 minute walk distance, ft
Texereau, 2006[77] N=42	Fair	Adult CF patients admitted to the ICU, who had never received a solid-organ transplant, between Jan 2000 and Jun 2003.	1 year	$\%FEV_1$, best value within six months preceding ICU visit $\%FEV_1$ decline per year BMI

Table 20. Characteristics of studies which report on the relationship between intermediate outcomes and mortality

Study, Year	Quality Rating	Population/Setting	Duration of Followup	Predictors Evaluated
Courtney, 2007[78] N=183	Fair	Adult patients (age≥17 in 2000) from Belfast and Cork, between 1995 and 2005.	10 years	$\%FEV_1$ BMI
Rosenthal, 2008[79] N=298	Poor	Patients with CF born before 1993 with at least four annual lung function measurements in the patient database at a Royal Brompton Hospital in London, UK.	Until death or transplant by Jan 4, 2007	FEV1 Z-score threshold -2 at age 8 FEV1 Z-score threshold -2 at age 9 FEV1 Z-score threshold -2 at age 10 FEV1 Z-score threshold -2 at age 11 FEV1 Z-score threshold -2 at age 12 FEV1 Z-score decline in 2 year prior to age 10 FEV1 Z-score decline in 2 year prior to age 11 FEV1 Z-score decline in 2 year prior to age 12 BMI Z-score threshold -2 at age 8 BMI Z-score threshold -2 at age 9 BMI Z-score threshold -2 at age 10 BMI Z-score threshold -2 at age 11 BMI Z-score threshold -2 at age 12 BMI Z-score decline in 2 year prior to age 10 BMI Z-score decline in 2 year prior to age 11 BMI Z-score decline in 2 year prior to age 12

Legend: BMI=body mass index; CF=cystic fibrosis; 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; IBW=ideal body weight; NR=not reported;; VE_{peak}=peak ventilation in 1 minute; $Vo_{2\text{-}peak}$=peak oxygen uptake; $\%Vo_{2\text{-}peak}$=percent predicted peak oxygen uptake W_{peak}=peak work rate; %Weight=percent predicted weight

2746

Table 21. Characteristics of studies which report on the relationship between intermediate outcomes and HRQoL

Study, Year	Quality Rating	Population/Setting	Duration of Followup	Outcomes	Predictors
Orenstein, 1989[81] N=44	Poor	Patients with CF, aged 7 to 36 years, seen at the Pittsburgh Cystic Fibrosis Center	Cross-sectional	QWB	FEV_1 $Vo_{2\text{-peak}}$
Czyzewski, 1994[82] N=54	Poor	Patients with CF from two metropolitan CF centers, younger than age 18 years that read and spoke English.	Cross-sectional	QWB	$\%FEV_1$ %FVC
Congleton, 1996[83] N=240	Poor	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	NHP Energy Subscore NHP Pain Subscore NHP Emotion Subscore NHP Sleep Subscore NHP Social isolation Subscore NHP Physical mobility Subscore	$\%FEV_1$ BMI
de Jong, 1997[84] N=15	Poor	Clinically stable patients with CF, aged 16 to 40 years.	Cross-sectional	SIP Overall Score SIP Physical Subscore SIP Psychosocial Subscore	$\%FEV_1$ W_{peak}
Staab, 1998[85] N=89	Fair	Adolescent and adult patients (n=89) attending four outpatient clinics in Germany.	Cross-Sectional	Alltagsleben (Every Day Life)	FEV_1 %IBW
Johnson, 2000[86] N=39 at initial survey N=32 at 1 year	Fair	All patients with CF over age 18 years at the University of Alberta Hospital CF clinic.	Cross-sectional, with 1 year followup survey	SF-36 PCS SF-36 MCS EQ-5D VAS EQ-5D VAS after 1 year	$\%FEV_1$ BMI
Abbott, 2001[87] N=84	Poor	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	SF-36 Physical functioning subscore SF-36 Physical role limitation subscore SF-36 Social functioning subscore SF-36 Mental health subscore SF-36 Mental role limitation subscore SF-36 Energy and vitality subscore SF-36 General health perceptions subscore SF-36 Changes in health subscore	$\%FEV_1$ BMI

Table 21. Characteristics of studies which report on the relationship between intermediate outcomes and HRQoL

Study, Year	Quality Rating	Population/Setting	Duration of Followup	Outcomes	Predictors
Powers, 2001[88] N=24	Poor	Adolescents with CF aged 11 to 18 years at two CF clinics in Massachusetts, USA, who spoke English.	Cross-sectional	CHQ Physical function subscore CHQ Role/social limitations – physical subscore CHQ General health perceptions subscore CHQ Bodily pain/discomfort subscore CHQ Role/social limitations – emotional subscore CHQ Role/social limitations – behavioral subscore CHQ Self-esteem subscore CHQ Mental health subscore CHQ General behavior subscore CHQ Family activities subscore	$\%FEV_1$
Gee, 2003 and 2005[89, 90] N=223	Fair	Patients with CF attending regional adult CF centers.	Cross-sectional	CFQoL Physical functioning subscore CFQoL Social functioning subscore CFQoL Treatment issues subscore CFQoL Chest symptoms subscore CFQoL Emotional functioning subscore CFQoL Concerns for the future subscore CFQoL Interpersonal relationships subscore CFQoL Body image subscore CFQoL Career concerns subscore	$\%FEV_1$ BMI

Table 21. Characteristics of studies which report on the relationship between intermediate outcomes and HRQoL

Study, Year	Quality Rating	Population/Setting	Duration of Followup	Outcomes	Predictors
Koscik, 2005[91] N=36	Poor	Patients with CF from the Wisconsin Newborn Screening (NBS) Project, at least age 6.5 years.	Cross-sectional	CHQ Physical function subscore CHQ Role/social limitations – physical subscore CHQ General health perceptions subscore CHQ Bodily pain/discomfort subscore CHQ Role/social limitations – emotional subscore CHQ Role/social limitations – behavioral subscore CHQ Self-esteem subscore CHQ Mental health subscore CHQ General behavior subscore CHQ Family activities subscore CHQ Family cohesion subscore CHQ Change in health subscore	FEV_1 Height-for-age Weight-for-age
Quittner, 2005[92] N=212	Poor	Adolescents and adults with CF at 18 centers across the United States.	Cross-sectional	CFQ Physical domain CFQ Role domain CFQ Vitality domain CFQ Emotion domain CFQ Social domain CFQ Body image domain CFQ Eating domain CFQ Treatment burden domain CFQ Health perceptions domain CFQ Respiratory domain CFQ Digestive domain CFQ Weight domain	$\%FEV_1$ BMI

Table 21. Characteristics of studies which report on the relationship between intermediate outcomes and HRQoL

Study, Year	Quality Rating	Population/Setting	Duration of Followup	Outcomes	Predictors
Koscik, 2006[93] N=45	Fair	Patients with CF from the Wisconsin Newborn Screening (NBS) Project between the age of 8 and 18.	Cross-sectional	CFQ Physical dimension CFQ Emotional dimension CFQ Social dimension	Adequate weight gain within 2 years of diagnosis BMI Z-score >-1
Goldbeck, 2007[94] N=108	Fair	Adolescent and adult patients with CF, at least age 15 years.	18 months	Questions on Life Satisfaction	%FEV_1 at second visit Change in %FEV_1 between two visits BMI
Riekert, 2007[95] N=76	Poor	Adults with CF seen at clinic between April 2002 and Nov 2003.	Cross-sectional	CFQ Physical domain CFQ Respiratory domain CFQ Vitality domain CFQ Social domain CFQ Health perceptions domain CFQ Treatment domain CFQ Role domain CFQ Emotion domain CFQ Body image domain CFQ Eating domain CFQ Digestion domain CFQ Weight domain	%FEV_1
Havermans, 2008 and 2009[96, 97] N=57	Fair	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	CFQ Physical domain CFQ Respiratory domain CFQ Vitality domain CFQ Social domain CFQ Health perceptions domain CFQ Treatment domain CFQ Role domain CFQ Emotion domain CFQ Body image domain CFQ Eating domain CFQ Digestion domain CFQ Weight domain	%FEV_1 BMI

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; 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; IBW=ideal body weight; MCS=mental composite score; NHP=Nottingham Health Profile; NR=not reported; PCS=physical composite score; QWB=Quality of Well-Being Scale; SF-36=Medical Outcomes Short-Form 36; SIP=Sickness Impact Profile; VAS=visual analog scale; $Vo_{2\text{-peak}}$=peak oxygen uptake; W_{peak}=peak work rate

Table 22. Characteristics of studies which report on the relationship between intermediate outcomes and bone fracture

Study, Year	Quality Rating	Population/Setting	Duration of Followup	Outcomes	Predictors
Aris, 1998[98] N=70	Fair	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	Bone Fracture	FEV_1 FVC BMI

Legend: BMI=body mass index; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity, NR=not reported

Key Question 4

In patients with CF, what is the frequency of nonmalignant serious adverse effects resulting from treatment with rhGH? Adverse effects of interest include, but are not limited to, glucose intolerance, diabetes, and hyperglycemia.

Key Points

- rhGH therapy causes a small but nonsignificant decrease in A1c in CF patients.
- In CF patients, rhGH therapy significantly increases fasting blood glucose concentrations but does not significantly alter random, postprandial and stimulated blood glucose concentrations.
- Most CF patients receiving rhGH do not develop glucose intolerance or diabetes.
- In CF patients receiving rhGH, injection site reactions are a rare and insignificant adverse effect.
- CF patients on rhGH may rarely experience a transient increase in liver transaminases.
- Study withdrawals were rare in trials evaluating rhGH in CF patients.

Detailed Analysis

Study Design and Population Characteristics

The studies which report nonmalignant adverse effects of rhGH therapy are derived from the same set of studies used to evaluate Key Question 1 and are summarized in Table 4-Table 8.

Outcome Evaluations

Glucose Parameters

Five controlled trials, summarized in Table 23, reported information on various glucose parameters including fasting, stimulated, and postprandial glucose concentrations as well as glycosylated hemoglobin (A1c) levels in patients with CF.[4, 23, 26, 33, 34]

Two single-arm observational studies, summarized in Table 24, also reported glucose parameters in patients on rhGH therapy while other studies only reported a general statement regarding the impact on glucose.[40-42, 44, 45]

Glycosylated Hemoglobin

Hemoglobin A1c levels were specifically reported in two controlled trials and were amenable to quantitative synthesis.[23, 33] Upon statistical pooling, hemoglobin A1c was nonsignificantly decreased in patients with CF receiving rhGH compared to those without treatment (WMD -0.10 percent, 95 percent CI -0.40 to 0.20 percent). (Figure 23) There were too few trials to conduct evaluations of publication bias and statistical heterogeneity. However, both trials showed a similar direction and magnitude of effect.

2790 A1c was also evaluated in two prospective, single-arm, observational studies which
2791 administered rhGH therapy to all participants. Both studies reported slight increases (0.2±0.8
2792 percent and 0.1±0.5 percent) from baseline.[41, 44]

2793 Random Blood Glucose

2794 Random blood glucose concentrations were evaluated in three controlled trials but
2795 quantifiable data was only reported in one trial, precluding quantitative synthesis. In the trial
2796 with quantifiable data, random glucose concentration increased by 5±10.2 mg/dl in the rhGH
2797 treatment group.[34] Since the trial only reported the change from baseline in the rhGH group,
2798 weighted mean differences could not be calculated.[34] In the other two trials, casual glucose
2799 concentrations, interpreted as random, were stated to have remained within the non-diabetic
2800 range in all subjects throughout the study.[15, 33]

2801 Fasting Blood Glucose

2802 Fasting blood glucose concentrations were evaluated in three controlled trials.[4, 23, 26] The first
2803 trial only reported the change from baseline in the rhGH group, so the weighted mean difference
2804 could not be calculated. In that trial, the fasting glucose concentration increased by 7.2±26.1
2805 mg/dl.[26] The other two trials were amenable to quantitative synthesis. One of the trials[4] evaluated
2806 both lower and higher rhGH doses versus placebo while the other compared rhGH to no
2807 therapy.[23] Upon statistical pooling, there was a significant increase in fasting blood glucose in
2808 the rhGH treated group versus control (WMD 5.68 mg/dl, 95 percent CI 0.43 to 10.93 mg/dl).
2809 (Figure 24) No statistical heterogeneity was detected. There were too few trials to conduct
2810 evaluation of publication bias. The direction of effect was qualitatively the same in both trials.
2811 Similarly, both arms of the Schnabel trial showed a similar direction and magnitude of effect
2812 suggesting a lack of a dose response effect with rhGH.[4]

2813 Fasting blood glucose levels were also reported in a prospective, single arm, observational
2814 study that administered rhGH therapy to all participants. A mean increase of 5±10 mg/dl was
2815 calculated for all the patients receiving rhGH, but it was not significant.[44]

2816 Stimulated Blood Glucose

2817 Stimulated blood glucose concentrations were evaluated in two controlled trials.[4, 26] The first
2818 trial only reported the change from baseline in the rhGH group so weighted mean difference
2819 could not be calculated. In that trial, the stimulated glucose concentration was reduced by
2820 25.2±149.3 mg/dl versus baseline.[26] The other trial evaluated a lower and higher dose of rhGH
2821 versus placebo.[4] Upon statistical pooling of the lower and higher dose arms versus placebo, there
2822 was a nonsignificant increase in stimulated glucose concentrations with rhGH versus no
2823 treatment (WMD 4.92 mg/dl, 95 percent CI -15.12 to 24.98 mg/dl). (Figure 25) There were too
2824 few trials to conduct evaluations of publication bias and statistical heterogeneity. However, the
2825 high dose rhGH group showed a nonsignificant decrease while the low dose rhGH cohort
2826 showed a nonsignificant increase versus placebo.

