Evidence-based Practice Center Systematic Review Protocol

Project Title: *Effectiveness of Recombinant Human Growth Hormone in the Treatment of Cystic Fibrosis*

I. Background and Objectives for the Systematic Review

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% 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 malnutrition, lung 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 each 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] Growth indices 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% of children will fall within 2 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]; these scores represent 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 FDA approved 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] Recombinant human growth hormone 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]

II. The Key Questions

Introduction: There were no public comments regarding the key questions; therefore, changes have not been made since the key questions were originally posted for comment.

KQ 1: In patients with CF, does treatment with rhGH as an adjuvant to usual care improve intermediate outcomes, including: pulmonary function (% 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 recombinant human growth hormone (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 and idiopathic short stature?

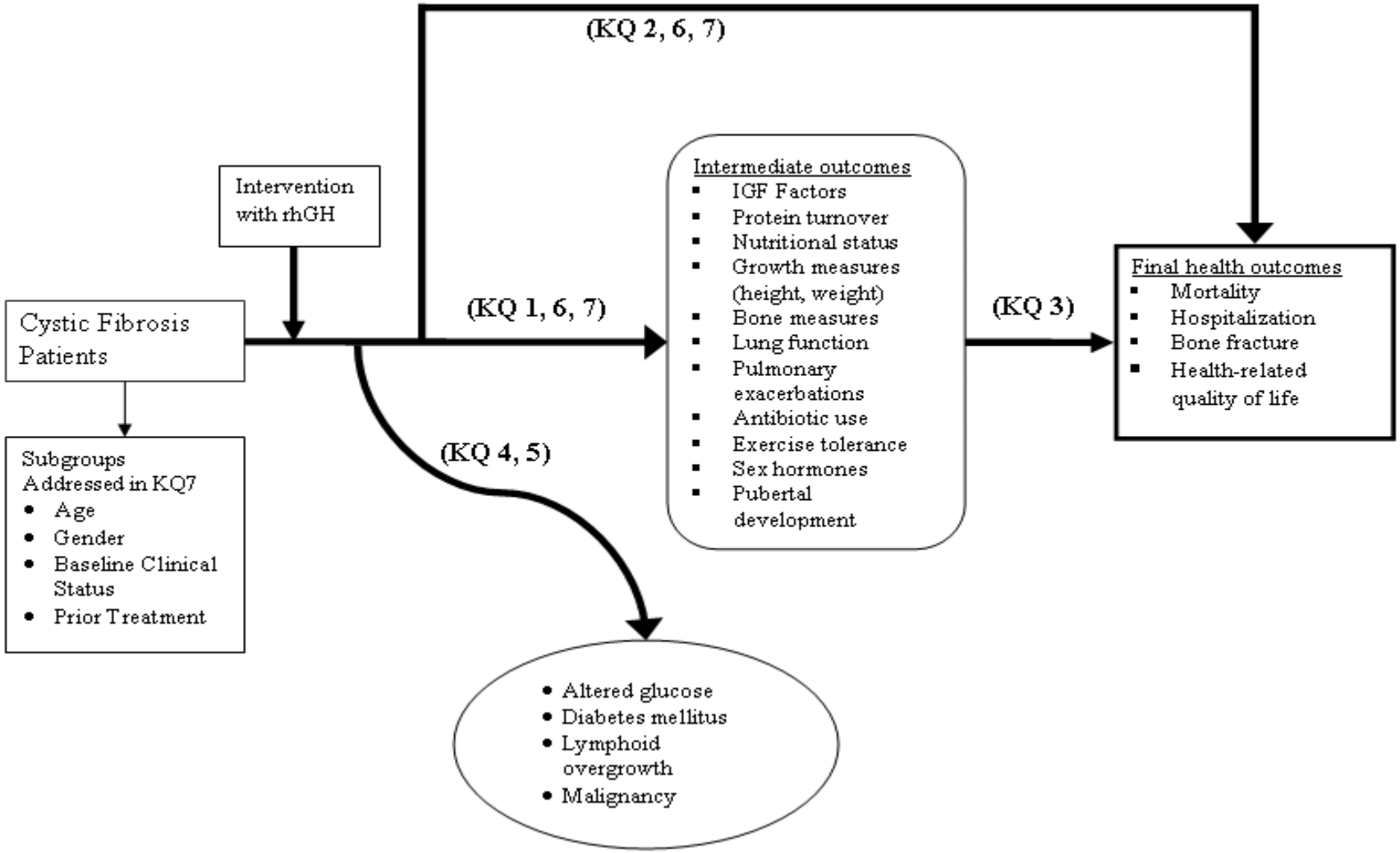
KQ 6: In patients with CF, how is efficacy, effectiveness, safety or adverse events impacted by rhGH dose, therapy duration, baseline nutritional status, and concurrent medical therapies?