2827 Postprandial Blood Glucose

2828 In the one controlled trial where it was evaluated, postprandial blood glucose concentrations
2829 were elevated by 10 mg/dl in the rhGH group versus placebo but this was not statistically
2830 significant.[23]

Other Blood Glucose Parameters

In one controlled trial evaluating glucose concentrations which were not defined, final blood glucose concentrations were higher in both the rhGH alone arm (97±12 mg/dl) and rhGH plus glutamine arm (95±6 mg/dl) of the trial versus glutamine alone arm (90±6 mg/dl). However, statistical significance is not known since the table within the paper suggests the p-value is less than 0.05 but the text in the results section specifies that it is not significant.[29]

One single-arm observational study reported no changes in glucose parameters with rhGH therapy versus baseline but did not specify which glucose outcomes were measured.[40] Another observational study reported a slight decrease in fasting insulin-blood glucose ratio with rhGH treatment in CF patients; however, it was not significant.[44]

Glucose Intolerance and Diabetes

The development of glucose intolerance and diabetes were reported in five controlled trials.[4, 23, 25, 33, 102] (Table 23) No patients developed glucose intolerance or diabetes over the duration of investigation in four of those studies.[23, 25, 33, 102] One trial did report a hyperglycemic episode in one patient receiving high dose rhGH, but no subjects in the study developed diabetes.[4]

Glucose intolerance was also reported in three single-arm observational studies.[41, 42, 44] In one study, none of the patients developed hyperglycemia while being treated with rhGH.[41] Furthermore, in the one study that monitored rhGH treatment patients for glucosuria, none of the patients had glucose in their urine.[44] However, two female patients receiving rhGH developed glucose intolerance during rhGH treatment in a study.[42] One patient was initiated on insulin therapy and continued rhGH therapy, while the other patient discontinued rhGH.[42] Since there was no information given on confounders, it is difficult to assess causality in these two patients.

The onset of diabetes was reported in a case report where a patient received rhGH therapy for three years.[45] While the temporal relationship between rhGH use and diabetes is reasonable, there was no report of improvement in glucose control after dechallenge, no rechallenge, and the patient had an important confounder. The patient had a pancreatic resection right before the onset of diabetes and endocrine function of the pancreas was specifically said to have been preserved until the pancreatic resection. As such, the causality between rhGH therapy and diabetes in this case is weak.[45]

Injection Site Reactions

Injection site reactions were reported in two observational studies.[40, 42] One observational study with seven patients reported minor bruising at the injection site in a majority of the subjects (actual number not provided) upon initial treatment, but this effect subsided with increased parental competence in administering rhGH.[40] One patient in another observational study reported discomfort secondary to injection, but remained in the study.[44] Further information regarding the injection site reactions was not provided in these studies.[40, 42]

Liver Transaminases

The impact of rhGH on liver transaminases was reported in two single-arm observational studies.[40, 46] Transient elevations in liver transaminase concentrations occurred unexpectedly in two patients receiving rhGH in one study but actual laboratory values and further information was not provided.[40] In another study, two patients with CF related liver disease experienced an

improvement in liver transaminases after rhGH therapy was initiated; however, one patient's liver function began to deteriorate again after 2 months of rhGH therapy.[46]

Study Withdrawals

There were no patient withdrawals in the majority of the controlled trials. (Table 25) One trial reported four withdrawals but did not specify from which treatment arm or the reason why the patients left the study.[4] Two patients each from both arms, treatment and no treatment, withdrew in one trial due to fear of injections, commencement of enteral feeds, loss to followup, and development of CF-related diabetes (CFRD).[102] Fear of injections was also a reason for one of the two patient withdrawals in another trial; the other withdrawal was due to geographic relocation.[23] In another study, a patient left the control group in order to be evaluated for a lung transplant.[26]

Discussion

Endogenous growth hormone (GH) regulates the utilization of glucose in many cells throughout the body and impacts insulin sensitivity.[116] In general, GH therapy decreases insulin sensitivity and induces a compensatory rise in insulin concentrations.[117] However, the impact of rhGH therapy on the development of diabetes remains uncertain. Blethen and colleagues collected data on 47,000 patient-years of rhGH treatment in children without CF and concluded that rhGH is unlikely to cause diabetes unless the patient has preexisting risk factors.[118] Another large study with 23,333 children without CF revealed that treatment with rhGH resulted in an increased risk for the development of diabetes.[119] Again, these authors suggested that rhGH-induced diabetes developed in predisposed individuals.

Due to the nature of CF, patients are at increased risk for developing impaired glucose tolerance or diabetes, which is also known as CF-related diabetes (CFRD). CFRD has been primarily attributed to a decrease in insulin secretion; however, a decrease in insulin sensitivity may also play a role.[120] The high viscosity of pancreatic secretions is responsible for damage to the beta cells within the pancreas. The loss of beta cells leads to a decrease in insulin production and development of CFRD. The role of insulin resistance in the development of CFRD is still uncertain due to inconsistent findings.[121, 122] The development of CFRD has been linked to a decrease in pulmonary function (FEV_1) and an increase in mortality.[120, 123] In one retrospective study, the increase in mortality due to diabetes was primarily manifested in females with CF.[124] However, prudent monitoring and early diagnosis along with aggressive treatment have attenuated the difference in mortality between patients with and without CFRD.[125] As such, it is important to determine the impact of rhGH therapy on glucose parameters in CF patients.

While numerous trials and studies evaluated the impact of rhGH on glucose parameters, almost all trials compared rhGH effect to no treatment, rather than placebo or another therapy. Since epinephrine is a counter-regulatory hormone and can be impacted based on conscious and unconscious stimuli, patients knowingly not receiving rhGH therapy might be nervous, resulting in elevated circulating epinephrine. This would have an effect of elevating glucose parameters in the control group.[126] The increase in fasting glucose concentrations was 6.0 mg/dl in the no treatment group of one trial and 1.2 mg/dl in the placebo group of another. One trial and the observational studies were single arm trials with no control group. As such, a slight increase in glucose concentrations might be related to the duration of the trial and not to the direct impact of rhGH on glucose. This limits the strength of evidence for this adverse event evaluation.

2915 Taken together, it seems that rhGH therapy may slightly increase transient markers of
2916 glucose control but does not seem to impact longer term markers of glucose control such as the
2917 A1c. However, trials did not report other preexisting risk factors for diabetes in these patients
2918 other than the presence of CF. Future placebo controlled trials need to stratify patients based on
2919 preexisting risk factors to see if rhGH has a significant effect on A1c as well as other blood
2920 glucose parameters.

2921 We had insufficient evidence to evaluate the impact of rhGH on injection site reactions.
2922 Some observational studies have reported minor bruising and discomfort at injection sites;
2923 however, the effect is limited and resolves with improved administration technique.[40, 44] Due to
2924 the nature of proteins, local reactions at the injection site may theoretically occur.[127] The limited
2925 occurrence of injection site reactions in non-CF patients, including pediatric patients, is further
2926 supported by the information in package inserts of several rhGH products.[127-129] Rotation of the
2927 injection site is proposed to minimize this adverse effect but this was not evaluated in CF
2928 patients.[127]

2929 We had insufficient evidence to evaluate the impact of rhGH on liver function. There have
2930 been reports of unexpected transient elevations in liver transaminases during rhGH therapy[40]. In
2931 the prescribing information for rhGH products, liver enzyme elevation is not listed as a potential
2932 side effect.[127-129] Furthermore, postmarketing surveillance has not uncovered any liver-related
2933 side effects.[129]

Table 23. Change from baseline in glucose parameters in controlled trials evaluating rhGH in CF patients

Study, year	Group	Dose/wk (mg/kg)	N	A1c (%)	Random BG (mg/dl)	Fasting BG (mg/dl)	Stimulated BG (mg/dl)	Postprandial BG (mg/dl)	Hyperglycemia (number of events)	Onset of Diabetes (number of patients)
Hardin, 2001[23, 24]	rhGH	0.3	10	0.5 (0.4)[c]	-	15 (10.2)[c]	-	-15 (30.8)[c]	-	0
	No treatment	NA	9	0.6 (10.8)[c]	-	6.0 (9.5)[c]	-	-25 (31.2)[c]	-	0
Hutler, 2002[25108]	rhGH	0.27 to 0.35	6	-	-	-	-	-	-	0
	No treatment	NA	4	-	-	-	-	-	-	0
Schibler, 2003[26]	rhGH	0.35	10	-	-	7.2 (26.1)[c]	-25.2 (149.3)[c]	-	-	-
	No treatment	NA	9	-	-	-	-	-	-	-
Darmaun, 2004[29]	rhGH	0.3	9	-	-	-	-	-	-	-
	rhGH+GLN	0.3/0.7[b]	9	-	-	-	-	-	-	-
	GLN	0.7[b]	9	-	-	-	-	-	-	-
Hardin, 2005a[32]	rhGH	0.3	16	-	-	-	-	-	-	-
	No treatment	0	16	-	-	-	-	-	-	-
Hardin, 2005b[33]	rhGH	0.3 to 0.35	13	-0.1 (0.7)[c]	-	-	-	-	-	0
	No treatment	NA	12	0.0 (0.7)[c]	-	-	-	-	-	0
Hardin, 2005c[34]	rhGH	0.3	9	-	5 (10.2)[c]	-	-	-	-	-
	No treatment	NA	9	-	-	-	-	-	-	-
Hardin, 2006[15]	rhGH	0.3	32	-	-	-	-	-	-	0
	No Treatment	NA	29	-	-	-	-	-	-	0
Schnabel, 2007[4]	Higher dose	0.49	20	-	-	4.9 (11.6)[c]	3.7 (60.9)[c]	-	1	-
	Lower dose	0.273	22	-	-	5.3 (13.9)[c]	18.3 (36.2)[c]	-	0	-
	Placebo	NA	21	-	-	1.2 (12.3)[c]	8.1 (33.1)[c]	-	0	-
Stalvey, 2008[38]	rhGH	0.3	29	-	-	-	-	-	-	-
	No treatment	NA	27	-	-	-	-	-	-	-

Legend: All values given as mean (standard deviation); - =not reported; A1c=glycosylated hemoglobin A1c; BG=blood glucose; GLN=glutamine; N=sample size; NA=not applicable; rhGH=recombinant human growth hormone

[a]Darmaun et al was a crossover study – all values presented are end values for that treatment period; Change from baseline could not be calculated due to limited baseline data; therefore, only final values are reported (mg/dl): rhGH: 97(12); rhGH + GLN: 95(6); GLN: 90(6).

[b]Glutamine dosing is 0.7 g/kg per day

[c]Change from baseline calculated from published baseline and final values

Table 24. Change from baseline in glucose parameters in single-arm observational studies evaluating rhGH in CF patients

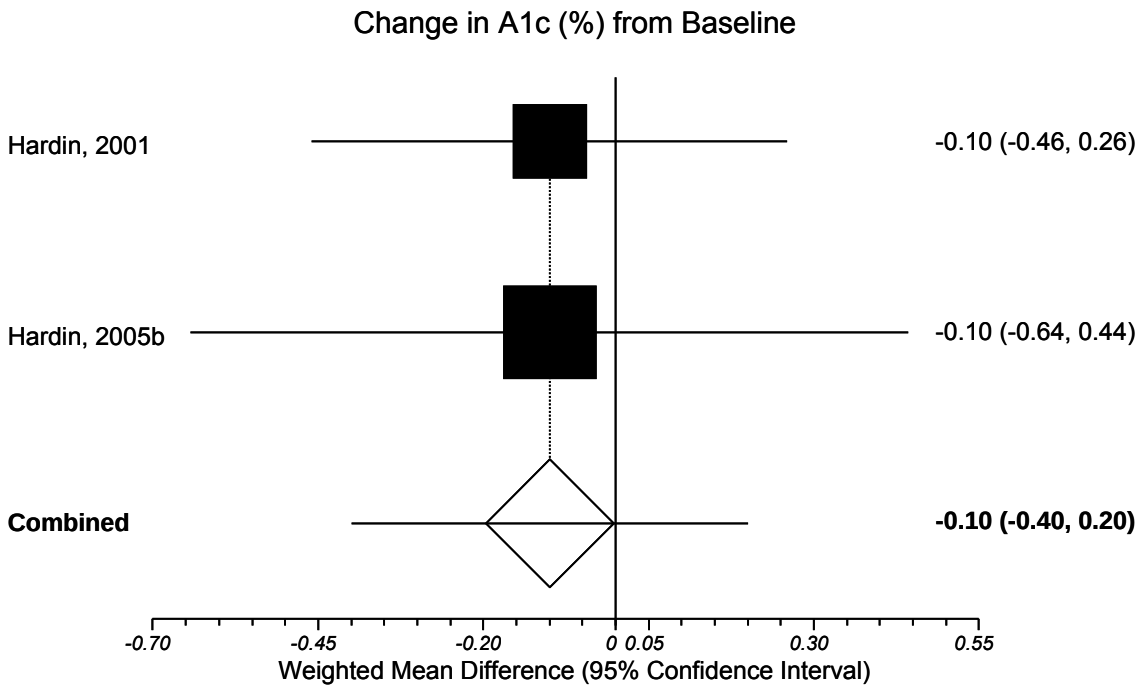
Study, year	Study Design	Product and Dose	Duration of Treatment	A1c (%)	Fasting BG (mg/dl)	Fasting insulin-BG ratio	Glucosuria (number of patients)	Hyperglycemia (number of patients)	Onset of Diabetes (number of patients)	Reported Results
Mullis, 1991[39] N=1	Case Report	Grorm Dose NR	8 months	-	-	-	-	-	-	-
Sackey, 1995[40] N=7	Prospective Single-group, all receiving rhGH	Humatrope 0.16 mg/kg/week given daily	6 months in three patients. 12 months in four patients.	-	-	-	-	-	-	No changes in blood glucose and HbA1c
Huseman, 1996[41] N=9	Prospective Single-group, all receiving rhGH	Product NR 0.3 mg/kg/wk given three times weekly	9 months in one patient. 12 months in eight patients.	0.2 (0.8)[a]	-	-	-	0	-	No significant change in routine chemistries including glucose values
Hardin, 1997[42] N=24	Retrospective Observational registry database	NR	Mean±SD 1.9±1.3 years	-	-	-	-	-	-	Two patients, both females who had progressed from Tranner stage 1 to 2, reported glucose intolerance
Alemzadeh, 1998[43] N=5	Prospective Single-group, all receiving rhGH	Humatrope 0.3 mg/kg/wk given daily 6 days of the week	2 years	-	-	-	-	-	-	-
Hardin, 1998[44] N=9	Prospective Single-group, all receiving rhGH	Somatotropin 0.35 mg/kg/wk given daily	1 year	0.1 (0.5)[a]	5 (10)[a]	-0.01 (0.03)[a]	0	-	-	No significant changes in glucose parameters

Table 24. Change from baseline in glucose parameters in single-arm observational studies evaluating rhGH in CF patients

Study, year	Study Design	Product and Dose	Duration of Treatment	A1c (%)	Fasting BG (mg/dl)	Fasting insulin-BG ratio	Glucosuria (number of patients)	Hyperglycemia (number of patients)	Onset of Diabetes (number of patients)	Reported Results
Petrowsky, 2006[45] N=1	Case Report	Norditropin 2.2 mg/day	3 years	-	-	-	-	-	1	Developed diabetes mellitus after pancreatic resection
Stalvey, 2008[46] N=2	Case Report	Product NR 0.3-0.35 mg/kg/wk	7-10 months	-	-	-	-	-	-	-

Legend: - =not reported; A1c=glycosylated hemoglobin A1c; BG=blood glucose; N=sample size; rhGH=recombinant human growth hormone
[a]Change from baseline calculated from published baseline and final values

Figure 23. KQ4 - Meta-Analysis of change from baseline in A1c in CF patients treated with rhGH



I^2 = NA
Egger's p-value = NA

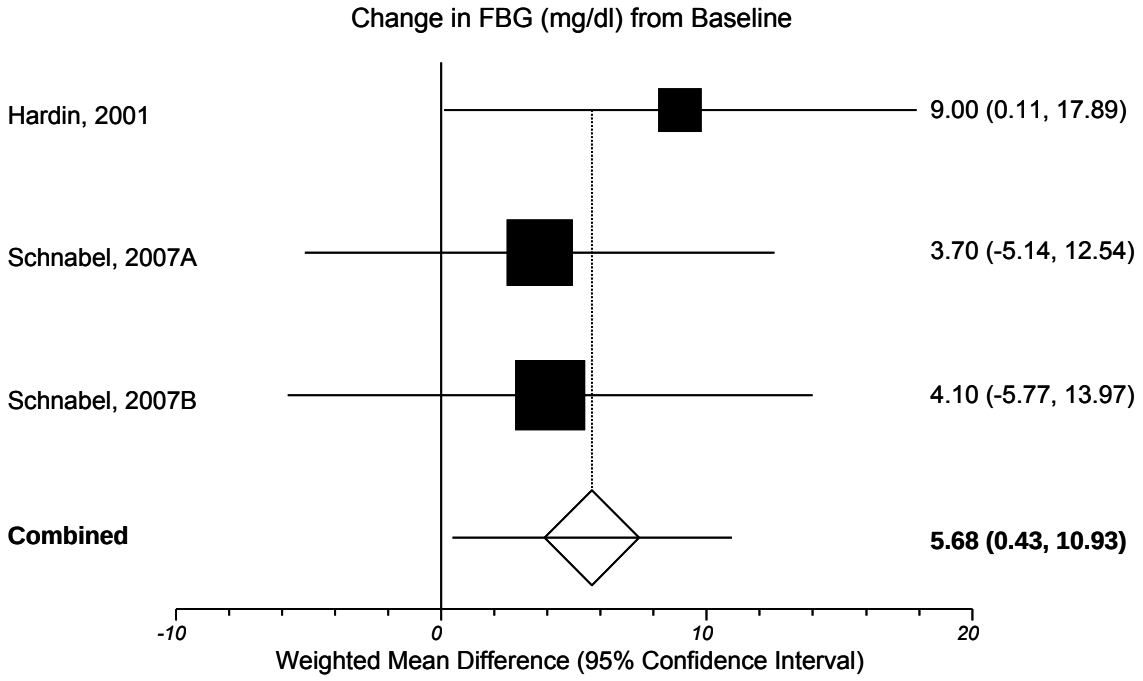
Legend: A1c=glycosylated hemoglobin; CF=cystic fibrosis; rhGH=recombinant human growth hormone

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Lowercase letters following a study year represent unique trials conducted within the same year.

Narrative: This figure depicts the meta-analysis of change from baseline in A1c. The first trial by Hardin and colleagues in 2001 provided a mean difference of -0.10 percent, with 95 percent confidence interval of -0.46 to 0.26. The second trial by Hardin and colleagues in 2005 showed a mean difference of -0.10 percent, with 95 percent confidence interval -0.64 to 0.44. The combined effect of two studies showed a weighted mean difference of -0.10 percent, with a 95 percent confidence interval of -0.40 to 0.20. The I-squared value was not applicable and the Egger's p-value was not applicable.

Figure 24. KQ4 - Meta-Analysis of change from baseline in fasting blood glucose in CF patients treated with rhGH



I^2 = 0%
Egger's p-value = NA

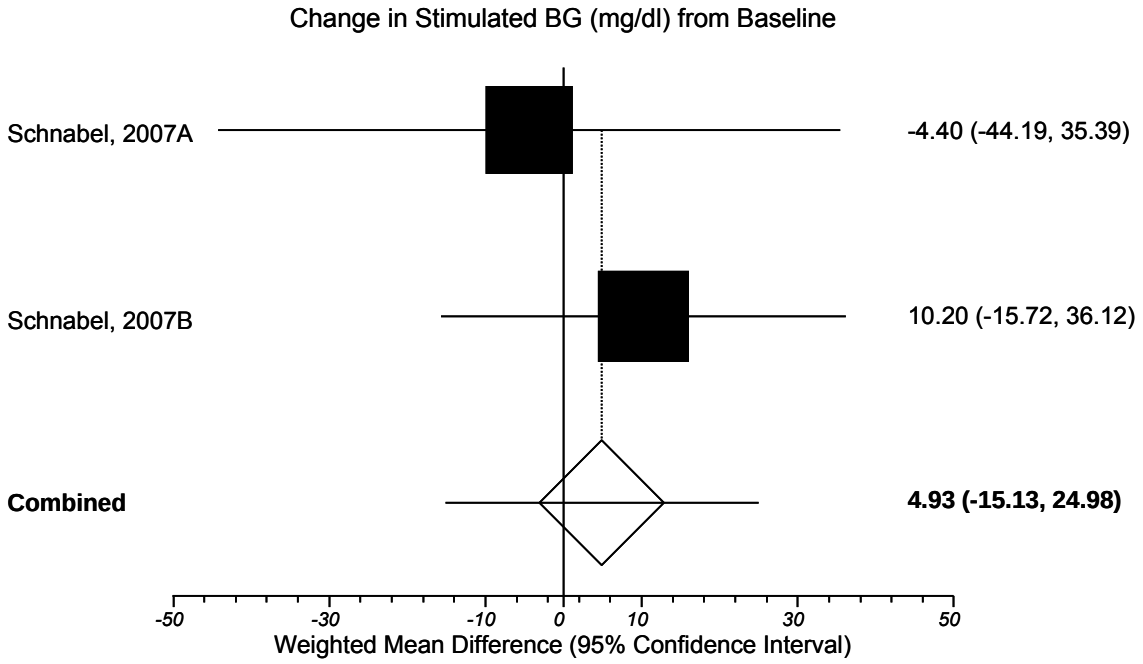
Legend: CF=cystic fibrosis; FBG=fastng blood glucose; rhGH=recombinant human growth hormone

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Uppercase letters represent study arms within the same trial.

Narrative: This figure depicts the meta-analysis of change from baseline in fasting blood glucose. The first trial by Hardin and colleagues in 2001 provided a mean difference of 9.00 mg/dl with a 95 percent confidence interval of 0.11 to 17.89 mg/dl. The second trial by Schnabel and colleagues in 2007 provided a mean difference of 3.70 mg/dl with a 95 percent confidence interval of -5.14 to 12.54 mg/dl with the higher dose of rhGH and a mean difference of 4.10 mg/dl with a 95 percent confidence interval of -5.77 to 13.97 mg/dl with the lower dose of rhGH. The combined effect of the studies showed a weighted mean difference of 5.68 mg/dl, with a 95 percent confidence interval of 0.43 to 10.93 mg/dl. The I-squared value was 0 percent and the Egger's p-value was not applicable.

Figure 25. KQ4 - Meta-Analysis of change from baseline in stimulated blood glucose in CF patients treated with rhGH



I^2 = NA
Egger's p-value = NA

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

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value.

Uppercase letters represent study arms within the same trial.

Narrative: This figure depicts the meta-analysis of change from baseline in stimulated blood glucose. The first trial by Schnabel and colleagues in 2007 provided a mean difference of -4.40 mg/dl with a 95 percent confidence interval of -44.19 to 35.39 mg/dl with the higher dose of rhGH and a mean difference of 10.20 mg/dl with a 95 percent confidence interval of -15.72 to 36.12 mg/dl with the lower dose of rhGH. The combined effect of the trial arms showed a weighted mean difference of 4.93 mg/dl with a 95 percent confidence interval of -15.13 to 24.98 mg/dl. The I-squared value was not applicable and the Egger's p-value was not applicable.

Table 25. Patient withdrawals and reasons from controlled trials evaluating the use of rhGH in CF patients

Study, year	Group	Dose/wk (mg/kg)	Enrolled	Withdrew	Reasons
Hardin, 2001[23, 24]	rhGH	0.3	21	2	One developed fear of injection; the other relocated. Treatment group not specified.
	No treatment	NA			
Hutler, 2002[25108a]	rhGH	0.27 to 0.35	10	0	NA
	No treatment	NA			
Schibler, 2003[26]	rhGH	0.35	10	0	NA
	No treatment	NA	10	1	Patient evaluated for lung transplantation.
Darmaun, 2004[29b]	rhGH	0.3	9	0	NA
	rhGH+GLN	0.3/0.7[c]			
	GLN	0.7[c]			
Hardin, 2005a[32]	rhGH	0.3	16	0	NA
	No treatment	0	16	0	NA
Hardin, 2005b[33]	rhGH	0.3 to 0.35	13	0	NA
	No treatment	NA	12	0	NA
Hardin, 2005c[34]	rhGH	0.3	9	0	NA
	No treatment	NA	9	0	NA
Hardin, 2006[15]	rhGH	0.3	32	2	One had fear of injection; the other started enteral feeds.
	No treatment	NA	29	2	One did not return for follow-up; the other developed CF-related diabetes.
Schnabel, 2007[4]	Higher dose	0.49	67	4	Reasons for withdrawal not reported. Treatment group not specified.
	Lower dose	0.273			
	Placebo	NA			

Legend: CF=cystic fibrosis; GLN=glutamine; N=sample size; NA=not applicable; rhGH=recombinant human growth hormone
[a]Hutler et al was a crossover study – results reported for entire enrolled population
[b]Darmaun et al was a crossover study – results reported for entire enrolled population
[c]Glutamine dosing is 0.7 g/kg per day

Key Question 5

What is the risk of malignancy associated with rhGH use as determined by: (a) markers of cancer risk with rhGH (IGF-I increases over 100 ng/ml or IGFBP-3 decreases over 1000 ng/ml) from studies of rhGH in people with CF and by (b) assessment of evidence on cancer incidence from non-CF patients receiving modest doses of rhGH (0.2mg/kg/week to 0.6mg/kg/week) for disorders such as growth hormone deficiency (GHD) and idiopathic short stature (ISS)?

Key Points

- In patients with CF, there appears to be an increase in IGF-I levels in patients treated with rhGH compared to control.
- There is insufficient evidence to determine the impact of rhGH treatment on IGFBP-3 levels.
- In patients with GHD or ISS, there is little evidence to evaluate the effects of rhGH treatment on cancer risk.