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.

III. Analytic Framework

To guide our assessment of studies examining the association recombinant human growth hormone 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 2.1). It is a logic chain that supports the link from the intervention to the outcomes of interest. 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, growth measures, bone measures, lung 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.



Source: www.effectivehealthcare.ahrq.gov
Published Online: January 22, 2010

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

Studies will be included in the evaluation of key questions 1, 2, 4, 6, and 7 if they are 1) studies of rhGH therapy, 2) conducted in patients with CF, 3) studies that reported data on pre-specified clinical or humanistic outcomes (Figure 2.1), and 4) reports of new discovery (specifically, randomized controlled trials, observational trials, systematic review/meta-analyses, or case reports). Studies will be included in the key question 3 evaluation if they are 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 will be included in the key question 5 evaluation if they are 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.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions.

Two independent investigators will conduct 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 will be conducted. The first search will be used to identify trials and studies to answer key questions 1, 2, 4, 6, and 7. This search strategy is for key questions that explicitly evaluate the impact of rhGH on outcomes in patients with CF. The two other searches will be 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 will utilize 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 will be imposed. In addition, a manual search of references from reports of clinical trials or review articles will be conducted. A preliminary search strategy is included in Appendix 1.

C. Data Abstraction and Data Management

Through the use of a standardized data abstraction tool, two reviewers will independently collect data, with disagreement resolved through discussion. The following information will be 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), co-morbidities, and use of concurrent standard medical therapies

(corticosteroids, antibiotics, etc.). Endpoints will include: pulmonary function, growth indices (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[18] or malignancy.

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

D. Assessment of Methodological Quality of Individual Studies

Validity assessment will be performed using the recommendations in the EPC Methods Guide. Each study will be 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 will be assessed for randomization technique and allocation concealment. Observational studies will be assessed for sample size, participant selection method, exposure measurement method, potential design biases, and appropriate analyses to control for confounding. Studies will then be given an overall score of good, bad, or poor (Table 1). Rationale will be provided for studies which rate poorly.

Table 1. Three Summary Ratings of Quality of Individual Studies

Quality Rating	Definition
Good (low risk of bias)	These studies have the lease 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.

E. Data Synthesis

The key questions follow the analytic framework along the continuum of intermediate to important health outcomes. Our review will continue with this organizational scheme and will answer 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 will be selected for meta-analysis, while the remaining outcomes will be reported qualitatively.

Growth indices are also reported in many ways, including absolute values of height, height percentile, height standard deviation or z-scores, height velocity, absolute values of weight, weight percentile, weight standard deviation or z-scores, weight velocity, and weight for height standard deviation score. Because of the variation in reporting, these outcomes are not meta-analyzable. While each has merit in clinical interpretation, data handling is difficult. When given multiple height and weight outcomes, the most commonly reported outcomes will be selected for meta-analysis and the rest will be 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 will model conversions of this data to z-score data using the WHO Anthro Plus software[19] and growth charts published by the CDC.[20]

Due to the limited reporting of the other intermediate outcomes (exercise tolerance and bone mineralization), they will likely be described qualitatively. However meta-analysis will be performed, if sufficient additional data is provided by the authors upon our request.

Important health outcomes in KQ2 and adverse events in KQ4 associated with rhGH will be meta-analyzed if data permits. The remaining KQs (3, 5-7) will likely be answered qualitatively.