Detailed Analysis

Study Design and Population Characteristics

The studies that evaluate markers of cancer risk with rhGH use in patients with CF are from the same set of studies used to evaluate Key Question 1 and are summarized in Table 4-Table 8. Two epidemiological studies reported the incidence of cancer subsequent to rhGH use in patients with idiopathic GHD or ISS, and there is one case report of cancer.[99-101]

Outcome Evaluations

Biomarkers in CF Populations

Only one controlled trial reported the change in IGF-I concentrations from baseline, precluding quantitative analysis (Table 26). In that trial, the change in IGF-I concentration from baseline was 188±160 ng/ml in the rhGH group and 31± 117 ng/ml in the no treatment group ($p<0.03$ for the comparison of values at the end of the study).[23, 24]

In three controlled trials, the final IGF-I concentrations identified with rhGH treatment were compared to no treatment (Table 26). In all of those trials, IGF-I concentrations were higher with rhGH therapy than no treatment ($p<0.05$ for all) with values at least 100 ng/ml higher with rhGH therapy than no treatment.[32-34] In another trial, the final IGF-I concentrations were compared between the rhGH group, rhGH plus glutamine group, and glutamine alone group (Table 26).[29] IGF-I concentrations in the rhGH group and rhGH plus glutamine group were over 100 ng/ml higher than the glutamine alone group.[29] The rhGH alone and rhGH and glutamine groups both had significant increases in IGF-I concentrations from baseline ($p<0.05$ for each group), while the glutamine alone group did not have a significant increase from baseline (p-value not reported). In a single-arm observational study (n=5), there were significant increases in IGF-I from baseline to 12 months and 24 months (baseline 0.67±0.13 ng/ml; 12 months 1.30±0.38 ng/ml, $p<0.01$ versus baseline; 24 months 1.86±0.83 ng/ml, $p<0.01$ versus baseline and $p<0.02$ versus 12 months).[43] Another single-arm observational study (n=9) also found significant increases in IGF-I from baseline (baseline 0.9±0.5 ng/ml; 6 months 3.33±1.9 ng/ml, p=0.003

versus baseline; 12 months 2.6±1.8, p=0.044 versus baseline).[44] Neither study experienced increases in IGF-I greater than 100 ng/ml during the study period.[43, 44]

No trials reported changes in IGFBP-3 concentrations from baseline, precluding quantitative analysis. The aforementioned study by Darmaun did report final IGFBP-3 concentrations in the rhGH, rhGH plus glutamine, and glutamine alone groups, where only the rhGH alone group provided significant difference from baseline ($p<0.05$).[29] IGFBP-3 concentrations were qualitatively higher in the rhGH group and rhGH plus glutamine group than the glutamine alone group but this was not statistically evaluated.[29] (Table 26) A single-arm observational study (n=5) reported IGFBP-3 levels subsequent to rhGH therapy, showing nonsignificant increases at 12 months and significant increases from baseline at 24 months (baseline 1700±490 ng/ml; 12 months 2200±310 ng/ml, p-value not reported; 24 months 3000±490 ng/ml, $p<0.01$ versus baseline).[43]

Malignancy

We identified no controlled rhGH trials evaluating malignancy in CF populations. There was one case report identified which described a CF patient who developed pancreatic cancer.[45] Two observational, single-group evaluations from the same registry and a case report evaluated the impact of rhGH on malignancy in non-CF populations with GHD or ISS (Table 27).[99-101]

A female with CF underwent bilateral lung transplantation at age 12 years and was treated with the following immunosuppressants: prednisone, cyclosporine A, and mycophenolate mofetil.[45] At age 15 years, rhGH 2.2 mg/day was initiated because of growth retardation.[45] Before initiating rhGH, IGF-I was 141 ng/ml but did not significantly improve in the 3 years of rhGH therapy, and linear growth remained poor.[45] At age 18 years, a pancreatic mass was detected and histology revealed a ductal pancreatic adenocarcinoma, treated with pancreatic resection.[45] The occurrence of cancer appeared to have a temporal relationship with the administration of rhGH, but other possible causes of malignancy were not reported. Eight months after pancreatic resection, the patient developed metastatic disease and died.[45] Because of the nature of the malignancy, it could not resolve on its own after withdrawal of rhGH and a rechallenge of rhGH therapy was not administered. Based on the presentation of the case, it is possible that the malignancy was related to rhGH therapy but more information would be needed to more clearly determine causality.

The risk of developing leukemia was evaluated in patients from the National Cooperative Growth Study (NCGS) using registry data from 1985 through 1995. Out of the 12,697 patients with either GHD or ISS but without risk factors for cancer, there were two cases of leukemia in 37,772 patient-years of rhGH treatment.[99] In a subsequent evaluation of the registry from 1985 through 2006 by NCGS investigators, the occurrence of all types of cancer was evaluated. Out of 33,171 patients with either GHD or ISS but without risk factors for cancer, 29 new-onset malignancy were observed in patients without previous risk factors out of 178,464 years of GH exposure.[101] Using background rates of cancer in an age-adjusted general population, Bell and colleagues calculated a standard incidence ratio (SIR) and 95 percent CI, which represent the number of observed cases over the number of expected cases.[101] No difference was seen between patients exposed to rhGH and the general population (SIR 1.12, 95 percent CI 0.75 to 1.61).[101] These observational studies are limited because the doses of rhGH utilized and the manufacturers are not reported and because cancers occurring after rhGH discontinuation would not be captured.

In 2,712 patients with cancer risk factors (which includes prior malignancy, radiation exposure, bone marrow transplant, chemotherapy, neurofibromatosis, immunosuppressant use, and certain chromosomal disorders like Down syndrome), there were eight cases of leukemia in 8,962 patient years of rhGH treatment in the original NCGS study.[99] In 2,500 patients with history of malignancy, 49 cases of second neoplasms among 10,750 years of exposure occurred in the followup NCGS study.[101] The most commonly identified cancer was leukemia, with 18 cases being observed.[101]

In a 9.7 year old male with short stature, rhGH was initiated to treat GHD.[100] The patient underwent a cranial MRI at age 13.4 years due to persistent headaches which revealed a large suprasellar mass. The patient was eventually diagnosed with intracranial suprasellar choriocarcinoma.[100] The occurrence of cancer appeared to have a temporal relationship with the administration of rhGH, but other possible causes of malignancy were not reported. Therapy with rhGH was discontinued, and the patient was successfully treated with radiation and chemotherapy.[100] Because of the nature of the malignancy, it could not resolve on its own after withdrawal of rhGH and a rechallenge of rhGH therapy was not administered. Based on the presentation of the case, the causality of malignancy from rhGH therapy is possible.

Discussion

According to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, patients with CF have a higher incidence of digestive cancers including cancers of the esophagus, intestine, liver, biliary tract, or pancreas but no increased rates of any other type of cancer.[130-132] As patients with CF are continuing to live longer, the potential risks that rhGH may have on cancer are important to evaluate.

It is hypothesized that IGF-I induces cellular proliferation and angiogenesis or inhibits apoptosis while IGFBP-3 inhibits IGF-I induced proliferation and may decrease migration and adhesion.[133, 134] Data in non-CF patients suggests that IGF-I and IGFBP-3 concentrations are associated with the development of certain types of cancer. In a prospective case-control study from the Physicians' Health Study, increases in IGF-I by 100 ng/ml were associated with a 1.69 relative risk of developing colorectal cancer (95 percent CI 1.07 to 2.67), while increases in IGFBP-3 by 1000 ng/ml corresponded with a 0.54 relative risk of developing cancer (95 percent CI 0.34 to 0.84).[135] Another case-control evaluation in patients with breast cancer from the Nurses' Health study found no relationship between IGF-I or IGFBP-3 with either premenopausal or postmenopausal breast cancer.[136] When evaluating patients stratified by quartiles of IGF-I levels, patients with highest IGF-I levels had no difference in the risk of breast cancer compared with patients with the lowest IGF-I levels (RR 1.00, 95 percent CI 0.73 to 1.37).[136] Similar results were seen when comparing the highest and lowest IGFBP-3 quartiles (RR 1.07, 95 percent CI 0.79 to 1.45).[136]

In a meta-analysis of cohort and case-control studies, elevated IGF-I concentrations were associated with increased risk of prostate (OR 1.83, 95 percent CI 1.03 to 3.26), colorectal (OR 1.58, 95 percent CI 1.11 to 2.27), and premenopausal breast cancer (OR 1.93, 95 percent CI 1.38 to 2.69) but not associated with postmenopausal breast (OR 0.95, 95 percent CI 0.62 to 1.33) or lung cancer (OR 1.01, 95 percent CI 0.49 to 2.11).[137] Elevated concentrations of IGFBP-3 were also associated with an increased risk of premenopausal breast cancer (OR 1.96, 95 percent CI 1.28 to 2.99); however, there was no effect on the rates of prostate (OR 0.88, 95 percent CI 0.61

3123 to 1.28), colorectal (OR 0.77, 95 percent CI 0.38 to 1.66), postmenopausal breast (OR 0.97, 95
3124 percent CI 0.53 to 1.77), or lung cancer (OR 0.83, 95 percent CI 0.38 to 1.84).[137]

3125 In our comparative effectiveness review, rhGH therapy in CF patients caused higher on-
3126 treatment IGF-I values than control patients and differences between the groups exceeded 100
3127 ng/ml. While data is limited to a single small RCT, IGFBP-3 concentrations were higher in the
3128 rhGH group than the glutamine group but the absolute difference was only 0.89 ng/ml and far
3129 away from difference of 1,000 ng/ml. Extrapolating from prospective case control data in non-
3130 CF populations, the increases in IGF-I seen with rhGH therapy in this trial may be clinically
3131 relevant but the relevance of slight IGFBP-3 elevations cannot be determined.

3132

3133

Table 26. Biomarkers in controlled trials of CF patients treated with rhGH

Study, year	Group	Dose/wk (mg/kg)	N	IGF-I (ng/ml) – Change from Baseline	IGF-I (ng/ml) – Values at Study End	IGFBP-3 (ng/ml) – Change from Baseline	IGFBP-3 (ng/ml) – Values at Study End
Hardin, 2001[23, 24]	rhGH	0.3	10	183 (160)[b]	-	-	-
	No treatment	NA	9	31 (117)[b]	-	-	-
Hutler, 2002[108]	rhGH	0.27 to 0.35	6	-	-	-	-
	No treatment	NA	4	-	-	-	-
Schibler, 2003[26]	rhGH	0.35	10	-	-	-	-
	No treatment	NA	9	-	-	-	-
Darmaun, 2004[29]	rhGH	0.3	9	-	304 (189)	-	3.16 (0.99)
	rhGH+GLN[a]	0.3/0.7	9	-	277 (234)	-	3.03 (1.41)
	GLN[a]	0.7	9	-	147 (129)	-	2.27 (0.81)
Hardin, 2005a[32]	rhGH	0.3	16	-	329 (104)	-	-
	No treatment	0	16	-	86 (40)	-	-
Hardin, 2005b[33]	rhGH	0.3 to 0.35	13	-	442 (89)	-	-
	No treatment	NA	12	-	221 (56)	-	-
Hardin, 2005c[34]	rhGH	0.3	9	-	286 (91)	-	-
	No treatment	NA	9	-	125 (27)	-	-
Hardin, 2006[15]	rhGH	0.3	32	-	-	-	-
	No Treatment	NA	29	-	-	-	-
Schnabel, 2007[4]	Higher dose	0.49	20	-	-	-	-
	Lower dose	0.273	22	-	-	-	-
	Placebo	NA	21	-	-	-	-
Stalvey, 2008[38]	rhGH	0.3	29	-	-	-	-
	No treatment	NA	27	-	-	-	-

Legend: All values given as mean (standard deviation); - =not reported; GLN=glutamine; N=sample size; NA = not applicable; rhGH=recombinant human growth hormone

[a]Glutamine dosing is 0.7 g/kg per day

[b]Change from baseline calculated from published baseline and final values

Table 27. Evidence of cancer with rhGH therapy in observational studies in GHD and ISS populations

Study, year	Study Design	Quality Rating	Product and Dose	Duration of Treatment	Population	Reported Results
Allen, 1997[99] N=12,697	Observational, single-group	Fair	Product and dose NR	Varied	Patients from the National Cooperative Growth Study (a database to study the safety and efficacy of rhGH in patients treated under normal clinical conditions), with idiopathic GHD or ISS.	In 8,102 patients with idiopathic GHD treated with rhGH, there was one case of leukemia. In 4,595 patients with ISS treated with rhGH, there was one case of leukemia.
Marx, 2000[100] N=1	Case report	Poor	Product NR 0.18 mg/kg/week	3.7 years	Short-statured male in whom rhGH therapy was started at 9.7 years for isolated GHD.	At age 13.4 years, the patient was diagnosed with intracranial suprasellar choriocarcinoma, treated successfully and discharged from hospital at age 14.7 years.
Bell, 2009[101] N=33,171	Observational, single-group	Fair	Product and dose NR	Varied	Patients from the National Cooperative Growth Study (a database to study the safety and efficacy of rhGH in patients treated under normal clinical conditions), with idiopathic GHD or ISS.	The rate of malignancy in patients with idiopathic GHD (n=23,393) and ISS (n=9,778) was 0.0 between 1985 and 2006. Over 178,464 years of GH exposure, there were 29 observed cases of new-onset malignancy in patients without previous risk factors.

Legend: GHD=growth hormone deficiency; ISS=idiopathic short stature; N=sample size; NR-=not reported; rhGH=recombinant human growth hormone

Key Question 6

In patients with CF, how is efficacy, effectiveness, safety or adverse events impacted by rhGH dose, therapy duration, baseline nutritional status, and concurrent medical therapies?

Key Points

- Only one trial provides insight into the dose response nature of rhGH in patients with CF. In this trial, no significant differences were seen between the higher and the lower dose groups for any evaluated parameter. We cannot be sure that any qualitative differences are not due to chance.
    - Pulmonary function, as measured by percent predicted FVC and percent predicted FEV_1, tended towards greater improvement in the higher dose group than the lower dose group but no difference was seen with FEV_1 Z-score.
    - Slightly greater increases in height velocity and height velocity Z-score was seen in the higher dose group but similar increases in weight were seen.
    - Higher dose rhGH therapy trends toward causing a higher IGF-I Z-scores which is a potential surrogate outcome for cancer but does not impact IGFBP-3 Z-scores.
- Several trials allow the evaluation of the duration of rhGH therapy and outcomes, suggesting that greater benefits are derived from longer-term therapy but that hyperglycemia is also more common. These are qualitative differences however, and we cannot be sure that they are not due to chance.
    - Trials with 1 year of rhGH therapy tend towards greater improvements in percent predicted FVC, absolute FEV_1, height, height velocity, weight, and exercise work rate than trials of 6 months duration.
    - Trials with 1 year of rhGH therapy show slight improvements in lean body mass than trials of 6-months duration and no impact on percent predicted FEV_1 was seen.
    - Trials with 1 year of rhGH therapy tend towards greater increased in fasting glucose concentrations than trials of 6 months duration.
- rhGH has not been studied in patients with CF who have nutritional deficiencies that are not being addressed with enteral nutrition. We cannot determine the benefits of rhGH therapy in patients with unaddressed nutritional deficiencies.
- The usage of concurrent medical therapies in patients enrolled in trials evaluating rhGH therapy was sparingly reported, so the differential effect on rhGH efficacy could not be assessed.

Detailed Analysis

Study Design and Population Characteristics

Studies to answer Key Question 6 are derived from the same set of studies used to evaluate Key Question 1 and are summarized in Table 4-Table 6.

Outcome Evaluations

Dose

All controlled trials except one used very similar doses of rhGH. Seven trials used 0.3 mg/kg/week doses,[15, 23, 26, 29, 32, 34, 38] another trial used 0.27 to 0.35 mg/kg/week doses,[25] and a third trial used 0.3 to 0.35 mg/kg/week doses.[33] None of these trials reported results in patients receiving different doses and does not provide insight into the impact of dose on outcomes. The exception is a three-arm trial with lower dose, a higher dose, and a placebo arm which will be used to assess the impact of dose on efficacy and safety.[4] Since the two rhGH arms in the trial only have 42 patients between them, it is underpowered and only qualitative insight can be garnered.

Efficacy

One randomized controlled trial evaluated two doses of rhGH therapy in CF patients, with patients being assigned to 0.273 mg/kg/week (n=22), a dose slightly lower than the other trials, or 0.49 mg/kg/week (n=20), or placebo (n=21).[4] Since p-values were not provided for the higher versus lower comparison, we compared the changes from baseline in the lower and higher groups using an unpaired Student t-test and calculated the p-value from the provided data using the Primer of Biostatistics (McGraw-Hill, Stanton, CA).

There were no qualitative differences between the higher and lower dose groups in FEV_1 Z-score (change from baseline -0.04±0.30 versus -0.03±0.32, p-value not reported, our calculated p=0.918).[4] However, there appears to be nonsignificantly greater improvements in the higher dose group than the lower dose group in percent predicted FVC (change from baseline 6.0±11.2 versus 3.1±13.1, p-value not reported, our calculated p=0.447) and percent predicted FEV_1 (change from baseline 4.3±13.4 versus 3.5±12.3, p-value not reported, our calculated p=0.841).[4]

The higher dose group experienced slightly greater increases than the lower dose group in both height velocity (change from baseline 6.8±4.3 versus 5.6±2.9 cm/year, p-value not reported, our calculated p=0.291) and height velocity Z-score (change from baseline: higher dose 2.6±2.7; lower dose 1.5±2.6, p-value not reported, our calculated p=0.186).[4]

The higher and lower dose groups experienced similar increases in weight (change from baseline 2.2±2.3 kg versus 2.4±1.9 kg, p-value not reported, our calculated p=0.759.), LBM (change from baseline 2.3±2.5 kg versus 2.5±2.4 kg, p-value not reported, our calculated p=0.793), and BMI Z-score (change from baseline 0.1±0.6 versus 0.0±0.6, p-value not reported, our calculated p=0.593).[4]

Safety

While not statistically significant, the higher dose group experienced qualitatively greater increases in IGF-I Z-scores (1.66±1.53 versus 1.00±1.06, p-value not reported, our calculated p=0.109) and IGFBP-3 Z-scores (0.66±1.41 versus 0.5±1.6, p-value not reported, our calculated p=0.734) than the lower dose group.[4]

Duration

Seven controlled trials had a duration of therapy of 1 year,[15, 23, 26, 32-34, 38] two trials had a 6 month duration,[4, 108] and a final trial had 1 month of followup.[29] Trials were amenable to

subgroup analysis based on duration of followup on the same outcomes meta-analyzed in Key Questions 1, 2, and 4. Results of subgroup analysis are presented in Table 29.

Efficacy

All controlled trials reporting absolute FVC were 1 year in duration precluding evaluation for this key question. There were trends toward greater improvement in percent predicted FVC and absolute FEV_1 in patients treated for 1 year compared to those treated for 6 months. (Table 29) However, there were no apparent effects of duration of therapy on percent predicted FEV_1.

There were trends towards greater improvement with 1 year of treatment compared with 6 months of treatment in absolute height and height velocity. (Table 29) Height Z-score was only reported in trials of 1 year duration. There were also trends towards greater improvement in weight outcomes with 1 year of treatment compared with 6 month in absolute weight, and lean body mass. (Table 29) Weight velocity, weight Z-score, BMI, and percent IBW were only reported in trials of 1 year duration. BMI Z-score was only reported in trials of 6 months duration. The differential effects of treatment duration on BMC could not be assessed because all trials were 1 year in duration. The differential effects of treatment duration on hospitalization rate could not be assessed because all trials were 1 year in duration.

In an open label extension trial, patients were given rhGH therapy for a second year, regardless of the treatment they were allocated to in the original 1 year clinical trial.[34] Those patients continuing rhGH treatment had similar effects over the second year of study as those newly initiating rhGH treatment in height velocity (5.9±2.1 versus 6.2±1.2 cm/year; p-value not reported) and change in LBM from the initiation of open-label rhGH (3.9±1.4 versus 4.1±2.0 kg, p-value not reported).[34] Weight velocity was qualitatively higher in those continuing rhGH as compared to those initiating rhGH (6.0±1.7 versus 4.6±3.1 kg/year, p-value not reported). Those continuing rhGH had similar pulmonary effects as those initiating rhGH in the change from baseline for absolute FVC (1.1±0.2 versus 1.6±0.1 L, p-value not reported), absolute FEV_1 (0.6±0.3 versus 0.5±0.4 L, p-value not reported), and BMC (177±69 versus 163±75 g, p-value not reported).[34] There was a qualitatively greater hospitalization rate in those continuing rhGH than those initiating rhGH (2.1±2.1 versus 0.8±0.4 events per year, p-value not reported).[34]

Safety

Upon subgroup analysis based upon rhGH treatment duration, the fasting blood glucose had nonsignificantly greater increases from baseline in the rhGH group compared to control groups in patients treated for 1 year versus those treated for 6 months. (Table 29) The differential effects of treatment duration could not be assessed for A1c because all trials were for 1 year, nor assessed for stimulated blood glucose because all trials were for 6 months.

Glucose parameters in the second year of rhGH treatment in the trial by Hardin and colleagues in 2005 were not reported.[34] After the second year of therapy, IGF-I levels increased in those initiating rhGH therapy (from 125±27 ng/ml to 324±29 ng/ml, p-value not reported) and did not significantly change from the initiation of open-label rhGH in those continuing rhGH therapy (from 286±91 ng/ml to 319±25 ng/ml, p-value not reported).[34]

Baseline Nutritional Status

The baseline nutritional status in patients enrolled in controlled trials evaluating rhGH therapy was sparingly reported. (Table 28) The nutritional status was not specified in five

trials.[25, 26, 29, 32, 38] The five remaining trials reported specific nutrition-related inclusion and exclusion criteria, which allude to the nutritional status of patients: three trials specified that patients must have good or adequate caloric intake,[4, 23, 33] one trial excluded patients who required parenteral caloric supplementation,[15] and one trial included only patients who required and received enteral nutrition.[34] No trial reported that patients had poor nutrition precluding comprehensive subgroup analysis. We focused on the trial where patients required and received enteral nutrition in this portion of the key question since it addresses, in part, the concern about whether rhGH would have effects over and above improving nutritional status in nutritionally at risk individuals.

Efficacy

One randomized controlled trial by Hardin and colleagues evaluated patients who had been receiving enteral nutrition overnight via gastronomy tube for at least 2 years prior to study enrollment.[34] Patients treated with growth hormone (n=9) showed statistically significant improvements over patients in the control group (n=9) during 12 months of therapy.[34] There were statistically significant improvements in pulmonary function as measured by absolute FVC ($p<0.05$ between groups at 12 months) and absolute FEV_1 ($p<0.05$ between groups at 12 months).[34] Significant improvements with rhGH therapy were also seen in anthropometric measures such as height velocity, height Z-score, weight velocity, weight Z-score ($p<0.05$ between groups for all endpoints at 12 months), BMI and LBM ($p<0.05$ between groups for change from baseline in endpoints at 12 months).[34] Benefits were seen with increases in BMC over 12 months of therapy as well (rhGH group 176±22 g/year; control group 34±15 g/year, $p=0.02$).[34] The rate of hospitalizations was also significantly fewer in patients receiving rhGH compared to patients with no therapy (rhGH group 1.1±1.0 hospitalizations/year; control group 3.0±2.0 hospitalizations/year, $p=0.003$).[34] The results of this trial are similar to the effects seen in the overall set of trials evaluating the use of rhGH in CF patients, suggesting that the effect of rhGH is applicable to patients who require and are receiving enteral nutrition.

Safety

In patients receiving enteral nutrition for 1 year, there was a nonsignificant increase from baseline in casual blood glucose in those treated with rhGH (baseline 87±11 mg/dl; 1 year 92±9 mg/dl, p=not significant).[34] Changes from baseline in casual blood glucose in the control group were not reported.[34] There were significant increases in IGF-I in the rhGH group compared to baseline after 1 year, but no changes in the control group (baseline for both groups 119±42 ng/ml; rhGH at 1 year 286±91; control at 1 year 125±27; p-values not reported).[34]

Concurrent Medical Therapies

The usage of concurrent medical therapies in patients enrolled in trials evaluating rhGH therapy was sparingly reported. (Table 28) Therefore, the effect that concurrent therapy may have on rhGH efficacy and safety could not be assessed.

Discussion

Evidence for a dose-response relationship is poor. Further study is required to establish efficacy of rhGH based upon dose. From the single trial which evaluated two different doses of rhGH, there were mixed results on the effect of a higher dose compared to a lower dose.[4] Pulmonary function as measured by percent predicted FVC and percent predicted FEV_1 trended

towards greater improvement in the higher dose group than the lower dose group.[4] There were slightly greater improvements in height parameters in the higher dose group but similar effects on weight outcomes.[4] None of these comparisons were statistically significant, and would require a larger sample size to determine the true differential effects of the two doses if any exist.

In general, controlled trials conducted for 1 year exhibited greater rhGH efficacy than those conducted for 6 months but greater increases in serum glucose occur. Trials which continued rhGH therapy for a second year continued to show improvement in intermediate outcomes. None of these comparisons were statistically significant and would require a larger sample size to determine the true differential effects of the two doses if any exist.

With regard to baseline nutritional status, none of the trials specified that they had patients with poor nutrition. There are no data available to assess the efficacy of rhGH in patients with inadequate nutrition. Therefore, consideration of rhGH therapy should occur after a patient is receiving adequate caloric intake. One trial evaluated patients who all received enteral nutrition, and showed that there is efficacy of rhGH in addition to enteral nutrition. No trials evaluated rhGH use in addition to parenteral nutrition, so its efficacy in this clinical scenario is uncertain.

The underreporting of concurrent medical therapies in patients precluded analysis or discussion on the benefit of rhGH in addition to specific therapies.