Quantitative analysis. In this systematic review, some of the data will allow for meta-analyses to pool the data. When pooling continuous endpoints, a weighted mean difference (WMD) will be calculated using a DerSimonian and Laird random effects model**.**[21] If mean change scores from baseline for each group are not reported, we will calculate the unadjusted difference between the mean baseline and mean followup scores for each group. Standard deviations (SDs) of the change scores will be calculated from the SD of the baseline values and of the followup values, using the formula: $SD_{baseline\text{-}followup}=sqrt(SD^2_{baseline} + SD^2_{followup} - 2*(correlation\ coefficient)SD_{baseline}*SD_{followup})$. Given sufficient evidence, the correlation coefficient will be approximated by utilizing the data from a trial that reports both the SDs of the change scores and the SDs of the baseline and followup values. If calculation is not possible, a correlation coefficient of 0.5 proposed by Follman and colleagues will be used.[22] For dichotomous endpoints, weighted averages will be reported as relative risks (RRs) with associated 95% confidence intervals (CIs). As heterogeneity between included studies is expected, a DerSimonian and Laird random-effects model will be used when pooling data and calculating RRs and 95% CIs.

Statistical heterogeneity will be addressed using Q Statistic (a p-value <0.10 considered representative of significant statistical heterogeneity) and I^2 (which assesses the degree of inconsistency across studies and ranges from 0-100% 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%, 50% and 75% have been regarded as representative of low, medium and high statistical heterogeneity, respectively. Visual inspection of funnel plots and Egger's weighted regression statistics will be used to assess for the

presence of publication bias. In order to assess the potential effect of publication bias on the meta-analysis results, the Trim and Fill method will be used.

Statistics will be performed using StatsDirect statistical software, version 2.4.6 (StatsDirect Ltd, Cheshire, England) and MIX statistical software (freely accessible at www.mix-for-meta-analysis.info). A p-value of Statistic (a p-value <0.05 will be considered statistically significant for all analyses, except where otherwise specified.

Subgroup and sensitivity analyses. To assess the effect of heterogeneity on our meta-analysis' conclusions, subgroup and sensitivity analyses will be conducted. Subgroup analyses will be conducted to assess the effect age, gender, and baseline clinical status on the intervention's efficacy. Sensitivity analyses will also be conducted whereby studies of weaker methodological quality will be excluded.

F. Grading the Evidence for Each Key Question

As it meets AHRQ CER recommendations, strength of evidence grade will be determined for each key question in accordance with the methodology suggested in the AHRQ EPC methods guide.[23] As such, the grade will be based on the number and quality of individual studies, duration of follow-up, consistency across studies, magnitude of effects, applicability, likelihood of publication bias, and the potential influence of plausible confounders. A separate grade will be given for all major outcomes, including benefits and harms. Two investigators will independently grade each outcome using required domains, comprising 4 major constructs, with discrepancies resolved by a third investigator. The domains will include, but may not be limited to: risk of bias, consistency, directness, and precision. We will first assess the risk of bias based on the study designs of the available evidence. We will then use the subsequent domains to modify the overall grade. For example, a lack of consistency or directness will weaken the strength of the evidence. The degree to which the grade is altered is subjective, and the rationale for the changes will be included in the final report. The evidence report will also include the definitions used, and the final grade of high, moderate, low, or insufficient will be given.

V. References

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VI. Definition of Terms

Not applicable.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

NOTE: The following protocol elements are standard procedures for all protocols.

VIII. Review of Key Questions

For Comparative Effectiveness reviews (CERs) the key questions were posted for public comment and finalized after review of the comments. For other systematic reviews, key questions submitted by partners are reviewed and refined as needed by the EPC and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed.

IX. Technical Expert Panel (TEP)

A TEP panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. The TEP

provides information to the EPC to identify literature search strategies, review the draft report and recommend approaches to specific issues as requested by the EPC. The TEP does not do analysis of any kind nor contribute to the writing of the report.

X. Peer Review

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. On some specific reports such as reports requested by the Office of Medical Applications of Research, National Institutes of Health there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

It is our policy not to release the names of the Peer reviewers or TEP panel members until the report is published so that they can maintain their objectivity during the review process.