Table 28. Concurrent therapies and nutrition in controlled trials evaluating rhGH

Study, year	Group	Dose/wk (mg/kg)	N	Enteral Nutrition (number of patients)	Pancreatic Enzymes (number of patients)	Inhaled Tobramycin (number of patients)	Recombinant Human DNase (number of patients)	Inhaled Corticosteroids (number of patients)	Systemic Corticosteroids (number of patients)
Hardin, 2001[23, 24]	rhGH	0.3	10	2	10	-	-	-	0
	No treatment	NA	9	2	9	-	-	-	0
Hutler, 2002[25108a]	rhGH	0.27 to 0.35	10	-	10	-	-	-	-
	No treatment	NA							
Schibler, 2003[26]	rhGH	0.35	10	-	-	-	-	-	-
	No treatment	NA	9	-	-	-	-	-	-
Darmaun, 2004[29b]	rhGH	0.3	9	-	-	-	-	-	1
	rhGH+GLN	0.3/0.7[c]							
	GLN	0.7[c]							
Hardin, 2005a[32]	rhGH	0.3	16	-	-	-	-	-	0
	No treatment	NA	16	-	-	-	-	-	0
Hardin, 2005b[33]	rhGH	0.3 to 0.35	13	-	13	-	-	2	0
	No treatment	NA	12	-	12	-	-	1	0
Hardin, 2005c[34]	rhGH	0.3	9	9	9	-	-	-	0
	No treatment	NA	9	9	9	-	-	-	0
Hardin, 2006[15]	rhGH	0.3	30	-	-	-	-	-	1
	No Treatment	NA	27	-	-	-	-	-	2
Schnabel, 2007[4]	Higher dose	0.49	20	0	-	-	-	-	0
	Lower dose	0.273	22	3	-	-	-	-	0
	Placebo	NA	21	0	-	-	-	-	0
Stalvey, 2008[38]	rhGH	0.3	29	-	-	-	-	-	-
	No treatment	NA	27	-	-	-	-	-	-

Legend: - =not reported, GLN=glutamate; N=sample size; NA=not applicable; rhGH=recombinant human growth hormone
[a]Hutler et al was a crossover study – results reported for entire enrolled population
[b]Darmaun et al was a crossover study – results reported for entire enrolled population
[c]Glutamate dosing is 0.7 g/kg per day

Table 29. Subgroup analyses based on duration of rhGH therapy

Outcome	Trials with 6 month duration Pooled effect (95%CI)	Trials with 1 year duration Pooled effect (95%CI)
Pulmonary Outcomes		
Absolute FVC (L)	NR	0.67 (0.24 to 1.09)
Percent predicted FVC	5.29 (-2.14 to 12.72)	11.37 (3.18 to 19.57)
Absolute FEV_1 (L)	0.04 (-0.16 to 0.24)	0.36 (0.06 to 0.66)
Percent predicted FEV_1	2.89 (-7.69 to 13.47)	2.16 (-5.91 to 10.23)
Anthropometrics		
Height (cm)	1.40 (-0.07 to 2.87)	4.32 (3.03 to 5.62)
Height velocity (cm/year)	2.56 (1.11 to 4.01)	3.65 (2.19 to 5.10)
Height Z-score	NR	0.51 (0.35 to 0.66)
Weight (kg)	0.93 (0.08 to 1.78)	2.50 (0.48 to 4.51)
Weight velocity (kg/year)	NR	2.15 (1.52 to 2.78)
Weight Z-score	NR	0.49 (-0.02 to 1.00)
BMI (kg/m^2)	NR	2.08 (1.20 to 2.96)
BMI Z-score	-0.05 (-0.30 to 0.20)	NR
Percent IBW	NR	12.57 (7.01 to 18.12)
LBM (kg)	1.57 (0.65 to 2.49)	2.05 (1.50 to 2.60)
Bone Outcomes		
BMC (g)	NR	192 (110 to 273)
Exercise Tolerance		
Exercise work rate (W)	8.08 (-2.76 to 18.91)	31.90 (4.54 to 59.26)
Important Health Outcomes		
Hospitalizations (events per year)	NR	-1.62 (-1.98 to -1.26)
Glucose Parameters		
A1c (%)	NR	-0.10 (-0.40 to 0.20)
Fasting BG (mg/dl)	3.89 (-2.62 to 10.41)	9.00 (0.11 to 17.89)
Stimulated BG (mg/dl)	4.93 (-15.13 to 24.98)	NR

Legend: A1c=glycosylated hemoglobin; BG=blood glucose; BMC=bone mineral content; BMI=body mass index; CI=confidence interval; FEV_1=forced expiratory flow in one second; FVC=forced vital capacity; IBW=ideal body weight; LBM=lean body mass; NR=not reported

Key Question 7

In patients with CF, how do the efficacy, effectiveness, safety or adverse events of treatment with rhGH differ between subgroups of patients? Subgroup characteristics of interest include, but are not limited to: age (pre-pubertal, pubertal, post-pubertal); gender; baseline clinical status (height, weight, lean body mass, pulmonary function, exercise tolerance, nutritional status); and/or the nature, extent, and effectiveness of prior treatment.

Key Points

- The age of the patient may impact rhGH efficacy.
  - In an individual patient data merged analysis of trials, both prepubertal and adolescent patients had significant improvements in height, weight, lean body mass, and hospitalizations as compared to their respective control populations. Prepubertal patients receiving rhGH did not have significant increases in FEV_1 and the percent predicted FEV_1 was significantly lower than prepubertal control patients. In contrast, adolescent patients receiving rhGH had significant improvements in FEV_1 and percent predicted FEV_1.
  - In a pooled analysis that should only be viewed qualitatively, prepubertal patients receiving rhGH seem to derive greater benefits on height than pubertal patients receiving rhGH but lesser benefits on weight, BMI, and percent ideal body weight. Pubertal patients receiving rhGH also seem to derive greater increases in absolute FVC, FEV1, and bone mineral content but fewer hospitalizations and smaller increases in percent predicted FVC than prepubertal patients.
- While most controlled trials were conducted predominantly in males, the impact of gender on outcomes of rhGH therapy could be qualitatively assessed in one pooled analysis. The authors of the analysis did not report p-values or whether the comparisons were statistically significant and did not provide patient numbers precluding our ability to calculate these p-values.
  - In prepubertal patients not receiving rhGH therapy, no difference in height velocity occurred between the genders the year before treatment allocation but females had greater weight velocity. In pubertal patients not receiving rhGH therapy, females had greater height and weight velocity than males the year before treatment allocation.
  - In prepubertal patients, the first 6 months of rhGH therapy provided similar increases in height and weight velocity between genders but in months 6 to 12, females had greater height velocity while males had greater weight velocity.
  - In pubertal patients, the first 6 months of rhGH therapy provided similar increases in height velocity between genders but females had greater increases in weight velocity. In months 6 to 12, females had greater height and weight velocities than males.
  - The occurrence of adverse effects associated with rhGH therapy in males and females was not individually determined.

- The impact of baseline clinical status on rhGHs clinical outcomes was assessed in two trials. In the first trial, those with a baseline height Z-score below -2.2 had a similar increase in height Z-score on rhGH therapy. In the second trial, a higher baseline percent predicted FEV_1 was positively correlated with the change of weight associated with rhGH therapy. The occurrence of adverse events associated with rhGH therapy in patients with different baseline clinical status could not be determined.

Detailed Analysis

Study Design and Population Characteristics

Studies to answer Key Question 7 are derived from the same set of studies used to evaluate Key Question 1 and are summarized in Table 4-Table 6.

Outcome Evaluations

Age

Six controlled trials specifically evaluated prepubertal patients,[15, 23, 29, 32, 34, 38] one trial evaluated pubertal adolescents exclusively,[33] and three trials did not specify the pubertal status of patients.[4, 26, 108]

Efficacy

Subgroup analysis was performed for controlled trials that evaluated only prepubertal patients and the trial which evaluated only pubertal patients. (Table 30) Although statistical comparison of the two subgroups was not conducted, the results can be assessed qualitatively. Patients who have reached puberty had qualitatively greater response to rhGH therapy in absolute FVC and absolute FEV_1 compared to prepubertal patients. (Table 30) However, prepubertal patients had greater improvement in percent predicted FVC than pubertal patients, and the differential effect on percent predicted FEV_1 could not be assessed.

For absolute changes in height, the prepubertal patients experienced greater response than pubertal patients. The effect that pubertal status may have on response to rhGH on height velocity and height Z-score could not be assessed. In contrast, pubertal patients experienced greater weight gain, BMI, and IBW with rhGH than prepubertal patients. (Table 30) Weight velocity, weight Z-score, BMI Z-score and LBM in prepubertal and pubertal patients on rhGH could not be assessed.

Pubertal patients accumulated greater BMC than prepubertal patients, likely due to the presence of mature sex hormones, which may aid in the response to rhGH. Exercise tolerance was only assessed in trials enrolling a mix of pubertal status and was not compared between subgroups. Hospitalization rate was reduced more in pubertal patients treated with rhGH than prepubertal patients. (Table 30)

In a meta-analysis by Hardin and colleagues presented as a poster in 2009, results were reported separately for prepubertal children and adolescents.[138] At 1 year of rhGH therapy, prepubertal patients in the rhGH group (n=87) experienced significantly better outcomes than prepubertal children in the control group (n=60) in height (138.7±11.7 cm versus 130.1±14.9 cm, p-value not reported but said to be statistically significant), weight (30.3±5.9 kg versus 26.2±6.8 kg, p-value not reported but said to be statistically significant), and LBM (25.8±5.7 kg versus

3407 20.4±3.4 kg, p-value not reported but said to be statistically significant).[138] There were no
3408 significant differences in absolute FEV_1 (1.43±1.5 L versus 1.74±2.7 L, p-value not reported),
3409 although the rhGH group had significantly worse percent predicted FEV_1 (73.6±24.8 versus
3410 77.0±26.6, p-value not reported but said to be statistically significant).[138] The rhGH group also
3411 had significantly fewer hospitalizations than the control group (0.55±1.1 versus 1.2±0.9, units of
3412 measure not reported, p-value not reported but said to be statistically significant).[138]

3413 Adolescent patients treated with rhGH (n=54) also had better outcomes than adolescent
3414 patients in the control group (n=22) in regards to height (158.2±8.8 cm versus 153.2±7.7 cm, p-
3415 value not reported but said to be statistically significant), weight (42.4±7.9 kg versus 39.1±6.5
3416 kg, p-value not reported but said to be statistically significant), and LBM (36.9±6.6 kg versus
3417 33.1±5.9 kg, p-value not reported but said to be statistically significant).[138] In contrast to
3418 prepubertal patients on rhGH, adolescent patients treated with rhGH experienced significantly
3419 better effects than control patients on both absolute FEV_1 (2.63±1.27 L versus 1.99±0.77 L, p-
3420 value not reported but said to be statistically significant) and percent predicted FEV_1 (80.4±23.8
3421 versus 61.7±26.9, p-value not reported but said to be statistically significant).[138] Adolescent
3422 patients treated with rhGH also experienced significantly fewer hospitalizations than control
3423 (0.84±0.84 versus 1.9±1.4, units of measure not reported, p-value not reported but said to be
3424 statistically significant).[138]

3425 The controlled trial by Hardin and colleagues in 2005, evaluating rhGH use exclusively in
3426 adolescent patients, included a report of anthropometric results divided by Tanner stage.[33]
3427 Patients in Tanner stage 3 treated with rhGH (n=6) experienced significantly better outcomes
3428 after 1 year of therapy than those without treatment (n=7) in height Z-score (-1.58 versus -3.01,
3429 p<0.002), weight Z-score (-1.89 versus -2.34, p<0.002), height velocity (8.3 cm/year versus 4.5
3430 cm/year), weight velocity (7.3 kg/year versus 1.4 kg/year, p<0.002), and BMI (17.5 kg/m^2 versus
3431 15.9 kg/m^2, p<0.002). [33] Patients in Tanner stage 4 treated with rhGH (n=7) also experienced
3432 significantly better outcomes after one year of therapy than those without treatment (n=5) in
3433 height Z-score (-1.19 versus -2.73, p<0.002), weight Z-score (-1.21 versus -1.54, p<0.002),
3434 height velocity (8.5 cm/year versus 5.7 cm/year, p<0.002), weight velocity (8.6 kg/year versus
3435 4.7 kg/year, p<0.002), and BMI (18.7 kg/m^2 versus 15.8 kg/m^2, p<0.002).[33] Measures of
3436 variance surrounding these mean values were not reported. [33]

3437 In the pooled study by Vanderwel and Hardin, three previous controlled trials[15, 23, 33] were
3438 combined to evaluate patients with CF in four mutually exclusive subgroups: prepubertal
3439 females, pubertal females, prepubertal males, and pubertal males.[37] Pubertal status did not appear
3440 to affect the response to rhGH on height velocity in female patients. Prepubertal females who did
3441 not receive therapy in 1 year (number of patients not reported) showed similar height velocity
3442 (5.7±2.4 cm/year) to pubertal females who did not receive rhGH therapy (number of patients not
3443 reported, 4.5±1.0 cm/year).[37] In the first 6 months of rhGH therapy, prepubertal females who
3444 received therapy showed similar height velocity to pubertal females (8.5±2.6 cm/year versus
3445 8.5±1.0 cm/year, p-value not reported).[37] During months 6 to 12 of therapy, there were also
3446 similar height velocities between prepubertal and pubertal females (7.7±2.7 cm/year versus
3447 8.2±1.3 cm/year, p-value not reported);[37] however, there appeared to be differential effects of
3448 pubertal status on weight velocity. Nontreated prepubertal females showed a weight velocity of
3449 3.7±2.4 kg/year after 1 year, while nontreated pubertal females showed a weight velocity of
3450 4.0±3.2 kg/year, p-value not reported.[37] In the first 6 months of rhGH therapy, prepubertal
3451 females experienced similar weight velocity to pubertal females (4.8±3.9 kg/year versus 5.5±3.1

kg/year, p-value not reported).[37] During months 6 to 12 of therapy, prepubertal females showed qualitatively lesser weight velocity than pubertal females (2.2±1.8 kg/year versus 6.4±4.6 kg/year).[37]

In the males evaluated with regard to pubertal status, there did not appear to be any differential effects of rhGH therapy on height velocity, although there were differences between groups in those who did not receive therapy. Prepubertal males who did not receive therapy (number of patients not reported) showed height velocity 5.1±1.0 cm/year in 1 year compared to nontreated pubertal males (number of patients not reported) showing height velocity 2.7±0.2 cm/year, p-value not reported.[37] In the first 6 months of rhGH therapy, prepubertal males experienced similar effects on height velocity as pubertal males (8.3±2.4 cm/year versus 8.2±3.6 cm/year, p-value not reported).[37] During months 6 to 12 of therapy, there were also similar results between prepubertal and pubertal males (6.8±2.6 cm/year versus 7.0±3.6 cm/year, p-value not reported).[37] Similar effects between prepubertal and pubertal males were also seen in weight velocity, although there were differences between groups in those who did not receive therapy. In the nontreated prepubertal males, weight velocity in 1 year was 1.9±1.4 kg/year compared to 3.0±0.4 kg/year in pubertal males, p-value not reported.[37] In the first 6 months of rhGH therapy, prepubertal males showed weight velocity 4.1±2.2 kg/year while pubertal males showed 3.3±2.0 kg/year, p-value not reported.[37] During months 6 to 12 of rhGH therapy, prepubertal males showed similar weight velocity than pubertal males (3.8±2.7 kg/year versus 5.0±3.0 kg/year, p-value not reported).[37] P-values were not reported for these comparisons; we could not conduct our own comparison using unpaired t-tests because the sample size for each treatment group within the pubertal and prepubertal subgroups were not reported.

In the trial by Schnabel and colleagues, the change from baseline in height was negatively correlated with chronological age ($r=0.61$, $p<0.0001$).[4]

Safety

Upon subgroup analysis, there were no qualitative differences between prepubertal and pubertal patients in A1c response to rhGH therapy. Differential effects that pubertal status may play on fasting and stimulated blood glucose could not be assessed.

Trials that reported results in subgroups based upon pubertal status did not report on safety parameters.

Gender

All controlled trials included patients of which more than half were male, precluding subgroup comparisons of trials based on predominant gender. In the pooled study by Vanderwel and Hardin, three previous trials[15, 23, 33] were combined to evaluate patients with CF in four mutually exclusive subgroups: prepubertal females, pubertal females, prepubertal males, and pubertal males.[37]

Efficacy

In the study by Vanderwel and Hardin, the height velocity in prepubertal females and prepubertal males who did not receive rhGH therapy (number of patients not reported) were similar in the year before trial initiation (5.7±2.4 cm/year versus 5.1±1.0 cm/year, p-value not reported).[37] In the first 6 months of rhGH therapy, prepubertal females responded similarly to prepubertal males in height velocity (8.5±2.6 cm/year versus 8.3±2.4 cm/year, p-value not

reported).[37] During months 6 to 12 of rhGH therapy, height velocity was qualitatively higher in prepubertal females and prepubertal males (7.7±2.7 cm/year versus 6.8±2.6 cm/year, p-value not reported).[37] Weight velocity in 1 year was qualitatively higher in nontreated prepubertal females than nontreated prepubertal males (3.7±2.4 kg/year versus 1.9±1.4 kg/year, p-value not reported).[37] In the first 6 months of rhGH therapy, weight velocity was similar between prepubertal males and females (4.8±3.9 kg/year versus 4.1±2.2 kg/year, p-value not reported).[37] During months 6 to 12 of rhGH therapy, there was a qualitatively lesser weight velocity in prepubertal females than prepubertal males (2.2±1.8 kg/year versus 3.8±2.7 kg/year, p-value not reported).[37]

Pubertal females tended to have qualitatively greater height velocity and weight velocity than pubertal males (number of patients not reported).[37] In the year before trial initiation, greater height velocity occurred in pubertal females than pubertal males (4.5±1.0 cm/year versus 2.7±0.2 cm/year, p-value not reported).[37] In the first 6 months of rhGH therapy, prepubertal females showed similar height velocity to prepubertal males (8.5±1.0 cm/year versus 8.2±3.6 cm/year, p-value not reported).[37] During months 6 to 12 of rhGH therapy, pubertal females showed qualitatively greater height velocity than pubertal males (8.2±1.3 cm/year versus 7.0±3.6 cm/year, p-value not reported).[37] Weight velocity in the year before trial initiation was also greater in pubertal females than pubertal males (4.0±3.2 kg/year versus 3.0±0.4 kg/year, p-value not reported).[37] In the first 6 months of rhGH therapy, pubertal females showed greater weight velocity than pubertal males (5.5±3.1 kg/year versus 3.3±2.0 kg/year, p-value not reported).[37] During months 6 to 12 of rhGH therapy, pubertal females continued to show greater weight velocity than pubertal males (6.4±4.6 kg/year versus 5.0±3.0 kg/year, p-value not reported).[37]

P-values were not reported for these comparisons; we could not conduct our own comparison using unpaired t-tests because the sample size for each treatment group within the pubertal and prepubertal subgroups were not reported.

Safety

The study by Vanderwel and Hardin did not report results on safety parameters.[37]

Baseline Clinical Status

Two trials reported results based on differences in baseline clinical status.[4, 15]

Efficacy

One trial conducted a planned subgroup analysis on the effect of rhGH on height outcomes with regard to baseline height (height Z-score <-2.2, n=9 versus height Z-score >-1.2, n=9).[15] Both subgroups experienced similar response to rhGH therapy, with increases of 0.42±0.13 and 0.47±0.4 in height Z-score from baseline, respectively (p=0.3).[15] Results for the subgroups in the control group were not reported.[15]

In the trial by Schnabel and colleagues, the change in weight in percentage from baseline was positively correlated with the baseline percent predicted FEV_1 (r=0.61, p<0.0001).[4]

Safety

No controlled trials reported effects of rhGH therapy on safety parameters, differentiating by baseline clinical status.

Prior Medical Therapy

No controlled trials reported prior medical therapies used and their potential impact on the efficacy of rhGH therapy.

Discussion

The results shown in subgroup analysis and in individual trials suggest that there is benefit to using rhGH therapy across all age groups. However, the magnitude of efficacy appears to differ between age groups.

Upon subgroup analysis, we found that prepubertal patients experienced greater rhGH benefit than pubertal patients in percent predicted FVC and absolute height. For all other outcomes, pubertal patients experienced qualitatively greater benefit to rhGH therapy. It is expected that the pubertal patients experienced less height gain than pubertal patients because they are likely closer to their maximal height.

One interesting finding in the meta-analysis conducted by Hardin and colleagues was that while pulmonary function did not significantly improve with rhGH therapy in prepubertal patients, it did significantly improve with rhGH therapy in adolescent patients.[138] It is possible that adolescent patients may not experience the dramatic changes in linear growth that prepubertal patients might, and therefore show improvements in pulmonary function independent of height. It would be most beneficial to know the changes from baseline in all of these parameters rather than the final results at the end of therapy, but the data are only available in an abstract form at this time. We look forward to the publication of the full manuscript of this analysis to elucidate the relationship that age or pubertal status may have on response to rhGH therapy.

When evaluating only Tanner stage 3 or Tanner stage 4 patients,[33] both groups of patients had significantly better outcomes with rhGH treatment than without in anthropometric outcomes. However, instead of the comparison of final values as reported, it would be more insightful to account for the variations in baseline status in these two pubertal groups. It would be interesting to see if the magnitude of rhGH effect varies based upon the pubertal status of the patient, rather than simply knowing that rhGH has an effect compared to control. This would be able to give clinicians insight on the value of adding rhGH to a post-pubertal patient's regimen.

In the study by Vanderwel and Hardin, similar effects on height and weight velocities were seen between prepubertal females and pubertal females and between prepubertal males and pubertal males.[37]

Schnabel and colleagues found a negative correlation between height gain and chronological age.[4] The negative correlation in height gain from baseline and chronological age is likely due the attainment of maximal height.

There is little evidence to determine the impact of gender on rhGH efficacy. In the study by Vanderwel and Hardin, prepubertal females had qualitatively greater response in height velocity than prepubertal males, while prepubertal males had greater weight velocity than prepubertal females.[37] In contrast, pubertal females had both greater height velocity and weight velocity than pubertal males.[37] These results must be interpreted with caution because it does not account for the height and weight velocities seen in the control groups. In order to make a strong comparison between males and females, we must first determine the mean differences in effect between the rhGH and control groups to find what additional benefit rhGH therapy would have to standard

3577 therapy. Ideally, we should be comparing the mean differences in females to the mean
3578 differences in males in order to judge the comparative efficacy of the treatment. Unfortunately,
3579 due to the underreporting of the sample size of each treatment group within each of the
3580 subgroups, we could not calculate the mean differences.

3581 One trial reported results of subgroup analyses on the tallest and shortest patients in the
3582 study, finding similar changes in height Z-score from baseline in rhGH-treated patients in either
3583 subgroup.[15] Results of subgroup analysis in the control group were not reported,[15] but this
3584 information would have been valuable to determine if the tallest and shortest patients experience
3585 different innate changes in height Z-score without therapy over 1 year. Without data in the
3586 control group, it is difficult to determine the effect of rhGH in addition to standard therapy.

3587 Schnabel and colleagues found a positive correlation between weight gain and baseline
3588 FEV_1,[4] suggesting that patients with better pulmonary function at baseline have greater weight
3589 response to rhGH therapy. Potential mechanisms for this relationship are unclear.

Table 30. Subgroup analyses based on pubertal status of patients enrolled

Outcome	Controlled trials which only enrolled prepubertal patients Pooled effect (95%CI)	Controlled trials which only enrolled pubertal patients Pooled effect (95%CI)
Pulmonary Outcomes		
Absolute FVC (L)	0.55 (0.10 to 1.00)	1.00 (0.32 to 1.68)
Percent predicted FVC	17.49 (-7.00 to 42.00)	12.70 (11.30 to 14.10)
Absolute FEV_1 (L)	0.28 (-0.03 to 0.58)	0.64 (0.05 to 1.23)
Percent predicted FEV_1	3.25 (-8.54 to 15.03)	NR
Anthropometrics		
Height (cm)	4.40 (2.95 to 5.85)	3.90 (0.52 to 7.28)
Height velocity (cm/year)	3.65 (2.19 to 5.10)	NR
Height Z-score	0.51 (0.35 to 0.66)	NR
Weight (kg)	1.78 (0.04 to 3.53)	5.50 (1.76 to 9.24)
Weight velocity (kg/year)	2.15 (1.52 to 2.78)	NR
Weight Z-score	0.74 (0.34 to 1.14)	NR
BMI (kg/m^2)	1.60 (0.95 to 2.25)	2.50 (2.07 to 2.93)
BMI Z-score	NR	NR
Percent IBW	10.00 (5.74 to 14.26)	15.70 (10.30 to 21.10)
LBM (kg)	2.04 (1.43 to 2.64)	NR
Bone Outcomes		
BMC (g)	144 (68 to 220)	650 (427 to 873)
Exercise Tolerance		
Exercise work rate (W)	NR	NR
Important Health Outcomes		
Hospitalizations (events per year)	-1.49 (-1.96 to -1.02)	-1.81 (-2.38 to -1.24)
Glucose Parameters		
A1c (%)	-0.10 (-0.46 to 0.26)	-0.10 (-0.64 to 0.44)
Fasting BG (mg/dl)	9.00 (0.11 to 17.89)	NR
Stimulated BG (mg/dl)	NR	NR

Legend: A1c=glycosylated hemoglobin; BG=blood glucose; BMC=bone mineral content; BMI=body mass index; CI=confidence interval; FEV_1=forced expiratory flow in 1 second; FVC=forced vital capacity; IBW=ideal body weight; LBM=lean body mass; NR=not reported

Chapter 4. Summary and Discussion

A succinct summary of evidence on benefits and harms of using rhGH therapy in patients with CF in addition to usual care is presented in Table 31. More elaborate discussions are provided at the end of the results for each Key Question. More detailed assessments of strength of evidence for major clinical outcomes and harms are summarized in an EPC grading table of evidence (Appendix Tables 9-12). Key Questions 1 and 2 focus on benefits while Key Question 4 focuses on nonmalignant harms and Key Question 6 focuses on malignancy. Benefits evaluated for included: pulmonary function (percent predicted FEV_1 and change in FEV_1), growth (height, weight, lean body mass, protein turnover), exercise tolerance, bone mineralization, frequency of required intravenous antibiotic treatments, frequency of hospitalization, quality of life, bone fracture or development of osteoporosis/osteopenia, or total mortality. Harms evaluated for included: glucose intolerance, diabetes, hypoglycemia, and malignancy. Members of the TEP identified these outcomes as important because they are most likely relevant to patients, clinicians, and policymakers. Key question 3 explored the associations between intermediate outcomes and final health outcomes. Key Questions 6 and 7 focused on factors that might impact the efficacy of rhGh in patients with CF or subpopulations that might receive rhGH therapy.