APPENDIX 1. SEARCH TERMS AND CITATIONS

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

A. KEY QUESTIONS 1, 2, 4, 6, AND 7 SEARCH

MEDLINE (OVID)

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

CENTRAL (OVID)

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

B. KEY QUESTION 3 SEARCH

MEDLINE (OVID)

1. Epidemiologic studies/
2. Exp case control studies/
3. Exp Cohort Studies/
4. Case control.tw.
5. (cohort adj (study or studies)).tw.
6. cohort analy$.tw.
7. (follow up adj (study or studies)).tw.
8. (observational adj (study or studies)).tw.
9. longitudinal.tw.
10. retrospective.tw.
11. cross sectional.tw.
12. Cross-Sectional Studies/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

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

CENTRAL (OVID)

1. Cystic Fibrosis/
2. cystic fibrosis.mp.
3. 1 or 2
4. Mortality/
5. mortality.mp.
6. death.mp.
7. Quality of Life/
8. $quality of life.mp.
9. $qol.mp.
10. Fractures, Bone/

11. bone fracture$.mp.
12. broken bones.mp.
13. Neoplasms/
14. neoplas$.mp.
15. malignan$.mp.
16. cancer.mp.
17. tumor.mp.
18. Or/ 4 – 17
19. **3 and 18**

C. KEY QUESTION 5 SEARCH

MEDLINE (OVID)

1. Epidemiologic studies/
2. Exp case control studies/
3. Exp Cohort Studies/
4. Case control.tw.
5. (cohort adj (study or studies)).tw.
6. cohort analy$.tw.
7. (follow up adj (study or studies)).tw.
8. (observational adj (study or studies)).tw.
9. longitudinal.tw.
10. retrospective.tw.
11. cross sectional.tw.
12. Cross-Sectional Studies/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. randomized controlled trial.pt.
15. controlled clinical trial.pt.
16. randomized.ab.
17. placebo.ab.
18. drug therapy.fs.
19. randomly.ab.
20. trial.ab.
21. groups.ab.
22. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. animals.sh not (humans.sh. and animals.sh.)
24. 22 not 23
25. 13 or 24
26. Human Growth Hormone/
27. human growth hormone.mp.
28. recombinant human growth hormone.mp.
29. rhgh.mp.

30. hgh.mp.
31. somatropin.mp.
32. genotropin.mp.
33. humatrope.mp.
34. hypertropin.mp.
35. jintropin.mp.
36. nordotropin.mp.
37. nutropin.mp.
38. omnitrope.mp
39. saizen.mp.
40. serostim.mp.
41. zomacton.mp.
42. zorbtive.mp.
43. crytropin.mp.
44. Or/ 26 – 43
45. Neoplasms/
46. neoplas$.mp.
47. malignan$.mp.
48. cancer.mp.
49. tumor.mp.
50. Or/ 45 – 49
51. idiopathic short stature.mp.
52. ISS.mp.
53. growth hormone deficiency.mp.
54. GHD.mp.
55. GH deficiency.mp.
56. Or/ 51 – 55
57. **25 and 44 and 50 and 56**

CENTRAL (OVID)

1. Human Growth Hormone/
2. human growth hormone.mp.
3. recombinant human growth hormone.mp.
4. rhgh.mp.
5. hgh.mp.
6. somatropin.mp.
7. genotropin.mp.
8. humatrope.mp.
9. hypertropin.mp.
10. jintropin.mp.
11. nordotropin.mp.
12. nutropin.mp.

13. omnitrope.mp
14. saizen.mp.
15. serostim.mp.
16. zomacton.mp.
17. zorbtive.mp.
18. crytropin.mp.
19. Or/ 1 – 18
20. Neoplasms/
21. neoplas$.mp.
22. malignan$.mp.
23. cancer.mp.
24. tumor.mp.
25. Or/ 20 – 24
26. idiopathic short stature.mp.
27. ISS.mp.
28. growth hormone deficiency.mp.
29. GHD.mp.
30. GH deficiency.mp.
31. Or/ 26 – 30
32. **19 and 25 and 31**