Table 31. Summary of results

Outcome	Type of Study	Number of Studies	Pooled	Conclusion	Strength of Evidence
KQ1. In patients with CF, does treatment with rhGH as an adjuvant to usual care improve intermediate outcomes, including: pulmonary function (percent predicted FEV_1 and change in FEV_1); growth (height, weight, lean body mass, protein turnover); exercise tolerance; and bone mineralization, compared with usual care alone?					
Pulmonary Function					
Absolute FVC	Controlled	3	Yes	rhGH better than control	Moderate
	Single-arm	1	No	Nonsignificant increase from baseline	Very Low
Percent predicted FVC	Controlled	5	Yes	rhGH better than control	Low
	Single-arm	2	No	Mixed results from baseline	Very Low
Absolute FEV_1	Controlled	4	Yes	rhGH better than control	Moderate
	Single-arm	1	No	Nonsignificant increase from baseline	Very Low
Percent predicted FEV_1	Controlled	4	Yes	No effect	Moderate
	Single-arm	2	No	No effect	Very Low
FEV_1 Z-score	Controlled	1	Yes	No effect	Very Low
	Single-arm	No data are available			Insufficient
Anthropometrics					
Height	Controlled	3	Yes	rhGH better than control	Low
	Single-arm	1	No	Improvement from baseline	Very Low
Height velocity	Controlled	3	Yes	rhGH better than control	Moderate
	Single-arm	4	No	Improvement from baseline	Very Low
Height Z-score	Controlled	3	Yes	rhGH better than control	Moderate
	Single-arm	3	No	Improvement from baseline	Low
Height percentile	Controlled	1	No	rhGH better than control	Very Low
	Single-arm	No data are available			NA
Weight	Controlled	5	Yes	rhGH better than control	Moderate
	Single-arm	1	No	Improvement from baseline	Very Low

Table 31. Summary of results

Outcome	Type of Study	Number of Studies	Pooled	Conclusion	Strength of Evidence
Weight velocity	Controlled	2	Yes	rhGH better than control	Moderate
	Single-arm	3	No	Nonsignificant increase from baseline	Low
Weight Z-score	Controlled	4	Yes	No effect	Low
	Single-arm	1	No	Improvement from baseline	Very Low
Weight percentile	Controlled	1	No	rhGH better than control	Very Low
	Single-arm	No data are available			Insufficient
Body mass index	Controlled	2	Yes	rhGH better than control	Moderate
	Single-arm	1	No	No effect	Very Low
BMI Z-score	Controlled	1	Yes	No effect	Very Low
	Single-arm	No data are available			Insufficient
Percent IBW	Controlled	2	Yes	rhGH better than control	Low
	Single-arm	No data are available			Insufficient
Lean body mass	Controlled	8	Yes	rhGH better than control	Moderate
	Single-arm	No data are available			Insufficient
Protein Markers					
Various	Controlled	2	No	Mixed results	Very Low
	Single-arm	1	No	Nonsignificant improvements from baseline	Very Low
Exercise Tolerance					
Various	Controlled	3	No	No effect	Very Low
	Single-arm	1	No	No effect	Very Low
Bone Mineralization					
Bone age	Controlled	2	No	No effect	Very Low
	Single-arm	3	No	No effect	Low
BMC	Controlled	4	Yes	rhGH better than control	Low
	Single-arm	No data are available			Insufficient
BMC Z-score	Controlled	1	No	rhGH better than control	Very Low
	Single-arm	No data are available			Insufficient
Sexual Maturation					
	Controlled	7	No	rhGH better than control	Low
	Single-arm	No data are available			Insufficient
KQ2. In patients with CF, does treatment with rhGH as an adjuvant to usual care improve health outcomes, including: frequency of required intravenous antibiotic treatments; frequency of hospitalization; quality of life; bone fracture or development of osteoporosis/osteopenia; or mortality, compared with usual care alone?					
Antibiotic Usage	Controlled	3	No	rhGH better than control	Very Low
	Single-arm	No data are available			Insufficient
Pulmonary Exacerbations	Controlled	1	No	No effect	Very Low
	Single-arm	No data are available			Insufficient
Hospitalization Rate	Controlled	4	Yes	rhGH better than control	Moderate
	Single-arm	No data are available			Insufficient
HRQoL	Controlled	2	No	rhGH better than control	Very Low
	Single-arm	No data are available			Insufficient
Bone Consequences	No data are available.				Insufficient
Mortality	No data are available.				Insufficient

Table 31. Summary of results

Outcome	Type of Study	Number of Studies	Pooled	Conclusion	Strength of Evidence
KQ3. In patients with CF, what is the strength of evidence that intermediate outcomes of pulmonary function, growth, and bone mineralization are associated with improvements in health outcomes of quality of life, bone fracture or development of osteoporosis/osteopenia, or mortality?					
Mortality					
Pulmonary function	Observational	28	No	Mixed results	NA
Anthropometrics	Observational	26	No	Mixed results	NA
Protein turnover	Observational	No data are available			NA
Exercise tolerance	Observational	10	No	Mixed results	NA
Bone mineralization	Observational	No data are available			NA
HRQoL					
Pulmonary function	Observational	14	No	Improved pulmonary function relates to improved HRQoL	NA
Anthropometrics	Observational	10	No	Mixed results	NA
Protein turnover	Observational	No data are available			NA
Exercise tolerance	Observational	2	No	Improved exercise tolerance relates to improved HRQoL	NA
Bone mineralization	Observational	No data are available			NA
Bone Consequences					
Pulmonary function	Observational	1	No	No association found	NA
Anthropometrics	Observational	1	No	No association found	NA
Protein turnover	Observational	No data are available			NA
Exercise tolerance	Observational	No data are available			NA
Bone mineralization	Observational	No data are available			NA
KQ4. In patients with CF, what is the frequency of nonmalignant serious adverse effects resulting from treatment with rhGH in patients with CF? Adverse effects of interest include, but are not limited to: glucose intolerance, diabetes, and hypoglycemia.					
Glucose Parameters					
A1c	Controlled	2	Yes	No effect	Low
	Single-arm	2	No	Nonsignificant increases from baseline	Low
Random BG	Controlled	3	Yes	Glucose levels remained stable	Very Low
	Single-arm	No data are available			Insufficient
Fasting BG	Controlled	2	Yes	Increased with rhGH compared to control	Moderate
	Single-arm	1	No	Nonsignificant increases from baseline	Very Low
Stimulated BG	Controlled	1	Yes	No effect	Very Low
	Single-arm	No data are available			Insufficient
Postprandial BG	Controlled	1	Yes	No effect	Very Low
	Single-arm	No data are available			Insufficient
Glucose Intolerance					
	Controlled	7	No	No patients developed	Low
	Single-arm	3	No	Few patients developed	Very Low

Table 31. Summary of results

Outcome	Type of Study	Number of Studies	Pooled	Conclusion	Strength of Evidence
Diabetes					
	Controlled	7	No	No patients developed	Low
	Single-arm	1	No	One case report of diabetes	Very Low
Injection Site Reactions					
	Controlled	No data are available			NA
	Single-arm	2	No	Minor discomfort and bruising reported	NA
Liver Transaminases					
	Controlled	No data are available			NA
	Single-arm	2	No	Limited report of liver transaminase elevations	NA
Study Withdrawals					
	Controlled	10	No	Majority of trials reported no withdrawals	NA
	Single-arm	No data are available			NA
KQ5. What is the risk of malignancy associated with rhGH use as determined by: (a) markers of cancer risk with rhGH (IGF-I increases over 100 ng/ml or IGFBP-3 decreases over 1000 ng/ml) from studies of rhGH in people with CF and by (b) assessment of evidence on cancer incidence from non-CF patients receiving modest doses of rhGH (0.2mg/kg/week to 0.6mg/kg/week) for disorders such as growth hormone deficiency and idiopathic short stature?					
Biomarkers					
IGF-I	Controlled	4	No	rhGH increases more than control	Very Low
	Single-arm	2	No	Increased from baseline	Very Low
IGFBP-3	Controlled	1	No	rhGH increases more than control	Very Low
	Single-arm	1	No	Increased from baseline	Very Low
Cancer Incidence in CF Patients					
	Controlled	No data are available			Insufficient
	Single-arm	1	No	Case report shows probable relationship between rhGH and cancer	Very Low
Cancer in non-CF Patients					
	Controlled	No data are available			Insufficient
	Single-arm	3	No	Insufficient data to conclude on rhGH effect on cancer	Low
KQ6. In patients with CF, how is efficacy, effectiveness, safety or adverse events impacted by rhGH dose, therapy duration, baseline nutritional status, and concurrent medical therapies?					
Dose	Controlled	1	No	No significant differences between dose groups in endpoints	NA
Duration	Controlled	9	Yes	One year therapy trends towards improved efficacy versus 6 months therapy. One year therapy trends towards increased glucose parameters versus 6 months therapy.	NA

Table 31. Summary of results

Outcome	Type of Study	Number of Studies	Pooled	Conclusion	Strength of Evidence
Baseline nutritional status	Controlled	1	No	There is limited evidence in patients with variable nutritional status. Efficacy exists in patients receiving enteral nutrition.	NA
Concurrent medical therapies	Controlled	No data are available			NA
KQ7. In patients with CF, how do the efficacy, effectiveness, safety or adverse events of treatment with rhGH differ between subgroups of patients? Subgroup characteristics of interest include, but are not limited to: age (pre-pubertal, pubertal, post-pubertal); gender; baseline clinical status (height, weight, lean body mass, pulmonary function, exercise tolerance, nutritional status); and/or the nature, extent, and effectiveness of prior treatment.					
Age	Controlled	6	Yes	Pubertal patients may derive greater benefit in pulmonary function, weight, and bone mineral content than prepubertal patients. Prepubertal patients may derive greater benefit in height than pubertal patients.	NA
Gender	Controlled	3	Yes[a]	Females (both prepubertal and pubertal) may experience greater benefit in height and weight than males.	NA
Baseline clinical status	Controlled	2	No	Patients with lower baseline height Z-score experienced greater height improvement than those with higher height Z-score. Higher baseline weight was correlated with greater improvement in pulmonary function.	NA
Prior treatment	No data are available				NA

Legend: A1c=glycosylated hemoglobin; BG=blood glucose; BMC=bone mineral content; BMI=body mass index; CF=cystic fibrosis; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; HRQoL=health-related quality-of-life; %IBW=percent ideal body weight; IGF-I=insulin-like growth factor-1; IGFBP-3=insulin-like growth factor binding protein-3; NA=not assessed

[a]Data pooled from three trials by Vanderwel and Hardin.

Future Research

Limitations of Current Research

While rhGH is a promising therapy for the treatment of CF there are a number of important research questions that should be answered before its role can truly be discerned.

In our analysis, we found improvements in height, weight, bone mineral content, and a few but not all measures of pulmonary function with rhGH therapy, but we do not know if this translates into fewer hospitalizations, deaths, or bone fractures or if therapy improves HRQoL in a meaningful way. Most of the trials compared rhGH therapy to no therapy rather than to placebo or an active control and did not rigorously assess for harms. While studies suggest that the risk of glucose metabolism problems with rhGH is low (based on A1c concentrations), longer durations of therapy may increase the risk of glucose intolerance more than shorter durations (based on glucose concentrations). RhGH also increases the concentrations of IGF-I, which may indicate an increased risk of neoplasms, but this is speculative.

The data linking improvements in pulmonary function with reductions in final health outcomes in CF patients is most apparent with percent predicted FEV_1. However, treatment with rhGH only nonsignificantly increases percent predicted FEV_1. In addition, preliminary data suggests that pubertal/adolescent patients may derive more pulmonary benefits from rhGH therapy than prepubertal patients even though there are dissimilar increases in height. This suggests that improvements in pulmonary function may not be tied directly to improvements in height and that the target population for rhGH therapy needs to be further explored.

In patients with osteoporosis but without CF, therapy with bisphosphonates improves bone mineralization with reductions in bone fractures.[139] However, sodium fluoride treatment dramatically increases bone mineral content but may not reduce vertebral fractures, and in high doses, may increase the risk of nonvertebral fractures.[139] As such, it cannot be simply assumed that improvements in bone mineralization will reduce bone fractures and complications such as death.[139]

Based on these research gaps we propose the following avenues for future research.

Future Avenues for Research

Individual Patient Data Meta-Analysis

- We believe that an individual patient data meta-analysis of completed trials evaluating rhGH therapy in patients with CF would yield important information if original trial investigators were willing to report on hospitalizations, deaths, or bone fractures. We attempted to contact all of the authors and explicitly ask for any information they had on these final health outcomes but were unsuccessful.
- An individual patient data meta-analysis may allow the determination of the benefits of rhGH therapy in patients with varying levels of nutritional status, pubertal status, age, and concurrent medical therapy; all important unanswered questions.

Clinical Trials

- We believe that a large, multicenter, randomized, placebo-controlled trial should be conducted to determine the impact of rhGH therapy on hospitalizations, mortality, bone fractures, and HRQoL.
    - Such a trial should be powered and conducted to analyze data in pubertal and prepubertal patients separately.
    - It may be worthwhile for the Cystic Fibrosis Foundation and key trialists to appoint a working group and establish a network of sites interested in prospectively evaluating the impact of rhGH in patients with CF so that such as trial could be conducted. The working group could also specify the HRQoL scale to be used in the trial.
- Even if a large multicenter trial is not feasible, we suggest that smaller future trials evaluating the impact of rhGH in patients with CF should be placebo controlled and prospectively collect data on hospitalizations, mortality, bone fractures, and HRQoL and report on their results even if they are not powered to be quantitatively analyzed.
    - There is value in conducting smaller scale trials with primary objectives to discern the impact of rhGH on pulmonary parameters, exercise tolerance, and HRQoL. While there was no significant improvement in percent predicted FEV_1 or exercise tolerance in our CER, there were qualitative improvements, and future studies would allow us to determine if these were real but underpowered effects.
    - For exercise tolerance and HRQoL, the Cystic Fibrosis Foundation and trialists should specify which exercise tolerance tests and HRQoL questionnaires should be used across future studies to facilitate pooling.
    - Like with the evaluation of benefits, future trials should prespecify the harms they will assess and report on their results even if they are underpowered to perform quantitative synthesis.
    - Trials with treatment durations of 6 or 12 months or longer would be helpful in subsequently determining the adequate duration of therapy.

Observational Studies

- Future observational trials should evaluate the relationship between:
    - The absolute change in FEV_1 and final health outcomes in patients with CF.
    - Bone mineralization and final health outcomes in patients with CF.
    - IGF-I concentrations on the occurrence of cancer in patients with CF.

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